Prior Authorization Criteria

Effective January 1, 2025

The following is the listing of Prescryptive Health prior authorization criteria that will be used to evaluate prior authorization requests. Prescryptive Health's prior authorization criteria are based on clinical monographs and National Pharmacy and Therapeutics guidelines. Prior Authorization Criteria will be updated regularly to reflect ongoing changes and is subject to change without notice. Members should check their specific plan information for coverage and confirmation that a prior authorization is required, prior to looking up the prior authorization criteria.

Prior Authorization Requests for Medications

Medications may be authorized when there is clinical justification for doing so. Clinicians can submit a prior authorization (PA) request to initiate a review with the following steps:

1. Download the Prior Authorization Request Form. This form can be found at: http://www.prescryptive.com/resources/

2. Fax the completed form with supporting documentation to **1 (877) 843-9375** for both standard and urgent requests.

Note: Urgent requests should be clearly labeled "URGENT" at the top of the prior authorization request form.

Accrufer (ferric maltol)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
ACCRUFER® (ferric maltol) Capsule	Treatment of iron deficiency in adults		1

CLINICAL RATIONALE

Iron deficiency	Iron deficiency (ID) is the most common nutritional disorder worldwide and accounts for approximately one-half of anemia cases. ID is defined as the decrease of the total content of iron in the body. ID may be the result of excessive iron loss, or, less frequently, decreased absorption. In general, the iron absorbed daily equals the amount needed to compensate its loss, so that the overall iron pool remains stable. This fine balance is easily broken, because the capability to absorb iron orally is limited. When the inputs are less than necessary or, more frequently, when the outputs increase and cannot be compensated for, ID develops. Deficient intake is the most frequent etiology in ID.(2) ID can be detected in an asymptomatic individual on a screening-analysis, or in a person with symptoms that include general weakness, fatigue, irritability, poor concentration, headache, and intolerance to exercise. These symptoms appear even in patients with ID and normal hemoglobin levels. Although the impact of ID on the quality of life of the subject is high, they often get used to their symptoms and these are assumed as normal. The patient becomes aware of an improvement only when the symptoms disappear. Some iron-deficient patients, with or without anemia, might have alopecia, atrophy of lingual papillae, or dry mouth due to loss of salivation. Pica, the eating disorder in which there is an irresistible desire to lick or eat non-nutritive and unusual substances, such as soil, chalk, gypsum, ice (pagophagia), or paper, might appear in some cases. Pagophagia is considered quite specific to ID and it responds quickly to treatment.(2)

Serum ferritin, in the absence of inflammation (usually defined as a normal C-reactive protein level), reflects total body iron deposits. Thus, a low serum ferritin (less than 30 ng/L) unequivocally means ID, whether accompanied by anemia or not. However, as serum ferritin is an acute phase reactant, a normal or even elevated ferritinemia does not exclude the presence of ID. ID could exist even with levels of ferritin up to 100 ng/mL in the presence of an inflammatory process. Another parameter of the normal "iron metabolism", especially useful when the determination of ferritin is equivocal, is the transferrin saturation index. This shows the percentage of transferrin that transports iron and thus a decrease (less than 20%) implies ID, either absolute or functional.(2)

In some cases, even taking into account all these determinations, ID can be difficult to diagnose. It generally occurs in situations where the anemia has a multifactorial origin.(2)

Oral iron supplementation is an inexpensive and effective option for treating ID in stable outpatients. Iron salts such as ferrous gluconate, ferrous sulfate, and ferrous fumarate remain the standard first-line therapy for treating ID. Other common iron formulations include ferrous ascorbate, ferrous succinate, carbonyl iron, ferric citrate, liposomal iron, heme iron peptide, and polysaccharide iron complexes. With consistent oral iron supplementation, reticulocytosis starts in 4-5 days, and hemoglobin (Hb) begins to improve by the second week. Oral iron therapy is often required for at least 3 to 6 months to replete iron stores and normalize ferritin levels, although more time may be required depending upon the severity and ongoing losses.(3)

Common elemental iron content of select available iron formulations in the United States and Canada:(3)

Product	**Dose per tablet (mg)**	**Elemental iron content per mg**
Ferrous gluconate	240	27
Ferrous gluconate	325	38
Ferrous sulfate	325	65
Ferrous fumarate	325	106
Heme iron polypeptide	398	11
Polysaccharide complex	150	150

	<table><tr><td>Ferric citrate</td><td>210</td><td>210</td></tr></table> The list of examples in this table is not exhaustive. Liquid formulations are also available. Approximately 10% of elemental iron ingested is absorbed.
Efficacy	Accrufer delivers iron for uptake across the intestinal wall and transfer to transferrin and ferritin. The safety and efficacy of Accrufer for the treatment of iron deficiency anemia was studied in two randomized, placebo-controlled trials (AEGIS 1 [NCT01252221] and AEGIS 2 [NCT01340872]). These trials enrolled 128 patients with quiescent inflammatory bowel disease (IBD) (58 patients with ulcerative colitis [UC] and 70 patients with Crohn's disease [CD]) and baseline ferritin less than 30 mcg/L and Hb concentrations between 9.5 g/dL and 12 g/dL for females and 9.5 g/dL and 13 g/dL for males. All patients had discontinued prior oral ferrous product treatment due to lack of efficacy or inability to tolerate oral iron replacement products.(1) The major efficacy outcome for AEGIS 1 and AEGIS 2 was the mean difference in Hb concentration from baseline to week 12 between Accrufer and placebo. The Least Square (LS) mean difference from baseline was 2.18 g/dL (p less than 0.0001).(1) Following completion of the 12-week placebo-controlled phase of the studies, eligible patients transitioned to Accrufer 30 mg twice daily open-label treatment for an additional 52 weeks.(1) The safety and efficacy of Accrufer for the treatment of iron deficiency anemia was studied in AEGIS 3 (NCT02968368) that enrolled 167 patients with non-dialysis chronic kidney disease (CKD) and a baseline Hb concentrations between 8 g/dL and 11 g/dL with a transferrin saturation (TSAT) less than 15%.(1) The major efficacy outcome for AEGIS 3 was the mean difference in Hb concentration from baseline to Week 16 between Accrufer and placebo. The LS mean difference was 0.52 g/dL (p=0.0149).(1)
Safety	Accrufer (ferric maltol) is contraindicated in:(1) • Patients with a hypersensitivity to the active substance or any excipient • Hemochromatosis and other iron overload syndromes • Patients receiving repeated blood transfusions

	Advise patients that they should not use Accrufer if they are experiencing an IBD flare as there is potential risk of increased inflammation in the gastrointestinal tract.(1)

REFERENCES

Number	Reference
1	Accrufer prescribing information. Shield TX (UK). December 2023.
2	Camaschella C. Iron deficiency: new insights into diagnosis and treatment. Hematology. 2015;2015(1):8-13. doi:10.1182/asheducation-2015.1.8
3	Ning S, Zeller MP. Management of iron deficiency. Hematology Am Soc Hematol Educ Program. 2019;2019(1):315-322. doi:10.1182/hematology.2019000034.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when BOTH of the following are met: 1. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent

Module	Clinical Criteria for Approval
	Length of Approval: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months

Acute Migraine Agents

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Elyxyb™ (celecoxib) Oral solution	Acute treatment of migraine headaches with or without aura in adults Limitations of Use: Elyxyb is not indicated for the preventive treatment of migraine.		12
MIGRANAL® (dihydroergotamine mesylate)* Nasal Spray	Acute treatment of migraine headaches with or without aura MIGRANAL is not intended for the prophylactic therapy of migraine or for the management of hemiplegic or basilar migraine	*generic available	1
REYVOW® (lasmiditan) Tablet	Acute treatment of migraine with or without aura in adults Limitations of Use: REYVOW is not indicated for the preventive treatment of migraine.		2
Trudhesa® (dihydroergotamine mesylate) Nasal aerosol	Acute treatment of migraine with or without aura in adults Limitations of Use: Trudhesa is not indicated for the preventive treatment of migraine or for the management of hemiplegic or basilar migraine.		10

CLINICAL RATIONALE

Migraine and Cluster Headache Management	Migraine is a common disabling primary headache disorder with high prevalence, ranking second globally in terms of years lost to disability.(6) Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia. Migraines can

present with or without aura, unilateral fully reversible visual, sensory, or other central nervous system symptoms that usually develop gradually and are most-often followed by headache and associated migraine symptoms.(4)

The International Classification of Headache Disorders 3rd Edition (ICHD-3) Diagnostic Criteria:(4)

Indication	Diagnostic Criteria
Migraine without aura	A. At least five attacks fulfilling criteria B-D B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated) C. Headache has at least TWO of the following: 1. unilateral location 2. pulsating quality 3. moderate to severe pain intensity 4. aggravation by causing avoidance of routine physical activity D. During headache at least ONE of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia E. Not better accounted for by another ICHD-3 diagnosis
Migraine with aura	A. At least two attacks fulfilling criteria B and C B. One or more of the following fully reversible aura symptoms: 1. visual 2. sensory

		3. speech and/or language 4. motor 5. brainstem 6. retinal C. At least THREE of the following: 1. at least one aura symptom spreads gradually over 5 minutes or more 2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5-60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive 6. the aura is accompanied, or followed within 60 minutes, by headache D. Not better accounted for by another ICHD-3 diagnosis
	Chronic Migraine	A. Headache (migraine-like or tension-type-like) on greater than or equal to 15 days/month for greater than 3 months AND fulfilling B and C B. Occurring in patient who has had at least 5 attacks fulfilling 1. criteria B-D for migraine without aura (noted above) and/or 2. criteria B and C for migraine with aura (noted above)

		C. On greater than or equal to 8 days/month for greater than 3 months, fulfilling any of the following: 1. criteria C and D for migraine without aura (noted above) 2. criteria B and C for migraine with aura (noted above) 3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative D. Not better accounted for by another ICHD-3 diagnosis
	Cluster Headache	A. At least 5 attacks fulfilling criteria B-D B. Severe to very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (untreated) C. At least one of the following: 1. At least one of the following signs or symptoms, ipsilateral to the headache a. conjunctival injection and/or lacrimation b. nasal congestion and/or rhinorrhea c. eyelid edema d. forehead and facial sweating

		e. miosis and/or ptosis 2. Sense of restlessness or agitation D. Occurring with frequency between one every other day and 8 per day E. Not better accounted for by another ICHD-3 diagnosis
	Episodic Cluster Headache	A. Attacks fulfilling criteria for Cluster Headache (noted above) occurring in bouts (cluster periods) B. At least two cluster periods lasting 7 days to 1 years (untreated) and separated by pain-free remission periods of at least 3 months

The IHS notes that cluster periods usually last between 2 weeks and 3 months.(4)

Migraine prevention may be of benefit in those with the following:(6,7,13)

- Frequent or long-lasting migraine headaches (greater than 4 headaches/month or headaches lasting greater than 12 hours)
- Attacks interfere significantly with patients' daily routines despite acute treatment
- Contraindication to acute therapies
- Failure of acute therapies
- Adverse effects with acute therapies
- Risk of medication overuse headache (MOH)
- Patient preference

The American Headache Society (AHS) and the American Academy of Neurology (AAN) suggest the following agents for the prevention of migraine:(3)

- Established as effective (Level A)
    - Antiepileptic drugs (AEDs)

	▪ Divalproex ▪ Valproate ▪ Topiramate ○ Beta blockers ▪ Metoprolol ▪ Propranolol ▪ Timolol ○ Triptans ▪ Frovatriptan for short term menstrually associated migraines (MAMs) prevention • Probably effective (Level B) ○ Antidepressants ▪ Amitriptyline ▪ Venlafaxine ○ Beta blockers ▪ Atenolol ▪ Nadolol ○ Triptans ▪ Naratriptan, zolmitriptan for short term MAMs prevention The 2021 American Headache Society Consensus Statement recommends the following indications for initiating treatment acute treatment with gepants and ditans agents:(13) • Prescribed by a licensed clinician • Patient is at least 18 years of age • Diagnosis of ICHD-3 migraine with aura, migraine without aura, or chronic migraine • Either of the following: ○ Contraindication to or inability to tolerate triptans ○ Inadequate response to two or more oral triptans, as determined by either of the following: ▪ Validated acute treatment patient-reported outcoming questionnaire (mTOQ, Migraine-ACT, PPMQ-R, FIS, PGIC) ▪ Clinician attestation Lasmiditan is a selective serotonin 5HT-1F receptor agonist that lacks vasoconstrictor activity. Lasmiditan is structurally different than triptans and therefore constitutes a new class of drugs called “ditans”.(13) Ditans are selective for the 5HT-1F receptor and its mechanism of action is neuronal without evidence of vasoactive effects.(14) Triptans non-specifically bind to the 5HT-1B and 5HT-1D receptors and with varying affinity bind the 5HT-

	1F receptors, causing direct vascular vasoconstriction. The safety, tolerability, and efficacy of co-administering lasmiditan with a triptan or a gepant has not been assessed.(13) Patients who do not respond to initial therapy with a triptan, may benefit from a second triptan or different therapy such as use of a gepant (ubrogepant or rimegepant) or a ditan (lasmiditan).(6) The 2021 American Headache Society Consensus Statement recommends the following indications for initiating treatment with a Calcitonin Gene-Related Peptide (CGRP) agent:(13) • Prescribed by a licensed clinician • Patient is at least 18 years of age • ONE of the following: o Diagnosis of migraine with or without aura (4-7 monthly headache days) and both of the following: ▪ Inability to tolerate (due to side effects) or inadequate response to an 8-week trial of at least two of the following: • Topiramate • Divalproex sodium/valproate sodium • Beta blocker: metoprolol, propranolol, timolol, atenolol, nadolol • Tricyclic antidepressant: amitriptyline, nortriptyline • Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine • Other Level A or B treatment according to AAN-AHS guideline ▪ At least moderate disability (Migraine Disability Assessment Questionnaire [MIDAS] greater than or equal to 11, Headache Impact Test-6 [HIT]-6 greater than 50) o Diagnosis of migraine with or without aura (8-14 monthly headache days [MHDs]) and inability to tolerate (due to side effects) or inadequate response to an 8-week trial of at least two of the following: ▪ • Topiramate • Divalproex sodium/valproate sodium • Beta blocker: metoprolol, propranolol, timolol, atenolol, nadolol • Tricyclic antidepressant: amitriptyline, nortriptyline • Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine

	• Other Level A or B treatment according to AAN-AHS guideline ○ Diagnosis of chronic migraine and one of the following: ▪ Inability to tolerate (due to side effects) or inadequate response to an 8-week trial of at least two of the following: • Topiramate • Divalproex sodium/valproate sodium • Beta blocker: metoprolol, propranolol, timolol, atenolol, nadolol • Tricyclic antidepressant: amitriptyline, nortriptyline • Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine • Other Level A or B treatment according to AAN-AHS guideline ▪ Inability to tolerate or inadequate response to a minimum of two quarterly injection (6 months) of onabotulinum toxin A The Medical Letter Treatment Guidelines (2023) and Institute for Clinical Systems Improvement Guideline Diagnosis and Treatment of Migraine Headache - Drugs for Migraine states that a triptan is the drug of choice for moderate to severe migraine. The short-acting oral serotonin (5-HT1B/1D) receptor agonists (triptans) sumatriptan (IMITREX, and others), almotriptan (Axert, and generics), eletriptan (RELPAX), rizatriptan (Maxalt, and generics), and zolmitriptan (Zomig, and generics) are similar in efficacy.(15,17) Onset of pain relief generally occurs 30-60 minutes after administration. The longer-acting oral triptans naratriptan (Amerge, and generics) and frovatriptan (Frova, and generics) have a slower onset of action and lower initial response rate than other triptans, but they are better tolerated. Patients with migraine who have nausea or vomiting may not be able to take an oral triptan. Intranasal triptan formulations have a more rapid onset of action than oral tablets, but their efficacy is partially dependent on GI absorption of the portion of the dose that is swallowed. Use of sumatriptan nasal powder (ONZETRA Xsail) results in a faster rise in sumatriptan plasma concentrations and higher peak concentrations than use of a similar dose of sumatriptan nasal spray, suggesting that a larger portion of the dose is absorbed intranasally with the powder. Subcutaneously administered sumatriptan relieves pain faster (in about 10 minutes) and more effectively than other triptan formulations, but it causes more adverse effects.(15) American Headache Society (AHS) (2015): Triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan [oral, nasal spray, injectable, transcutaneous patch], zolmitriptan [oral and nasal spray]) are effective (Level A)

	and considered by AHS guidelines (2015) to be the gold standard for acute treatment of moderate to severe migraine headaches.(7) Dihydroergotamine is recommended for use as a second- or third-line therapy for select patients or for those with refractory migraine. Intranasal dihydroergotamine has strong evidence of effectiveness but more adverse effects than triptans because of its decreased receptor specificity.(11) An assessment of new migraine treatments by the AHS (2018; updated 2021) reaffirms previous migraine guidelines. The update lists triptans, dihydroergotamine, the oral gepants (Nurtec ODT [rimegepant] and UBRELVY [ubrogepant]), and REYVOW (lasmiditan) as effective treatment of moderate or severe acute attacks and mild to moderate attacks that respond poorly to non-specific nonsteroidal anti-inflammatory drugs (NSAIDs), non-opioid analgesics, acetaminophen, or caffeinated combinations (e.g., aspirin/acetaminophen/caffeine). The recommendation remains that prescribers must consider medication efficacy and potential medication-related adverse effects, potential adverse events, patient-specific contraindications to use with a particular medication, and drug-drug interactions when prescribing acute medications for migraine.(6,7,13) The American Academy of Neurology (AAN) 2010 Guideline: Acute and preventive pharmacologic treatment of cluster headache (CH) state that sumatriptan subcutaneous injection and zolmitriptan nasal spray are first-line options for acute treatment of CH.(16,17) American Headache Society Since the publication of the 2010 AAN review, re-reviewed in 2016, there is no new data from randomized, double-blind, controlled trials that contribute to determining the efficacy or safety for a number of acute treatments, including specifically sumatriptan and zolmitriptan. For acute treatment, sumatriptan subcutaneous, zolmitriptan nasal spray, and high flow oxygen remain the treatments with a Level A recommendation.(18) Guidelines suggest that prophylactic therapy should be started and continued for the duration of the CH period. Prophylactic pharmacological therapy includes verapamil, corticosteroids, lithium, topiramate, melatonin, gabapentin, valproic acid, ergotamine, and capsaicin. Verapamil is commonly considered the first option for prophylactic therapy in practice.(5,16,22) Corticosteroids can be used as transitional or bridging therapy until another prophylaxis agent is established.(22) Corticosteroids may be used by some practitioners for short periods of CH.(5,16) The American Academy Neurology lists the following agents as option that maybe considered or should be advised as preventative treatments: • Civamide • Suboccipital steroid injection • Melatonin • Verapamil

	• Lithium
	
	The European Headache Federation and WHO consensus article (2019) states the following:(8)
	
	• Individuals with migraine headaches should always be managed in primary care with the exception being chronic migraine, which likely requires specialist management
	• Any headache not responding satisfactorily in primary care or chronic migraine, should be referred to a specialist
	• In adults and children, regular high frequency use (greater than 2 day/week) of acute medication risks the development of MOH
	• Treatment of episodic acute migraine headaches should be approached in a step wise manner and should treat three attacks at each step before moving to the next step if needed:
	  ○ Step 1:
	  ▪ Use non-opioid analgesics, plus an antiemetic when needed
	  ○ Step 2 for adults:
	  ▪ Use triptan products
	  ▪ Triptans should not be used regularly for 10 or more days per month to avoid the risk of MOH
	  ▪ Triptan efficacy is highly variable between individuals, so patients should try different triptans and formulations. Sumatriptan subcutaneous injection should be considered when all other triptans are ineffective.
	  ▪ When vomiting is present, zolmitriptan nasal spray or sumatriptan subcutaneous injection may be preferred
	  ○ Step 2 for children and adolescents:
	  ▪ Failure of Step 1 in children should lead to specialist referral. No specific anti-migraine drugs have shown efficacy in children under 12 years of age.
	  ▪ Failure of Step 2 in adolescents (12-17 years of age), the following have shown efficacy and are approved:
	  • Sumatriptan nasal spray
	  • Zolmitriptan nasal spray
	• Episodic migraine prophylaxis:
	  ○ Indication for migraine prophylaxis include:
	  ▪ Attacks cause disability on two or more days per month, and

	▪ Acute therapy has been optimized but does not prevent this, or is poorly tolerated, or there is a risk of over-frequent use of acute therapy, even when it is effective, and ▪ Patient is willing to take daily medication ▪ Failure of acute therapy is an indication for migraine prophylaxis ▪ For children, frequent absence from school is an additional indication for prophylaxis ○ Migraine prophylaxis agents may take 2-3 months to show efficacy ○ Children requiring prophylactic medication should be referred to a specialist ○ Medications which are effective in adult prophylaxis of episodic migraine include: ▪ Beta blockers: • Atenolol, bisoprolol, metoprolol, propranolol ▪ Amitriptyline ▪ Topiramate ▪ Candesartan ▪ Sodium valproate ▪ Flunarizine ▪ CGRP ○ Onabotulinum toxin A is not effective in episodic migraine and not recommended ○ When prophylaxis therapy fails: ▪ May be due to subtherapeutic dosage or duration of therapy ▪ Failure of one therapy does not predict the failure of another therapy in a different class ▪ Review of the following are recommended: • Diagnosis • Adherence • Other medications, especially for MOH causes ▪ The prophylaxis therapy should be discontinued if it fails to show clear benefit ▪ If all prophylaxis therapies fail, a specialist should be referred • Chronic migraine management: ○ Chronic migraine patients should be referred to a specialist ○ Medications with efficacy in chronic migraine include: ▪ Topiramate

	▪ Onabotulinum A ▪ CGRP • Cluster Headache management: ○ Patients should be referred to a specialist ○ Acute therapies include: ▪ Triptans: • Sumatriptan subcutaneous injection • Sumatriptan nasal spray • Zolmitriptan nasal spray ▪ Oxygen ○ Transition and maintenance therapies include: ▪ Prednisone ▪ Greater occipital nerve blockade ▪ Verapamil ▪ Lithium carbonate ▪ Topiramate ○ Neuromodulation is another treatment option ○ Failure of one prophylactic therapy does not predict the failure of other therapies ○ Combination prophylaxis therapy can be considered though the potential for toxicity is high ○ Long-term prophylaxis therapy may need to be continued The European Headache Federation guideline states the following on combining migraine prophylaxis therapy:(9) • In episodic migraine, guidelines suggest to stop oral prophylaxis migraine agents before starting CGRPs, unless the patient previously had chronic migraine prior to prophylaxis. In such patients, the suggestion is to add CGRP to the ongoing oral prophylaxis therapy • In chronic migraine, guidelines suggest to add CGRP to ongoing oral prophylaxis therapy • In chronic migraine patients on onabotulinum A therapy and are receiving inadequate treatment response, guidelines suggest to stop onabotulinum A therapy before starting CGRPs • In patients with chronic migraine who are on treatment with CGRP and may benefit from additional prevention, guidelines suggest to add on oral preventative agents • In patients with medication overuse, guidelines suggest to use CGRPs before or after withdrawal of acute medications

	The clinical trials referenced in FDA labeled package inserts for the preventative CGRP agents excluded patients that had received botulinum toxin within 4 months prior to receiving the CGRP agent.(19,20,21) However the 2021 American Headache Society consensus statement states that CGRP monoclonal antibody treatment (e.g., eptinezumab-jjmr, erenumab, fremanezumab, galcanezumab) may be added to greater than or equal to one established preventative treatment, based on clinical judgement, in adults who meet the ICHD-3 criteria for the following conditions:(4,13) • Migraine with/without aura (4–7 monthly migraine days [MMDs]) with at least moderate disability (Migraine Disability Assessment greater than or equal to 11 or 6-item Headache Impact Test greater than 50) and failure of an 8-week trial of greater than or equal to 2 preventive treatments with established efficacy (e.g., topiramate, divalproex sodium, beta-blocker, tricyclic antidepressant, and others) • Migraine with/without aura (8–14 MMDs) and failure of an 8-week trial of greater than or equal to 2 established preventive treatments • Chronic migraine (greater than or equal to 15 MMDs) with any level of disability and either failure of an 8-week trial of greater than or equal to two established preventive treatments or inadequate tolerability or response to onabotulinum toxin A for two quarterly injections

Medication overuse headache (MOH)	The European Headache Federation and WHO consensus article (2019) states the following:(8)
	
	•
	  ○ Prevention is preferred
	  ○ The four objectives of management are:
	  ▪ Stop the overused medication
	  ▪ Recovery from MOH
	  ▪ Review and reassess the underlying headache disorder
	  ▪ Prevent relapse while allowing acceptable use of medications
	  ○ Comorbidities may require management

Safety	Elyxyb has the following boxed warnings:(12) • Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in the treatment and may increase with duration of use

	• Elyxyb is contraindicated in the setting of coronary artery bypass graft (CABG) surgery • NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events Elyxyb is contraindicated in the following:(12) • Patients with known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to celecoxib, any components of the drug product • Patients with a history of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients. • In the setting of CABG surgery • Patients who have demonstrated allergic-type reactions to sulfonamides MIGRANAL has the following boxed warning:(1) • Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of dihydroergotamine with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of dihydroergotamine, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated. MIGRANAL is contraindicated in the following:(1) • Patients with ischemic heart disease (angina pectoris, history of myocardial infarction, or documented silent ischemia) or patients who have clinical symptoms or findings consistent with coronary artery vasospasm including Prinzmetal's variant angina • Patients with uncontrolled hypertension • Use within 24 hours of 5-HT1 agonists (e.g., sumatriptan), ergotamine-containing or ergot-type medications, or methysergide • Patients with hemiplegic or basilar migraine • Patients with known peripheral arterial disease, sepsis, following vascular surgery, and severely impaired hepatic or renal function

	• Pregnant women • Patients who have previously shown hypersensitivity to ergot alkaloids • Use with peripheral and central vasoconstrictors because the combination may result in additive or synergistic elevation of blood pressure REYVOW has no FDA labeled contraindications for use.(2) Trudhesa has the following boxed warning:(10) • Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of dihydroergotamine with strong CYP3A4 inhibitors. Because CYP3A4 inhibition elevates the serum levels of dihydroergotamine, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of Trudhesa with strong CYP 3A4 inhibitors is contraindicated. Trudhesa is contraindicated in the following:(10) • Concomitant use of strong CYP 3A4 inhibitors • Patients with ischemic heart disease or coronary artery vasospasm • Patients with uncontrolled hypertension, peripheral arterial diseases, sepsis, following vascular surgery, or severe hepatic or renal impairment • Patients with hypersensitivity to ergot alkaloids • Concomitant use of other 5-HT1 agonists (e.g., sumatriptan) or ergotamine-containing or ergot-type medications within 24 hours • Concomitant use of peripheral and central vasoconstrictors

REFERENCES

Number	Reference
1	MIGRANAL prescribing information. Bausch Health US, LLC. September 2022.
2	REYVOW prescribing information. Eli Lilly and Company. September 2022.
3	Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: Report of the Quality Standards Subcommittee of the

Number	Reference
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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met:

Module	Clinical Criteria for Approval
	1. ONE of the following: A. The requested agent is being used for acute migraine treatment AND ALL of the following: 1. ONE of the following: A. The patient has tried and had an inadequate response to ONE triptan agent **OR** B. The patient has an intolerance or hypersensitivity to ONE triptan agent **OR** C. The patient has an FDA labeled contraindication to ALL triptan agents **AND** 2. ONE of the following: A. The requested agent is NOT REYVOW **OR** B. The requested agent is REYVOW AND the patient will NOT be using the requested agent in combination with another acute migraine therapy (i.e., 5HT-1F, acute use CGRP, ergotamine, triptan) **AND** 3. Medication overuse headache has been ruled out **OR** B. The patient has another FDA labeled indication for the requested agent and route of administration **OR** C. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met:

Module	Clinical Criteria for Approval
	1. The patient has been approved for the requested agent previously through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. ONE of the following: A. The requested agent is being used for acute migraine treatment AND ALL of the following: 1. The patient has had clinical benefit with the requested agent **AND** 2. ONE of the following: A. The requested agent is NOT REYVOW **OR** B. The requested agent is REYVOW AND the patient will NOT be using the requested agent in combination with another acute migraine therapy (i.e., 5HT-1F, acute use CGRP, ergotamine, triptan) **AND** 3. Medication overuse headache has been ruled out **OR** B. The patient is using the requested agent for an indication other than acute migraine treatment AND has had clinical benefit with the requested agent **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	C. The patient has greater than 4 migraine headaches per month AND ONE of the following: 1. The patient is currently being treated with a migraine prophylactic medication [i.e., anticonvulsants (i.e., divalproex, valproate, topiramate), beta blockers (i.e., atenolol, metoprolol, nadolol, propranolol, timolol), antidepressants (i.e., amitriptyline, venlafaxine), candesartan, prophylactic use CGRP (e.g., Aimovig, AJOVY, Emgality, Nurtec, QULIPTA, Vyepti), onabotulinum toxin A (Botox)] **OR** 2. The patient has an intolerance or hypersensitivity to therapy with migraine prophylactic medication [i.e., anticonvulsants (i.e., divalproex, valproate, topiramate), beta blockers (i.e., atenolol, metoprolol, nadolol, propranolol, timolol), antidepressants (i.e., amitriptyline, venlafaxine), candesartan, prophylactic use CGRP (e.g., Aimovig, AJOVY, Emgality, Nurtec, QULIPTA, Vyepti), OR onabotulinum toxin A (Botox)] **OR** 3. The patient has an FDA labeled contraindication to ALL migraine prophylactic medications [i.e., anticonvulsants (i.e., divalproex, valproate, topiramate), beta blockers (i.e., atenolol, metoprolol, nadolol, propranolol, timolol), antidepressants (i.e., amitriptyline, venlafaxine), candesartan, prophylactic use CGRP (e.g., Aimovig, AJOVY, Emgality, Nurtec, QULIPTA, Vyepti), AND onabotulinum toxin A (Botox)] **OR** 4. There is support that the patient's migraines are manageable with acute therapy alone **AND** D. There is support of therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Attention Deficit [Hyperactivity] Disorder (ADHD/ADD) Agents

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Adderall XR® (amphetamine/dextroamphetamine ER)* Capsule	Treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years and older	Stimulant *generic available	2
Adderall® (amphetamine/dextroamphetamine)* Tablet	Treatment of attention deficit hyperactivity disorder (ADHD) in patients 3 years or older Treatment of narcolepsy	Stimulant *generic available	1
Adhansia XR® (methylphenidate ER) Capsule	Treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older	Stimulant	3
Adzenys XR-ODT® (amphetamine ER) Orally disintegrating tablet	Treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older	Stimulant	5
Aptensio XR® (methylphenidate ER)* Capsule	Treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older Limitations of use: • Pediatric patients younger than 6 years of age experienced higher	Stimulant *generic available	6

Agent(s)	FDA Indication(s)	Notes	Ref#
	plasma exposure than patients 6 years and older at the same dose and high rates of adverse reactions, most notably weight loss.		
Azstarys® (serdexmethylphenidate/dexmethylphenidate) Capsules	Treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years of age and older	Stimulant	43
Concerta® (methylphenidate osmotic ER)* Tablet	Treatment of attention deficit hyperactivity disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65	Stimulant *generic available	7
Cotempla XR ODT® (methylphenidate ER) Orally disintegrating tablet	Treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients 6 to 17 years of age	Stimulant	8
Daytrana® (methylphenidate)* Transdermal system	Treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients 6 to 17 years of age	Stimulant *generic available	9
Desoxyn® (methamphetamine)* Tablet	Attention Deficit Disorder with Hyperactivity: Desoxyn tablets are indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children over 6 years of age	Stimulant *generic available	10

Agent(s)	FDA Indication(s)	Notes	Ref#
	with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.		
Dexedrine Spansules® (dextroamphetamine ER)* Capsule	Treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients (6 years of age to 16 years of age) Treatment of narcolepsy	Stimulant *generic available	11
Dyanavel XR® (Amphetamine ER) Chewable tablet Oral suspension	Treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older	Stimulant	12
Evekeo ODT® (amphetamine) Orally disintegrating tablet	Treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients 6 to 17 years of age	Stimulant	14

Agent(s)	FDA Indication(s)	Notes	Ref#
Evekeo® (amphetamine)* Tablet	Treatment of narcolepsy Treatment of attention deficit hyperactivity disorder (ADHD) in children 3 years of age and older Treatment of exogenous obesity in patients 12 years and older	Stimulant *generic available	13
Focalin XR® (dexmethylphenidate ER)* Capsule	Treatment of attention deficit hyperactivity disorder (ADHD)	Stimulant *generic available	16
Focalin® (dexmethylphenidate)* Tablet	Treatment of attention deficit hyperactivity disorder (ADHD)	Stimulant *generic available	15
Intuniv® (guanfacine ER)* Tablet	Treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy or as adjunctive therapy to stimulant medications in patients 6 years and older	Non-Stimulant *generic available	33
Jornay PM® (methylphenidate delayed ER) Capsule	Treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older	Stimulant	17
Kapvay® (clonidine ER)* Tablet	Treatment of attention deficit hyperactivity disorder (ADHD) as monotherapy or as adjunctive therapy to stimulant medications	Non-Stimulant *generic available	32

Agent(s)	FDA Indication(s)	Notes	Ref#
Metadate CD® (methylphenidate ER)* Capsule	Treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients 6 to 15 years of age	Stimulant *generic available	4
Methylin® (methylphenidate)* Oral solution	Treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years and older Treatment of narcolepsy	Stimulant *generic available	18
Mehylphenidate ER, 24HR* Tablet	Treatment of attention deficit hyperactivity disorder (ADHD) in adults up to the age of 65 and pediatric patients 6 years of age and older	Stimulant *generic available	22
Mydayis® (amphetamine ER)* Capsule	Treatment of attention deficit hyperactivity disorder (ADHD) in patients 13 years and older	Stimulant *generic available	23
Onyda™ XR (clonidine ER) Oral suspension	Treatment of Attention Deficit Hyperactivity Disorder (ADHD) as monotherapy and as adjunctive therapy to central nervous system (CNS) stimulant medications in pediatric patients 6 years of age and older	Non-Stimulant	19
Qelbree® (viloxazine) Tablet	Treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years and older	Non-Stimulant	42

Agent(s)	FDA Indication(s)	Notes	Ref#
Quillichew ER® (methylphenidate ER) Chewable tablet	Treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older	Stimulant	25
Quillivant XR® (methylphenidate ER) Oral suspension	Treatment of attention deficit hyperactivity disorder (ADHD) in patients 6 years and older	Stimulant	26
Relexxii®, Methylphenidate ER Osmotic Release (methylphenidate osmotic release ER) Tablet	Treatment of attention deficit hyperactivity disorder (ADHD) in adults (up to the age of 65) and pediatric patients 6 years of age and older	Stimulant	27, 45
Ritalin LA® (methylphenidate ER)* Capsule	Treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients 6 to 12 years of age	Stimulant *generic available	29
Ritalin® (methylphenidate)* Tablet	Treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients 6 years and older and adults Treatment of narcolepsy	Stimulant *generic available	28
Strattera® (atomoxetine)* Capsule	The treatment of attention deficit hyperactivity disorder (ADHD)	Non-Stimulant *generic available	34
Vyvanse® (lisdexamfetamine)* Capsule	Treatment of attention deficit hyperactivity disorder (ADHD) in pediatric patients 6 years and older Treatment of moderate to	Stimulant *generic available	30

Agent(s)	FDA Indication(s)	Notes	Ref#
Chewable tablet	severe binge eating disorder (BED) in adults		
Xelstrym® (dextroamphetamine) Transdermal patch	Treatment of attention deficit hyperactivity disorder (ADHD) in adults and pediatric patients 6 years and older	Stimulant	44

CLINICAL RATIONALE

ADHD/ADD	Attention deficit hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders of childhood and can profoundly affect children's academic achievement, well-being, and social interactions. Most children with ADHD will continue to have symptoms and impairment through adolescence and into adulthood. Estimates indicate that approximately 3 to 4 percent of adults meet the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) diagnostic criteria for ADHD.(35) A study looking at the Diagnostic and Statistical manual of Mental Disorders, 5th edition (DSM-5) ADHD criteria for adults suggests a prevalence rate of 3.55% in adults compared to an earlier estimated prevalence of DSM-4 ADHD being 2.8% for adults. Changes to DSM-5 criteria for ADHD suggest a 27 percent increase in the expected prevalence of ADHD among young adults.(37) ADHD in adulthood is associated with significant impairment in occupational and academic functioning such as academic underachievement, unemployment, and problems in work performance. Adults with ADHD also often experience social and interpersonal difficulties. A third area of concern in adult ADHD is criminal and antisocial behavior.(38) Guidelines from the American Academy of Pediatrics recommend behavioral therapy as first line treatment for preschoolers (age 4-5). Methylphenidate may be considered if behavior interventions do not provide significant improvement and there is moderate-to-severe continued disturbance in the child's functioning. If behavioral treatment is unavailable, risks of starting medication before age 6 against harm of delaying treatment need to be considered. For children (ages 6–11) and adolescents (ages 12-18), medications for ADHD/ADD combined with behavioral therapy is recommended. The evidence is strong for stimulant medications and sufficient but less strong for atomoxetine, ER guanfacine, and

	ER clonidine (in that order). In addition, diversion of ADHD medication is a special concern among adolescents. Clinicians may consider prescribing nonstimulant medications that minimize abuse potential, such as atomoxetine and extended-release guanfacine or extended-release clonidine.(35) Pharmacotherapy is the mainstay of treatment for ADHD in adults. Guidelines recommend stimulant medications and atomoxetine as first line therapy, followed by antidepressants (bupropion, desipramine). Medications should be started at a low dose and titrated slowly until maximal benefit is achieved or adverse effects become intolerable. A trial of four to six weeks should be allowed for each dosing change.(36)
Narcolepsy	Narcolepsy is a chronic neurological disorder caused by the brain's inability to regulate sleep-wake cycles. It affects males and females equally and is a lifelong problem but does not usually worsen with age. Patients with narcolepsy all have excessive daytime sleepiness (EDS) which is characterized by unwillingly falling asleep during the day even if they are in the middle of an activity such as driving, eating, or talking regardless of how much sleep they get at night. Other symptoms include cataplexy, sleep paralysis, and hallucinations. If left undiagnosed or untreated, narcolepsy can interfere with psychological, social, and cognitive function and development and can inhibit academic, work, and social activities. Although there is no cure for narcolepsy, some of the symptoms can be treated with medication and lifestyle changes. Medication options include modafinil, amphetamine-like stimulants, antidepressants, sodium oxybate, and pitolisant. Nonpharmacological therapy involves lifestyle changes, such as avoiding caffeine, alcohol, or smoking and improving sleep hygiene.(39)
Safety	Adderall, Adderall XR, Adzenys XR-ODT, Azstarys, Concerta, Cotempla XR-ODT, Daytrana, Desoxyn, Dexedrine Spansule, Dyanavel XR, Evekeo, Evekeo ODT, Focalin, Focalin XR, Jornay PM, Metadate CD, Methylin, Methylphenidate ER Osmotic Release, Mydayis, QuilliChew ER, Quillivant XR, Relexxii, Ritalin, Ritalin LA, Vyvanse, and Xelstrym have a boxed warning for abuse, misuse, and addiction.(1,2,4,5,7-18,23,25-30,43-45) • These medications have a high potential for abuse and misuse, which can lead to the development of a substance use disorder, including addiction. Misuse and abuse of CNS stimulants can result in overdose and death, and this risk is increased with higher doses or unapproved methods of administration, such as snorting or injection. • Before prescribing these medications, assess each patient's risk for abuse, misuse, and addiction. Educate patients and their families about these risks, proper storage of the drug, and proper disposal of any unused drug. Throughout treatment, reassess each patient's risk of abuse,

	misuse, and addiction and frequently monitor for signs and symptoms of abuse, misuse, and addiction. Adhansia XR, Aptensio XR have a boxed warning for abuse and dependence.(3,6) • CNS stimulants, other methylphenidate-containing products, and amphetamines have a high potential for abuse and dependence. • Assess the risk of abuse prior to prescribing and monitor for signs of abuse and dependence while on therapy. Qelbree has a boxed warning for suicidal thoughts and behaviors.(42) • In clinical trials, higher rates of suicidal thoughts and behavior were reported in pediatric patients with ADHD treated with Qelbree than in patients treated with placebo. Closely monitor all Qelbree-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. Strattera has a boxed warning for suicidal ideation in children and adolescents.(34) • STRATTERA (atomoxetine) increased the risk of suicidal ideation in short-term studies in children or adolescents with Attention-Deficit/Hyperactivity Disorder (ADHD). Anyone considering the use of STRATTERA in a child or adolescent must balance this risk with the clinical need. Co-morbidities occurring with ADHD may be associated with an increase in the risk of suicidal ideation and/or behavior. Patients who are started on therapy should be monitored closely for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. STRATTERA is approved for ADHD in pediatric and adult patients. STRATTERA is not approved for major depressive disorder. Adderall, Adderall XR, Adhansia XR, Adzenys XR-ODT, Aptensio XR and XR-ODT, Azstarys, Concerta, Cotempla XR-ODT, Desoxyn, Dexedrine Spansule, Dyanavel XR, Evekeo, Evekeo ODT, Focalin, Focalin XR, Jornay PM,

	Methylin, Methylphenidate ER Osmotic Release Mydayis, QuilliChew ER, Quillivant XR, Relexxii, Ritalin, Ritalin LA, Vyvanse, and Xelstrym are contraindicated in patients:(1-3,5-8,10-18,23,25-30,43-45) • Known hypersensitivity to the product. Hypersensitivity reactions such as angioedema, anaphylactic reactions, urticaria, Stevens-Johnson Syndrome have been reported in patients or observed in postmarketing reports. • Taking monoamine oxidase inhibitors (MAOIs), or within 14 days of stopping MAOIs (including MAOIs such as linezolid or intravenous methylene blue), because of an increased risk of hypertensive crisis. Daytrana is contraindicated in patients:(9) • Known hypersensitivity to methylphenidate or other components of the product (polyester/ethylene vinyl acetate laminate film backing, acrylic adhesive, silicone adhesive, and fluoropolymer-coated polyester). • Taking monoamine oxidase inhibitors (MAOIs), or within a minimum of 14 days following discontinuation of treatment with an MAOI (hypertensive crises may result). Intuniv is contraindicated in patients with a history of a hypersensitivity reaction to Intuniv or its inactive ingredients, or other products containing guanfacine. Rash and pruritus have been reported.(33) Kapvay and Onyda XR are contraindicated in patients with a history of a hypersensitivity reaction to clonidine. Reactions have included generalized rash, urticaria, and angioedema.(19,32) Metadate CD is contraindicated in patients with:(4) • known hypersensitivity to methylphenidate or other component of Metadate CD. Angioedema has been reported in patients treated with Metadate CD. Anaphylactic reactions have been reported in patients treated with other methylphenidate products. • Concomitant treatment with monoamine oxidase inhibitors (MAOIs), or within 14 days following discontinuation of treatment with an MAOI, because of the risk of hypertensive crisis.

	• Metadate CD contains sucrose. Therefore, patients with hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrase-isomaltase insufficiency should not take this medicine. Qelbree is contraindicated in patients:(42) • Receiving concomitant treatment with monoamine oxidase inhibitors (MAOI), or within 14 days following discontinuing an MAOI, because of an increased risk of hypertensive crisis. • Receiving concomitant administration of sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic range. Strattera is contraindicated in patients with:(34) • Known to be hypersensitive to atomoxetine or other constituents of the product. • Taking monoamine oxidase inhibitors (MAOIs), or within a minimum of 14 days following discontinuation of treatment with an MAOI. With other drugs that affect brain monoamine concentrations, there have been reports of serious, sometimes fatal reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) when taken in combination with an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Such reactions may occur when these drugs are given concurrently or in close proximity. • Narrow angle glaucoma due to increased risk of mydriasis with Strattera use. • Pheochromocytoma: serious reactions, including elevated blood pressure and tachyarrhythmia, have been reported in patients with pheochromocytoma or a history of pheochromocytoma who received Strattera. • Severe cardiovascular disorders: do not use in patients with severe cardiac or vascular disorders whose condition would be expected to deteriorate if they experience increases in blood pressure or heart rate that could be clinically important (for example, 15 to 20 mm Hg in blood pressure or 20 beats per minute in heart rate).

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4	Metadate CD prescribing information. Lannett Company, Inc. October 2023.
5	Adzenys XR ODT prescribing information. Neos Therapeutics, Inc. October 2023.
6	Aptensio XR prescribing information. Rhodes Pharmaceuticals L.P. October 2023.
7	Concerta prescribing information. Janssen Pharmaceuticals, Inc. October 2023.
8	Cotempla XR ODT prescribing information. Neos Therapeutics, Inc. October 2023.
9	Daytrana prescribing information. Noven Therapeutics, LLC. October 2023.
10	Desoxyn prescribing information. Recordati Rare Diseases Inc. October 2023.
11	Dexedrine Spansule prescribing information. Amneal Pharmaceuticals LLC. October 2023.
12	Dyanavel XR prescribing information. Tris Pharma, Inc. October 2023.
13	Evekeo prescribing information. Arbor Pharmaceuticals, LLC. October 2023.
14	Evekeo ODT prescribing information. Arbor Pharmaceuticals, LLC. October 2023.
15	Focalin prescribing information. Novartis Pharmaceuticals Corporation. October 2023.
16	Focalin XR prescribing information. Novartis Pharmaceuticals Corporation. October 2023.
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40	Reference no longer used
41	Reference no longer used
42	Qelbree prescribing information. Supernus Pharmaceutics, Inc. April 2022.
43	Azstarys prescribing information. Corium, Inc. October 2023.
44	Xelstrym prescribing information. Noven Pharmaceuticals, Inc. October 2023.
45	Methylphenidate ER Osmotic Release tablets prescribing information. Trigen Laboratories, LLC. October 2023.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL Standalone	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Agamree (vamorolone), Emflaza (deflazacort)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Agamree® (vamorolone) Oral suspension	Treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older		6
Emflaza® (deflazacort)* Tablet Oral suspension	Treatment of Duchenne muscular dystrophy (DMD) in patients 2 years of age and older	* generic available	1

CLINICAL RATIONALE

Duchenne Muscular Dystrophy	Duchenne muscular dystrophy (DMD) is a genetic disorder characterized by progressive muscle degeneration and weakness due to alterations in a protein called dystrophin that helps keep muscle cells intact. DMD is the most common childhood form of muscular dystrophy as well as the most prevalent of the muscular dystrophies. DMD is an X-linked recessive inherited genetic condition primarily affecting males, although females who carry the defective gene may show some symptoms. Prevalence is 15.9 per 100,000 live male births in the US and 19.5 per 100,000 live male births in the UK. Dystrophin is the protein associated with this affected gene and provides structural stability to skeletal muscles. Mutations in this gene, and subsequent lack of dystrophin in muscle fiber, result in a rapidly progressing disease involving muscle degeneration and weakness. Symptom onset is in early childhood and many children lose the ability to walk by early adolescence. Beyond muscle weakness, other symptoms include enlargement of the calf muscles, lumbar lordosis, and eventually cardiomyopathy and poor respiratory function. Until relatively recently, boys with

	DMD usually did not survive much beyond their teen years. Due to advances in cardiac and respiratory care, life expectancy is increasing and many young adults with DMD are surviving into their early 30s. Currently, there is no cure for DMD, and therapies are supportive in nature. Physical therapy, occupational therapy, respiratory care, speech therapy, braces/wheelchairs/contractures and glucocorticoid therapy are among the most common therapies.(2-4) Dystrophin gene deletion and duplication testing is usually the first confirmatory test.(8) Corticosteroid (glucocorticoids) are the standard of care for DMD, although they remain non-curative. Their use improves muscle strength, improves timed motor function, delays loss of ambulation, improves pulmonary function, reduces the need for scoliosis surgery, delays onset of cardiomyopathy, increases survival, and maintains quality of life. The choice of which glucocorticoid to use depends on cost, formulation, and perceived side-effect profiles.(3) The updated American Academy of Neurology practice guidelines concluded that prednisone and deflazacort are possibly equally effective for improving motor function in patients with DMD (2 Class III studies). There is insufficient evidence to directly compare the effectiveness of prednisone vs deflazacort in cardiac function in patients with DMD (1 Class III study of a combined cohort). The AAN states that deflazacort could be offered as an intervention for patients with DMD to improve strength and timed motor function and delay the age at loss of ambulation by 1.4–2.5 years (Level C), improve pulmonary function (Level C), reduce the need for scoliosis surgery (Level C), delay the onset of cardiomyopathy by 18 years of age (Level C), increase survival at 5 and 15 years of follow-up (Level C). Prednisone is possibly associated with greater weight gain in the first 12 months of treatment, with no significant difference in weight gain with longer-term use compared with deflazacort (2 Class III studies). Deflazacort is possibly associated with an increased risk of cataracts compared with prednisone, although most are not vision-impairing (2 Class III studies).(5) Vamorolone is a first-in-class anti-inflammatory steroidal drug that has shown to have dissociative properties. The structure of vamorolone is similar to other glucocorticoids: it binds to the glucocorticoid receptor and retains the anti-inflammatory effects characteristic of traditional steroids, preferentially inducing transrepression with little-to-no transactivation or cis-repression. Transrepression is the suppression of the pro-inflammatory nuclear factor kappa B (NF-κB) signaling pathway, to exert the well-known potent anti-inflammatory effects of steroids. By not inducing transactivation or cis-repression, vamorolone is purported to elicit fewer adverse effects. Vamorolone is also a mineralocorticoid receptor antagonist, and thus may have the potential to treat DMD-associated cardiomyopathy through modulation of blood pressure.(7)

Efficacy	**Emflaza** The effectiveness of Emflaza for the treatment of DMD was established in a multicenter, randomized, double-blind, placebo-controlled, 52-week study. The study enrolled 196 male patients between the ages of 5 and 15 years old with documented mutation of the dystrophin gene, onset of weakness before 5 years of age, and serum creatinine kinase activity at least 10 times the upper limit of normal at some stage in their illness. Patients were randomized to receive Emflaza (0.9 or 1.2 mg/kg/day), an active comparator, or placebo. After 12 weeks, placebo patients were re-randomized to receive either Emflaza or the active comparator. All patients continued treatment for an additional 40 weeks. Efficacy was evaluated by assessing the change between Baseline and Week 12 in average strength of 18 muscle groups. The change in average muscle strength score between Baseline and Week 12 was significantly greater for the deflazacort 0.9 mg/kg/day dose group than for the placebo group. (p-value 0.017). Although not a pre-specified statistical analysis, compared with placebo, the deflazacort 0.9 mg/kg/day dose group demonstrated at Week 52 the persistence of the treatment effect observed at Week 12.(1) A second randomized, double-blind, placebo-controlled, 104-week clinical trial evaluated deflazacort in comparison to placebo. The study population consisted of 29 male children 6 to 12 years of age with a DMD diagnosis confirmed by the documented presence of abnormal dystrophin or a confirmed mutation of the dystrophin gene. The results of the analysis of the primary endpoint of average muscle strength scores in this 2nd study (graded on a 0-5 scale) at 2 years were not statistically significant, possibly because of a limited number of patients remaining in the placebo arm (subjects were discontinued from the trial when they lost ambulation). Although not statistically controlled for multiple comparisons, average muscle strength scores at Months 6 and 12, as well as the average time to loss of ambulation, numerically favored deflazacort in comparison with placebo.(1) **Agamree** The effectiveness of Agamree for the treatment of DMD was evaluated in a multicenter, randomized, double-blind, parallel-group, placebo- and active-controlled, multinational 24-week study (Study 1; NCT03439670). The study randomized 121 male patients with DMD to one of the following treatment groups: AGAMREE 6 mg/kg/day (n=30), AGAMREE 2 mg/kg/day (n=30), prednisone 0.75 mg/kg/day (n=31), or placebo (n=30) for 24 weeks. After 24 weeks, patients on prednisone and placebo received either AGAMREE 6 mg/kg/day (n=29) or AGAMREE 2 mg/kg/day (n=29) for an additional 20 weeks.

	The study included patients 4 to less than 7 years of age at time of enrollment in the study who were corticosteroid naïve and ambulatory, with a confirmed diagnosis of DMD.(6) The primary endpoint was the change from baseline to Week 24 in Time to Stand Test (TTSTAND) velocity for AGAMREE 6 mg/kg/day compared to placebo. TTSTAND velocity is a measure of muscle function that measures the time required for the patient to stand to an erect position from a supine position (floor). The key secondary endpoints consisted of change from baseline to Week 24 in TTSTAND velocity (AGAMREE 2 mg/kg/day vs placebo), 6 Minute Walk Test (6MWT) distance (AGAMREE 6 mg/kg/day vs placebo and 2 mg/kg/day vs placebo) and Time to Run/Walk 10 meters (TTRW) velocity (AGAMREE 6 mg/kg/day vs placebo and 2 mg/kg/day vs placebo). The 6MWT measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes and TTRW measures the time that it takes a patient to run or walk 10 meters. The fixed sequential testing process was applied to the key secondary endpoints in the order listed above.(6) The primary endpoint and key secondary endpoints were met for the AGAMREE 6 mg/kg/day treatment group. The AGAMREE 2 mg/kg/day treatment group was statistically significant vs. placebo for TTSTAND and 6MWT, but was not statistically significant vs. placebo for TTRW.(6)
Safety	Emflaza is contraindicated in patients with known hypersensitivity to deflazacort or to any of the inactive ingredients. Instances of hypersensitivity, including anaphylaxis, have occurred in patients receiving corticosteroid therapy.(1) Agamree is contraindicated in patients with known hypersensitivity to vamorolone or to any of the inactive ingredients in Agamree.(6)

REFERENCES

Number	Reference
1	Emflaza prescribing information. PTC Pharmaceuticals. May 2024.
2	Duchenne muscular dystrophy (DMD). Muscular Dystrophy Association. https://www.mda.org/disease/duchenne-muscular-dystrophy.

Number	Reference
3	Biggar, W. D., Skalsky, A., & McDonald, C. M. (2022). Comparing deflazacort and prednisone in Duchenne Muscular Dystrophy. Journal of Neuromuscular Diseases, 9(4), 463–476. https://doi.org/10.3233/jnd-210776
4	U.S. Department of Health and Human Services. Muscular dystrophy. National Institute of Neurological Disorders and Stroke. https://www.ninds.nih.gov/health-information/disorders/muscular-dystrophy
5	Gloss, D., Moxley, R. T., Ashwal, S., & Oskoui, M. (2016). Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy. Neurology, 86(5), 465–472. Reaffirmed January 2022. https://doi.org/10.1212/wnl.0000000000002337.
6	Agamree prescribing information. Catalyst Pharmaceuticals Inc. June 2024.
7	Kourakis, Stephanie, Timpani, Cara A., (2021). Standard of Care Versus New-Wave Corticosteroids in the Treatment of Duchenne Muscular Dystrophy: Can we Do Better? Orphanet Journal of Rare Diseases. 2021.16(1):117. DOI: 10.1186/s13023-021-01758-9.
8	Birnkrant, D. J., Bushby, K., Bann, C. M., Apkon, S. D., Blackwell, A., Brumbaugh, D., Case, L. E., Clemens, P. R., Hadjiyannakis, S., Pandya, S., Street, N., Tomezsko, J., Wagner, K. R., Ward, L. M., & Weber, D. R. (2018). Diagnosis and management of Duchenne muscular dystrophy, part 1: Diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *The Lancet Neurology*, *17*(3), 251–267. https://doi.org/10.1016/s1474-4422(18)30024-3.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Module	Clinical Criteria for Approval

Agents Eligible for Continuation of Therapy
All target agents are eligible for continuation of therapy

1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR**
2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR**

B. ALL of the following:

1. ONE of the following:
   A. The patient has a diagnosis of Duchenne Muscular Dystrophy confirmed by genetic analysis (i.e., dystrophin deletion or duplication mutation) (genetic test required) **OR**
   B. The patient has another FDA labeled indication for the requested agent and route of administration **AND**
2. If the patient has an FDA labeled indication, then ONE of the following:
   A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**
   B. There is support for the use of the requested agent for the patient's age for the requested indication **AND**
3. ONE of the following:
   A. The patient has tried and had an inadequate response after 6 months of therapy with generic prednisone (or prednisolone) **OR**
   B. The patient has an intolerance or hypersensitivity to generic prednisone (or prednisolone) that is NOT expected to occur with the requested agent **OR**
   C. The patient has an FDA labeled contraindication to generic prednisone (or prednisolone) **AND**

2. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:

Brand	**Generic Equivalent**
Emflaza	deflazacort

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
C. There is support for the use of the requested brand agent over the generic equivalent AND
3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., pediatric neurologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent AND
5. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose based on the patient's weight

Length of Approval: 6 months for Agamree, 12 months for Emflaza

NOTE: If Quantity Limit applies, please refer to Quantity Limit criteria.

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] AND
2. The patient has had improvements or stabilization with the requested agent (e.g., slowed disease progression, improved strength, timed motor function, pulmonary function; reduced need for scoliosis surgery) AND
3. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:

<table>
<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Emflaza</td><td>deflazacort</td></tr>
</table>

A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
</td></tr>
</table>

Module	Clinical Criteria for Approval
	B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent **OR** C. There is support for the use of the requested brand agent over the generic equivalent **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., pediatric neurologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose based on the patient's weight **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested agent strength does not have a program quantity limit **OR** 3. The request agent is Emflaza and ONE of the following: A. The requested agent is Emflaza SUSPENSION **OR** B. BOTH of the following: 1. The requested quantity (dose) exceeds the program quantity limit **AND** 2. The requested quantity (dose) cannot be achieved with a lower quantity of any combination of the four Emflaza tablet strengths **OR** 4. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Approval Length:** up to 12 months

Alinia

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Alinia® (nitazoxanide) Tablet* Suspension	Oral suspension (patients 1 year of age and older) and tablets (patients 12 years of age and older) indicated for the treatment of diarrhea caused by *Giardia lamblia* or *Cryptosporidium parvum* Limitations of Use: • Nitazoxanide has not been shown to be effective for the treatment of diarrhea caused by *C. parvum* in HIV-infected or immunodeficient patients	*generic available	1

CLINICAL RATIONALE

Infectious Diarrhea	Persistent watery diarrhea generally should not be treated in the absence of an identified cause. When persistent diarrhea is caused by infection, the most common etiologic agents are protozoal (including parasites such as *Giardia lamblia*, *Cryptosporidium* species, *Cyclospora cayetanensis*, and *Cystoisospora belli*) and are best managed with pathogen-specific therapy (rather than empiric therapy before the infection is diagnosed).(7) Giardiasis is caused by the anaerobic protozoan parasite *Giardia duodenalis* (e.g., *G. lamblia* or *G. intestinalis*). Effective treatments include metronidazole, tinidazole, and nitazoxanide. Among the many protozoan parasites in the genus *Cryptosporidium*, the species *C. hominis* and *C. parvum* cause greater than 90% of human infections. Nitazoxanide is FDA approved as a treatment of cryptosporidiosis in immunocompetent patients.(8) IBM Micromedex lists the following non-FDA approved uses with a Class IIa Strength of Recommendation (treatment is generally considered to be useful, and is indicated in most cases) or higher:

	• Infection by *Fasciola* in adults (IIa)(2)
	  ○ Nitazoxanide appeared to be well tolerated and effective when used in the treatment of human fascioliasis, in an open-label study. Adult patients received an oral regimen of nitazoxanide 500 mg twice daily for 6 consecutive days.(3)
	• General intestinal parasitism in adults and pediatrics (IIa)(2)
	  ○ A 3-day course of nitazoxanide (NTZ) 500 mg twice daily was a safe and effective treatment for diarrhea associated with infection by the intestinal parasites *Giardia intestinalis*, *Entamoeba histolytica*, or *Entamoeba dispar*.(4)
	  ○ Results of a large field study in Egypt indicate that nitazoxanide is safe and effective for treating intestinal protozoan and helminthic infections. Patients took medication with food at 12-hour intervals over 3 days; those older than 12 years received 500 mg of nitazoxanide, children aged 4 to 11 years received 200 mg of drug, and children aged 1 to 3 years received 5 mL of a 100 mg per 5-mL suspension.(5)
	  ○ Nitazoxanide and metronidazole have been similarly effective in treating symptomatic intestinal giardiasis in children.(6)

REFERENCES

Number	Reference
1	Alinia prescribing information. Romark, L.C. January 2022.
2	IBM Micromedex. Alinia Non-FDA Uses. Last modified February 2024.
3	Kabil SM, El Ashry E, Ashraf NK. An open-label clinical study of nitazoxanide in the treatment of human fascioliasis. *Curr Ther Res* 2000;61(6):339-345.
4	Rossignol J-F, Ayoub A, Ayers MS. Treatment of Diarrhea caused by *Giardia intestinalis* and *Entamoeba histolytica* or *E. dispar*: A Randomized, Double-Blind, Placebo-Controlled Study of Nitazoxanide. *J Infect Dis*. 2001;184(3):381-384.
5	Abaza H, El-Zayadi AR, Kabil SM, Rizk H. Nitazoxanide in the treatment of patients with intestinal protozoan and helminthic infections: A report on 546 patients in Egypt. *Curr Ther Res Clin Exp* 1998;59(2):116-121.

Number	Reference
6	Ortiz JJ, Ayoub A, Gargala G, Chegne NL, Favennec L. Randomized Clinical Study of Nitazoxanide Compared to Metronidazole in the Treatment of Symptomatic Giardiasis in Children from Northern Peru. *Aliment Pharm Ther*. 2001;15(9):1409-15.
7	2017 Infectious Diseases Society of America (IDSA) Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea. Clin Infec Dis. 2017 Dec;65:e45-e80.
8	2020 Centers for Disease Control and Prevention (CDC) Yellow Book: Health Information for International Travel.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when BOTH of the following are met: 1. The patient has ONE of the following diagnoses: A. Diarrhea caused by Giardia lamblia or Cryptosporidium parvum **OR** B. Adult with Fasciola infection **OR** C. General intestinal parasitism **AND** 2. ONE of the following: A. The patient has been re-infected AND requires an additional course of therapy **AND** ONE of the following: 1. The requested quantity (dose) is less than or equal to the following: A. For diarrhea caused by Giardia lamblia or Cryptosporidium parvum, 3000 mg over 3 days **OR** B. For adults with Fasciola infection, 6000 mg over 6 days **OR** C. For general intestinal parasitism, 3000 mg over 3 days **OR** 2. There is support of therapy with a higher dose and/or duration for the requested indication **OR** B. The patient is seeking a higher dose and/or duration of therapy for the same infection AND there is support of therapy with a higher dose and/or duration for the requested indication **Length of Approval:** up to 3 months

Alternative Dosage Form

Prior Authorization with Quantity Limit

Your health benefit plan may not cover certain prescription drug products or drug categories included in this document. Please consult your benefit plan materials for details about your particular benefit. This document may include drugs that are not included on your plan's formulary. For drug coverage status, please consult your plan's formulary.

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Adlarity® (donepezil) Patch	Treatment of mild, moderate, and severe dementia of the Alzheimer's type.		29
ASPRUZYO Sprinkle™ (ranolazine) Granules	Treatment of chronic angina.		30
Carafate® (sucralfate) Oral suspension*	Indicated in the short-term (up to 8 weeks) treatment of active duodenal ulcer.	*generic available	12
CaroSpir® (spironolactone) Oral suspension*	Treatment of NYHA Class III-IV heart failure and reduced ejection fraction to increase survival, manage edema, and to reduce the need for hospitalization for heart failure. Use as an add-on therapy for the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal	*generic available	1

Agent(s)	FDA Indication(s)	Notes	Ref#
	cardiovascular events, primarily strokes and myocardial infarctions. The management of edema in adult cirrhotic patients when edema is not responsive to fluid and sodium restrictions.		
Cimetidine Oral solution*	Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks and there is rarely reason to use cimetidine at full dosage for longer than 6 to 8 weeks. Concomitant antacids should be given as needed for relief of pain. However, simultaneous administration of oral cimetidine and antacids is not recommended, since antacids have been reported to interfere with the absorption of oral cimetidine. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of active ulcer. Patients have been maintained on continued treatment with cimetidine 400 mg h.s. for periods of up to 5 years. Short-term treatment of active benign gastric ulcer. There is no information concerning usefulness of treatment periods of longer than 8 weeks. Erosive gastroesophageal reflux disease (GERD). Erosive esophagitis diagnosed by endoscopy. Treatment is indicated for 12 weeks for healing of lesions and control of symptoms. The use of cimetidine beyond 12 weeks has not been established. The treatment of pathological hypersecretory conditions (i.e., Zollinger-Ellison Syndrome, systemic mastocytosis, multiple endocrine adenomas).	*generic available	2

Agent(s)	FDA Indication(s)	Notes	Ref#
Cuvposa® (glycopyrrolate) Oral solution*	Reduce chronic severe drooling in patients aged 3-16 years with neurologic conditions associated with problem drooling (e.g., cerebral palsy).	*generic available	3
Dartisla® ODT (glycopyrrolate) Orally disintegrating tablet	Indicated in adults to reduce symptoms of a peptic ulcer as an adjunct to treatment of peptic ulcer. Limitations of Use: Not indicated as monotherapy for treatment of peptic ulcer because effectiveness in peptic ulcer healing has not been established.		27
Digoxin Oral solution*	Treatment of mild to moderate heart failure and for the control of resting ventricular rate in patients with chronic atrial fibrillation. In pediatric patients with heart failure, digoxin is indicated to increase myocardial contractility.	*generic available	5
Diuril® (chlorothiazide) Oral suspension	Adjunctive therapy in edema associated with congestive heart failure, hepatic cirrhosis, and corticosteroid and estrogen therapy. Diuril has also been found useful in edema due to various forms of renal dysfunction such as nephrotic syndrome, acute glomerulonephritis, and chronic renal failure. Management of hypertension either as the sole therapeutic agent or to enhance the effectiveness of other antihypertensive drugs in the more severe forms of hypertension.		6
Entresto Sprinkle® (sacubitril and valsartan) Oral Pellet	Indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal.		4

Agent(s)	FDA Indication(s)	Notes	Ref#
	Treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Entresto reduces NT-proBNP and is expected to improve cardiovascular outcomes.		
Epaned® (enalapril) Oral solution*	Treatment of hypertension in adults and children older than one month, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. Treatment of symptomatic heart failure. Treatment of asymptomatic left ventricular dysfunction, to decrease the rate of development of overt heart failure and reduce hospitalization for heart failure.	*generic available	7
Exservan™ (riluzole) Oral film	Treatment of amyotrophic lateral sclerosis (ALS).		32
famotidine Powder for suspension*	Treatment of active duodenal ulcer (DU), active gastric ulcer (GU), symptomatic nonerosive gastroesophageal reflux disease (GERD), erosive esophagitis due to GERD, diagnosed by biopsy, treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome, multiple endocrine neoplasias), and reduction of the risk of DU recurrence in adult patients. Treatment of peptic ulcer and GERD with or without esophagitis and ulcerations in pediatric patients 1 year of age and older. Treatment of GERD in pediatric patients from birth to less than 1 year of age.	*generic available	8
Nitrofurantoin	Treatment of urinary tract infections when due to susceptible strains of Escherichia coli, enterococci,	*generic available	34

Agent(s)	FDA Indication(s)	Notes	Ref#
Oral Suspension*	Staphylococcus aureus, and certain susceptible strains of Klebsiella and Enterobacter species.		
Furosemide Oral solution	Used in adults and pediatric patients for the treatment of edema associated with congestive heart failure, cirrhosis of the liver and renal disease, including the nephrotic syndrome. Furosemide is particularly useful when an agent with greater diuretic potential is desired. Used in adults for the treatment of hypertension alone or in combination with other antihypertensive agents. Hypertensive patients who cannot be adequately controlled with thiazides will probably also not be adequately controlled with furosemide alone.		10
Indocin®, Indomethacin Suppositories*	Moderate to severe rheumatoid arthritis including acute flares of chronic disease. Moderate to severe ankylosing spondylitis. Moderate to severe osteoarthritis. Acute painful shoulder (bursitis and/or tendinitis). Acute gouty arthritis.	*generic available	11
Jylamvo® (methotrexate) Oral solution	Treatment of adults with acute lymphoblastic leukemia (ALL) as part of a combination chemotherapy maintenance regimen. Treatment of adults with mycosis fungoides. Treatment of adults with relapsed or refractory non-Hodgkin lymphoma as part of a metronomic combination regimen. Treatment of adults with rheumatoid arthritis. Treatment of adults with severe psoriasis.		15

Agent(s)	FDA Indication(s)	Notes	Ref#
Katerzia® (amlodipine) Oral suspension	Hypertension: • Treatment of hypertension in adults and children 6 years and older, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. Coronary Artery Disease: • Chronic Stable Angina. • Vasospastic Angina (Prinzmetal's or Variant Angina). • Angiographically Documented Coronary Artery Disease in patients without heart failure or an ejection fraction < 40%.		13
LIKMEZ™ (metronidazole) Oral suspension	Indicated for: • Trichomoniasis in adults. • Amebiasis in adults and pediatric patients. • Anaerobic Bacterial Infections in adults. To reduce the development of drug-resistant bacteria and maintain the effectiveness of LIKMEZ and other antibacterial drugs, LIKMEZ should be used only to treat or prevent infections that are proven or strongly suspected to be caused by bacteria.		9
memantine Oral solution*	Treatment of moderate to severe dementia of the Alzheimer's type.	*generic available	14
Nizatidine Oral solution	Up to 8 weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within 4 weeks. Maintenance therapy for duodenal ulcer patients at a reduced dosage of 150 mg h.s. after healing of an active duodenal ulcer. The consequences of		16

Agent(s)	FDA Indication(s)	Notes	Ref#
	continuous therapy with nizatidine for longer than 1 year are not known. Up to 12 weeks for the treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn due to GERD. Up to 8 weeks for the treatment of active benign gastric ulcer. Before initiating therapy, care should be taken to exclude the possibility of malignant gastric ulceration. For pediatric patients, ages 12 years and older up to 8 weeks for the treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn due to GERD.		
Norliqva® (amlodipine) Oral solution	Hypertension • Treatment of hypertension in adults and children 6 years of age and older, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. Coronary Artery Disease (CAD) • Chronic Stable Angina. • Vasospastic Angina (Prinzmetal's or Variant Angina). • Angiographically Documented Coronary Artery Disease in patients without heart failure or an ejection fraction < 40%.		28
Nymalize®	Improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in adult patients with subarachnoid hemorrhage (SAH)		17

Agent(s)	FDA Indication(s)	Notes	Ref#
(nimodipine) Oral solution	from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (i.e., Hunt and Hess Grades I-V).		
Propranolol Oral solution*	Management of hypertension. It may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. Propranolol is not indicated in the management of hypertensive emergencies. Decrease angina frequency and increase exercise tolerance in patients with angina pectoris. To control ventricular rate in patients with atrial fibrillation and a rapid ventricular response. To reduce cardiovascular mortality in patients who have survived the acute phase of myocardial infarction and are clinically stable. Prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established, and propranolol is not indicated for such use. Management of familial or hereditary essential tremor. Familial or essential tremor consists of involuntary, rhythmic, oscillatory movements, usually limited to the upper limbs. It is absent at rest, but occurs when the limb is held in a fixed posture or position against gravity and during active movement. Propranolol causes a reduction in the tremor amplitude, but not in the tremor frequency. Propranolol hydrochloride is not indicated for the treatment of tremor associated with Parkinsonism. To improve NYHA functional class in symptomatic patients with hypertrophic subaortic stenosis.	*generic available	19

Agent(s)	FDA Indication(s)	Notes	Ref#
	Adjunct to alpha-adrenergic blockade to control blood pressure and reduce symptoms of catecholamine-secreting tumors.		
Qbrelis® (lisinopril) Oral solution	Treatment of hypertension in adults and pediatric patients 6 years of age and older. Reduce signs and symptoms of systolic heart failure. Treatment of acute myocardial infarction.		20
Riomet® (metformin) Oral suspension*	Adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus.	*generic available	21
Sotylize® (sotalol) Oral solution	The treatment of ventricular arrhythmias, such as sustained ventricular tachycardia, that in the judgment of the physician are life-threatening. Limitations of Use: • Use in patients with less severe arrhythmias, even if the patients are symptomatic, is generally not recommended. Treatment of patients with asymptomatic ventricular premature contractions should be avoided. The maintenance of normal sinus rhythm [delay in time to recurrence of atrial fibrillation/atrial flutter (AFIB/AFL)] in patients with symptomatic AFIB/AFL who are currently in sinus rhythm. Limitations of Use • Sotalol can cause life-threatening ventricular arrhythmias, reserve it for patients in whom AFIB/AFL is highly symptomatic. Patients with paroxysmal AFIB whose AFIB/AFL that is easily reversed (by Valsalva maneuver, for		22

Agent(s)	FDA Indication(s)	Notes	Ref#
	example) should usually not be given this Sotylize.		
SYNDROS® (dronabinol) Oral solution	Anorexia associated with weight loss in patients with Acquired Immune Deficiency Syndrome (AIDS). Nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments.		23
Teglutik®, Tiglutik® (riluzole) Oral suspension	Treatment of amyotrophic lateral sclerosis (ALS).		33
Xatmep® (methotrexate) Oral solution	Treatment of pediatric patients with acute lymphoblastic leukemia (ALL) as a component of a combination chemotherapy maintenance regimen. Management of pediatric patients with active polyarticular juvenile idiopathic arthritis (pJIA) who are intolerant of or had an inadequate response to first-line therapy.		18
ZYVOX® (linezolid) Powder for suspension*	Indicated in adults and children for the treatment of the following infections caused by susceptible Gram-positive bacteria: Nosocomial pneumonia; Community-acquired pneumonia; Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis; Uncomplicated skin and skin structure infections; Vancomycin-resistant Enterococcus faecium infections. To reduce the development of drug-resistant bacteria and maintain the effectiveness of Zyvox formulations and other antibacterial drugs, Zyvox should be used only to treat infections that are proven or strongly suspected to be caused by bacteria.	*generic available	26

CLINICAL RATIONALE

Safety	The following products have boxed warnings:[1-34]
	
	• Entresto
	  ○ When pregnancy is detected, discontinue Entresto as soon as possible
	  ○ Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus
	• Epaned
	  ○ When pregnancy is detected, discontinue Epaned as soon as possible
	  ○ Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus
	• Furosemide
	  ○ Furosemide is a potent diuretic which, if given in excessive amounts, can lead to a profound diuresis with water and electrolyte depletion. Therefore, careful medical supervision is required and dose schedule must be adjusted to the individual patient's needs.
	• Indocin, Indomethacin suppositories
	  ○ Cardiovascular Thrombotic Events
	  ▪ Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use.
	  ▪ Indocin is contraindicated in the setting of coronary artery bypass graft (CABG) surgery.
	  ○ Gastrointestinal Bleeding, Ulceration, and Perforation
	  ▪ NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events.
	• Jylamvo
	  ○ Methotrexate can cause embryo-fetal toxicity, including fetal death. For non-neoplastic diseases, Jylamvo is contraindicated in pregnancy. For neoplastic diseases, advise females and males of

	reproductive potential to use effective contraception during and after treatment with Jylamvo. ○ Contraindicated in patients with a history of severe hypersensitivity reactions to methotrexate, including anaphylaxis. ○ Serious adverse reactions, including death, have been reported with methotrexate. Closely monitor for infections and adverse reactions of the bone marrow, gastrointestinal tract, liver, lungs, skin, and kidneys. Withhold or discontinue Jylamvo as appropriate. • LIKMEZ ○ Metronidazole has been shown to be carcinogenic in mice and rats. Avoid unnecessary use of LIKMEZ. Reserve LIKMEZ for use in the following indications: trichomoniasis, amebiasis and anaerobic bacterial infections. • Qbrelis ○ When pregnancy is detected, discontinue Qbrelis as soon as possible. ○ Drugs that act directly on the renin-angiotensin system can cause injury and death to the developing fetus. • Riomet ○ Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin- associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Metformin- associated lactic acidosis was characterized by elevated blood lactate levels (>5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL [see Warnings and Precautions. ○ Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment. ○ Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high-risk groups are provided.

	○ If metformin-associated lactic acidosis is suspected, immediately discontinue Riomet and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. • Sotylize ○ To minimize the risk of induced arrhythmia, patients initiated or re-initiated on oral sotalol, and patients who are converted from intravenous sotalol to oral administration should be hospitalized in a facility that can provide cardiac resuscitation, continuous electrocardiographic monitoring and calculations of creatinine clearance. ○ Sotalol can cause life-threatening ventricular tachycardia associated with QT interval prolongation. ○ Do not initiate sotalol therapy if the baseline QTc is longer than 450 milliseconds (ms). If the QT interval prolongs to 500 ms or greater, the dose must be reduced, the interval between doses prolonged, or the drug discontinued. ○ Adjust the dosing interval based on creatinine clearance. • Xatmep ○ Methotrexate can cause severe or fatal toxicities. Monitor closely and modify dose or discontinue for the following toxicities: bone marrow suppression, infection, renal, gastrointestinal, hepatic, pulmonary, hypersensitivity and dermatologic. ○ Methotrexate can cause embryo-fetal toxicity and fetal death. Use in polyarticular juvenile idiopathic arthritis is contraindicated in pregnancy. Consider the benefits and risks of Xatmep and risks to the fetus when prescribing Xatmep to a pregnant patient with a neoplastic disease. Advise patients to use effective contraception during and after treatment with Xatmep. The following products have contraindications:[1-34] • Adlarity ○ Known hypersensitivity to donepezil or to piperidine derivative ○ History of allergic contact dermatitis with use of Adlarity • ASPRUZYO Sprinkle ○ Strong CYP3A inhibitors (e.g., ketoconazole, clarithromycin, nelfinavir) ○ CYP3A inducers (e.g., rifampin, phenobarbital, St. John's wort) ○ Liver cirrhosis • Carafate ○ known hypersensitivity reactions to the active substance or to any of the excipients

	• CaroSpir
	  ○ Hyperkalemia
	  ○ Addison's disease
	  ○ Concomitant use of eplerenone
	• Cimetidine oral solution
	  ○ hypersensitivity to the product
	• Cuvposa
	  ○ Medical conditions that preclude anticholinergic therapy.
	  ○ Concomitant use of solid oral dosage forms of potassium chloride
	• Dartisla ODT
	  ○ Patients at risk for anticholinergic toxicity due to various underlying medical conditions.
	  ○ Hypersensitivity to glycopyrrolate or the inactive ingredients
	• Digoxin oral solution
	  ○ Known hypersensitivity to digoxin or other forms of digitalis
	  ○ Ventricular fibrillation
	• Diuril
	  ○ Anuria
	  ○ Hypersensitivity to this product or to other sulfonamide-derived drug
	• Entresto
	  ○ Hypersensitivity to any component
	  ○ History of angioedema related to previous ACEi or ARB therapy
	  ○ Concomitant use with ACE inhibitors
	  ○ Concomitant use with aliskiren in patients with diabetes
	• Epaned
	  ○ Hypersensitivity related to previous treatment with an ACEI
	  ○ Hereditary or idiopathic angioedema
	  ○ Do not co-administer aliskiren in patients with diabetes
	  ○ In combination with a neprilysin inhibitor
	• Exservan
	  ○ Patients with a history of severe hypersensitivity reactions to riluzole or to any of its components
	• famotidine powder for suspension
	  ○ Hypersensitivity to any component of these products. Cross sensitivity in this class of compounds has been observed. Therefore, Famotidine should not be administered to patients with a history of hypersensitivity to other H2-receptor antagonists.
	• Furosemide oral solution
	  ○ Anuria
	  ○ History of hypersensitivity to furosemide

	• Indocin, Indomethacin suppositories
	  ○ Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to indomethacin or any components of the drug product.
	  ○ History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients.
	  ○ In the setting of coronary artery bypass graft (CABG) surgery.
	  ○ In patients with a history of proctitis or recent rectal bleeding.
	• Jylamvo
	  ○ Pregnant patients with non-neoplastic diseases.
	  ○ History of severe hypersensitivity to methotrexate.
	• Katerzia
	  ○ Known sensitivity to amlodipine.
	• LIKMEZ
	  ○ Prior history of hypersensitivity to metronidazole or other nitroimidazole derivatives.
	  ○ Patients who have used disulfiram within the last two weeks.
	  ○ Patients who consume alcohol or products containing propylene glycol during and for at least three days after LIKMEZ therapy.
	  ○ Patients with Cockayne syndrome.
	• memantine oral solution
	  ○ Patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.
	• Nitrofurantoin
	  ○ Anuria, oliguria, or significant impairment of renal function (creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine) are contraindications. Treatment of this type of patient carries an increased risk of toxicity because of impaired excretion of the drug.
	  ○ Because of the possibility of hemolytic anemia due to immature erythrocyte enzyme systems (glutathione instability), the drug is contraindicated in pregnant patients at term (38-42 weeks gestation), during labor and delivery, or when the onset of labor is imminent. For the same reason, the drug is contraindicated in neonates under one month of age.
	• Nizatidine
	  ○ Patients with known hypersensitivity to the drug. Because cross-sensitivity in this class of compounds has been observed, H2-receptor antagonists, including nizatidine, should not be

	administered to patients with a history of hypersensitivity to other H2-receptor antagonists.
	• Norliqva
	  ○ Sensitivity to amlodipine.
	• Propranolol oral solution
	  ○ Cardiogenic shock.
	  ○ Sinus bradycardia and greater than first degree block.
	  ○ Bronchial asthma.
	  ○ In patients with known hypersensitivity to propranolol hydrochloride.
	• Qbrelis
	  ○ Angioedema or a history of hereditary or idiopathic angioedema.
	  ○ Hypersensitivity
	  ○ Co-administration of aliskiren with Qbrelis in patients with diabetes.
	  ○ In combination with a neprilysin inhibitor.
	• Sotylize
	  ○ Baseline QT interval >450 msec.
	  ○ Sinus bradycardia, second or third degree AV block, sick sinus syndrome Congenital or acquired long QT syndromes.
	  ○ Serum potassium <4 mEq/L.
	  ○ Cardiogenic shock, decompensated heart failure.
	  ○ Bronchial asthma or related bronchospastic conditions.
	  ○ Hypersensitivity to sotalol.
	• SYNDROS
	  ○ Sensitivity to dronabinol or alcohol.
	  ○ History of hypersensitivity reaction to alcohol.
	  ○ Patients receiving, or have received, disulfiram- or metronidazole-containing products within the past 14 days.
	• Teglutik, Tiglutik
	  ○ Patients with a history of severe hypersensitivity reactions to riluzole or to any of its components.
	• Xatmep
	  ○ Pregnancy (patients with pJIA).
	  ○ Severe hypersensitivity to methotrexate.
	• ZYVOX
	  ○ Known hypersensitivity to linezolid or any of the other product components.
	  ○ Patients taking any monoamine oxidase inhibitors (MAOI) or within two weeks of taking an MAOI.

REFERENCES

Number	Reference
1	CaroSpir prescribing information. CMP Pharma, Inc. August 2023.
2	Cimetidine oral solution prescribing information. Hi-Tech Pharmacal Co., Inc. October 2022.
3	Cuvposa prescribing information. Merz Pharmaceuticals, LLC. January 2023.
4	Entresto prescribing information. Novartis. April 2024.
5	Digoxin oral solution prescribing information. VistaPharm, LLC. November 2022.
6	Diuril prescribing information. Salix Pharmaceuticals, Inc. November 2021.
7	Epaned prescribing information. Azurity Pharmaceuticals, Inc. March 2020.
8	famotidine for suspension prescribing information. Camber Pharmaceuticals, Inc. March 2023.
9	LIKMEZ prescribing information. Saptalis Pharmaceuticals LLC. September 2023.
10	Furosemide oral solution prescribing information. Morton Grove Pharmaceuticals, Inc. January 2019.
11	Indocin suppositories prescribing information. Zyla Life Sciences US LLC. July 2023.
12	Carafate oral suspension prescribing information. Allergan, Inc. July 2023.
13	Katerzia prescribing information. Azuirty Pharmaceuticals, Inc. March 2020.
14	memantine oral solution prescribing information. Seton Pharmaceuticals. June 2021.
15	Jylamvo solution prescribing information. Lukare Medical. November 2022.
16	Nizatidine oral solution. Amneal Pharmaceuticals LLC. December 2022.
17	Nymalize prescribing information. Azurity Pharmaceuticals, Inc. March 2023.
18	Xatmep prescribing information. Silvergate Pharmaceuticals, Inc. March 2018.

Number	Reference
19	Propranolol solution prescribing information. Hikma Pharmaceuticals USA, Inc. September 2023.
20	Qbrelis prescribing information. Azurity Pharmaceuticals, Inc. April 2023.
21	Riomet prescribing information. Sun pharmaceutical Industries, Inc. December 2018.
22	Sotylize prescribing information. Azurity Pharmaceuticals, Inc. January 2024.
23	SYNDROS prescribing information. Benuvia Therapeutics Inc. September 2022.
24	Reference no longer used.
25	Reference no longer used.
26	ZYVOX prescribing information. Pharmacia & Upjohn Company LLC. July 2023.
27	Dartisla ODT prescribing information. Edenbridge Pharmaceuticals, LLC. December 2021.
28	Norliqva prescribing information. CMP Pharma, Inc. Feb 2022.
29	Adlarity prescribing information. Corium, Inc. February 2023.
30	ASPRUZYO prescribing information. Sun Pharmaceutical Industries Ltd. March 2022.
31	Reference no longer used.
32	Exservan prescribing information. Mitsubishi Tanabe Pharma America, Inc. December 2022.
33	Teglutik, Tiglutik prescribing information. ITF Pharma, Inc. February 2024.
34	Nitrofurantoin Oral Suspension prescribing information. Rising pharmaceuticals. June 2023.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when BOTH of the following are met: 1. ONE of the following: A. The patient is 12 years of age or younger **OR** B. There is support for why the patient is unable to use a solid dosage form (e.g., difficulty swallowing tablets or capsules) **AND** 2. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Ops Set Up	Validation Options	Other Explanation
	Validation: Apply Baseline and go to Validation Options	Other (see Other explanation field)	Age verification - The patient is 12 years of age or younger - There is support for why the patient is unable to use a solid dosage form (e.g., difficulty swallowing tablets or capsule)

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Amantadine Extended Release

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Gocovri® (amantadine ER) Extended-release capsule	Treatment of dyskinesia in patients with Parkinson's disease receiving levodopa-based therapy, with or without concomitant dopaminergic medications Adjunctive treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes		1
Osmolex ER® (amantadine ER) Extended-release tablet	Treatment of: • Parkinson's disease • Drug-induced extrapyramidal reactions in adult patients		3

CLINICAL RATIONALE

Parkinson's Disease	Parkinson's disease (PD) is a chronic, progressive, neurodegenerative disorder resulting from the loss of dopamine-producing cells of the substantia nigra.(5) The four primary symptoms of PD are tremor, or trembling in hands, arms, legs, jaw, and face; rigidity, or stiffness of the limbs and trunk; bradykinesia, or slowness of movement; and postural instability, or impaired balance and coordination.(2,5) Other symptoms may include depression and other emotional changes; difficulty swallowing, chewing, and speaking; urinary problems or constipation; skin problems; and sleep disruptions.(2,5) There are currently no blood or laboratory tests that have been proven to help in diagnosing PD. Therefore, diagnosis is based on medical history and neurological examinations. The disease is difficult to accurately diagnose, thus doctors may request (and sometimes repeat) brain scans or laboratory tests in order to rule out other diseases.(7) However, noninvasive diagnostic imaging, such as

	positron emission tomography (PET) can support a doctor's diagnosis. Conventional methods for diagnosis include the following:(11) • The presence of two of the three primary symptoms • The absence of other neurological signs upon examination • No history of other possible causes of parkinsonism, such as the use of tranquilizer medications, head trauma or stroke • Responsiveness to Parkinson's medications, such as levodopa Management of PD requires consideration of patient's symptoms, age, stage of disease, degree of functional disability, and level of physical activity and production. A comprehensive care plan should be in place, as agreed to by the person, their family members, and specialist and secondary healthcare providers.(5) Treatment of early stage PD typically includes levodopa, dopamine agonists (e.g., bromocriptine, pramipexole, ropinirole, rotigotine), and monoamine oxidase B inhibitors (MAO-B; e.g., rasagiline, selegiline). Treatment as PD advances includes additional agents such as anticholinergic agents, catechol-O-methyltransferase (COMT) inhibitors, and amantadine.(2,4,5) Levodopa is converted into dopamine by the body, and therefore helps to replace the dopamine that is lost as part of PD. It is currently the first choice (and thus the most commonly prescribed) treatment for the motor symptoms of PD.(4,5) Dopamine agonists mimic the role of dopamine in the brain but aren't as effective as levodopa, thus typically reserved for those whose motor symptoms do not impact quality of life. Dopamine agonists may be employed as either monotherapy in early PD or in combination with other antiparkinsonian drugs for the treatment of more advanced disease.(4,5) MAO-B inhibitors block an enzyme that metabolizes dopamine, thereby increasing the amount of dopamine available in the brain. MAO-B inhibitors are typically added as adjunct to levodopa if motor fluctuations develop despite optimal levodopa therapy, and/or if dyskinesia has developed.(5,7) Although initially effective, dopaminergic therapies are eventually complicated by the development of motor complications such as motor fluctuations and dyskinesia. Motor fluctuations include "on" and "off" states, where patients experience periods of when the medication wears off and the PD symptoms reappear. "Wearing off", characterized by reemergence of symptoms near the end of the dose interval, is the first and most commonly encountered motor fluctuation in patients with PD. Dyskinesia is defined as drug-induced involuntary movements including chorea and dystonia. Motor complications are usually addressed with levodopa adjustments and the addition of adjunctive

	medications. Motor fluctuations and dyskinesia can be resistant to medical therapy.(8) Amantadine increases dopamine release and inhibits dopamine uptake. Amantadine may be considered for patients with dyskinesias not adequately managed by modifying existing therapy.(5) Amantadine also has shown additional benefit in reducing “off” time.(8,9) Until there is a comparison between ER formulations of amantadine and generic amantadine, it is uncertain whether the potential benefits justify the cost.(10)
Efficacy	Amantadine for the treatment of dyskinesia in patients with PD was assessed in two randomized, double-blind, placebo-controlled efficacy trials. In both studies, the primary efficacy endpoint was the change in total score of the Unified Dyskinesia Rating Scale (UDysRS) between baseline and Week 12. In both studies, a significant decrease in mean UDysRS total score (reduction in dyskinesia) was observed at Week 12 compared to placebo.(1) The effect of amantadine IR formulation on dyskinesias has been examined in multiple small studies. In a 6-week, placebo-controlled, double-blind, crossover study, PD patients (n=18) receiving amantadine IR (average dose of 350 mg/day) had around a 60% reduction in dyskinesia compared with placebo.(6) The authors conducted a follow-up study and found that 13 of 17 patients originally treated in the short-term study had a 56% reduction in dyskinesia scores at 1 year.(7) In a randomized, double-blind, placebo-controlled trial, 126 patients with levodopa-induced dyskinesia were randomly assigned to ER amantadine (274 mg capsule at bedtime) or placebo. At 12 weeks compared with placebo, the active drug reduced the duration, severity, and impact of dyskinesia as measured by the UDysRS. In addition, treatment with the active drug reduced mean "off" time by 0.6 hours, while mean "off" time increased 0.3 hours with placebo. The most common significant adverse effects were mild and reversible visual hallucinations.(8) A subsequent trial with 77 patients reported similar results at 12 weeks, demonstrating reduced severity of dyskinesia and reduced mean "off" time by 0.5 hours, while mean "off" time increased 0.6 hours with placebo.(9)
Safety	Gocovri and Osmolex ER are both contraindicated in patients with end-stage renal disease (i.e., creatinine clearance below 15 mL/min/1.73 m^2).(1,3)

REFERENCES

Number	Reference
1	Gocovri prescribing information. Adamas Pharma, LLC. January 2021.
2	National Institute of Neurological Disorders and Stroke. Parkinson's Disease Information Page. Updated April 2020. Available at: www.ninds.nih.gov/Disorders/All-Disorders/Parkinsons-Disease-Information-Page.
3	Osmolex ER prescribing information. Vertical Pharmaceuticals LLC. March 2021.
4	Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and Movement Disorder Society Evidence-Based Medicine Review: Update on Treatments for the Motor Symptoms of Parkinson's Disease. Mov Disord. 2018 Aug;33(8):1248-1266.
5	National Institute for Health and Care Excellence (NICE). Guideline on Parkinson's Disease in Adults (NG71). July 2017. Available at: https://www.nice.org.uk/guidance/ng71.
6	Verhagen Metman L, Del Dotto P, van den Munckhof P, Fang J, Mouradian MM, Chase TN. Amantadine as Treatment for Dyskinesias and Motor Fluctuations in Parkinson's Disease. Neurology. 1998;50(5):1323–1326.
7	Verhagen Metman L, Del Dotto P, LePoole K, Konitsiotis S, Fang J, Chase TN. Amantadine for Levodopa-Induced Dyskinesias: A 1-Year Follow-Up Study. Arch Neurol. 1999;56:1383-1386.
8	Pahwa R, Tanner CM, Hauser RA, et al. ADS-5102 (Amantadine) Extended-Release Capsules for Levodopa-Induced Dyskinesia in Parkinson Disease (EASE-LID Study). JAMA Neurol. 2017 Aug;74(8):941-949.
9	Oertel W, Eggert K, Pahwa R, et al. Randomized, Placebo-Controlled Trial of ADS-5102 (Amantadine) Extended-Release Capsules for Levodopa-Induced Dysinesia in Parkinson's Disease (EASE-LID-3). Mov Disord. 2017 Dec;32(12):1701-1709.
10	Shukla AW. Extended-Release Amantadine – A Smart Pill for Treatment of Levodopa-Induced Dyskinesia but Does the Evidence Justify the Cost? JAMA Neurol. 2017;74(8):904-905.
11	American Association of Neurological Surgeons. Parkinson's Disease. Updated 2022. Available at: https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Parkinsons-Disease.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is Gocovri AND ALL of the following: 1. The patient has a diagnosis of Parkinson's disease **AND** 2. ONE of the following: A. The requested agent will be used for the treatment of dyskinesia **OR** B. The requested agent will be used for the adjunctive treatment in patients experiencing "off" episodes **AND** 3. BOTH of the following: A. The patient is currently treated with levodopa-based therapy **AND** B. The patient will continue levodopa-based therapy in combination with the requested agent **OR** B. The requested agent is Osmolex ER **AND** ONE of the following: 1. The patient has a diagnosis of Parkinson's disease **OR** 2. The patient has a diagnosis of drug-induced extrapyramidal reactions AND the prescriber has assessed and adjusted, if applicable, any medications known to cause extrapyramidal symptoms **OR** C. The patient has another FDA approved indication for the requested agent **AND** 2. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response to immediate release amantadine **OR** B. The patient has an intolerance or hypersensitivity to immediate release amantadine that is not expected to occur with the requested agent **OR** C. The patient has an FDA labeled contraindication to immediate release amantadine that is not expected to occur with the requested agent **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months

Module	Clinical Criteria for Approval
	NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. If the requested agent is Gocovri, the patient will be using levodopa-based therapy in combination with the requested agent **AND** 3. The patient has had clinical benefit with the requested agent **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	C. The prescriber has provided information in support of therapy with a higher dose for the requested indication **Length of Approval**: 12 months

Amifampridine

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Firdapse® (amifampridine) Tablet	Treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults and pediatric patients 6 years of age and older		1

CLINICAL RATIONALE

Lambert-Eaton myasthenic syndrome	Lambert-Eaton myasthenic syndrome (LEMS) is a rare autoimmune disorder characterized by the gradual onset of muscle weakness, especially of the pelvic and thigh muscles. Approximately 60 percent of LEMS cases are associated with a small cell lung cancer (SCLC), and the onset of LEMS symptoms often precedes the detection of the cancer. The LEMS patients with cancer tend to be older and nearly always have a long history of smoking. In cases in which there is no associated cancer, disease onset can be at any age.(3) LEMS may affect the patient's ability to engage in strenuous exercise and may make such activities as climbing stairs or walking up a steep walkway difficult. Onset is gradual, typically taking place over several weeks to many months. There is often a progression of symptoms whereby the shoulder muscles, muscles of the feet and hands, speech and swallowing muscles and eye muscles are affected in a stepwise fashion. The symptoms progress more quickly when LEMS is associated with cancer. Most LEMS patients also exhibit the following autonomic symptoms: dry mouth, constipation, impotence, and decreased sweating. LEMS patients with or without cancer may also undergo significant weight loss. The tendon reflexes are diminished or absent on examination. In summary, LEMS is often described as a clinical "triad" of proximal muscle weakness, autonomic symptoms and reduced tendon reflexes.(3) LEMS occurs because autoantibodies damage the "voltage-gated calcium channels (VGCC)" on the motor nerve membrane at the neuromuscular junction.

	These channels normally conduct calcium into the nerve resulting in release of acetylcholine. Acetylcholine helps in the communication between nerve cells and muscles and is one of a group of chemicals known as neurotransmitters, which help to transmit nerve impulses. The autoantibodies attack the VGCC resulting in less acetylcholine release. In LEMS cases associated with cancer, it is believed that autoantibodies created against the VGCC on the small-cell lung tumor damage the VGCC on the nerve. It is unknown what causes autoantibody production in cases not associated with cancer.(3) A differential diagnosis of LEMS must be determined due to its similarities in presentation to myasthenia gravis. Diagnosis of LEMS is based on clinical signs and symptoms, electrophysiological studies, and antibody testing. LEMS can be diagnosed when the patient is positive for antibodies against voltage-gated calcium channels (VGCC) unlike myasthenia gravis which as anti-acetylcholine receptor (AChR) and anti-muscle-specific tyrosine kinase (MuSK) antibodies.(4) The triad of electrophysiologic abnormalities in LEMS consists of the following: • Diffusely reduced motor amplitudes on motor nerve conduction studies, often less than 50% of the laboratory's lower limits of normal • Decrement with low-frequency stimulation; as opposed to myasthenia gravis, where the decrement is usually maximal at the fourth or fifth stimulation in the train, in LEMS the maximal decrement may occur later in the train • Increment with high-frequency stimulation or facilitation after 10 seconds of maximal voluntary contraction. Increments of more than 100% are very suggestive for LEMS but not specific for LEMS and occur in some cases of botulism and myasthenia gravis The most effective symptomatic treatment in LEMS is 3,4-diaminopyridine (3,4-DAP), also known as amifampridine. Through blocking voltage-gated potassium channels,3,4-DAP prolongs nerve terminal depolarization and increases acetylcholine release. In theory, pyridostigmine should be synergistic with 3,4-DAP but many patients with LEMS have no benefit from pyridostigmine either on its own or in combination with 3,4-DAP.(4)
Efficacy	The mechanism by which Firdapse (amifampridine) exerts its therapeutic effect in LEMS patients has not been fully elucidated. Amifampridine is a broad-spectrum potassium channel blocker. The efficacy of Firdapse for the treatment of LEMS was demonstrated in two randomized, double-blind, placebo-controlled discontinuation studies. A total of

	64 adults with LEMS (confirmed by either neurophysiology studies or a positive anti-P/Q type voltage-gated calcium channel antibody test. Patients were required to be on an adequate and stable dosage (30 to 80 mg daily) of amifampridine prior to entering the randomized discontinuation phases of both studies.(1) The two co-primary measures of efficacy in both studies were the change from baseline to the end of the discontinuation period in the Quantitative Myasthenia Gravis (QMG) score and in the Subject Global Impression (SGI) score. The QMG is a 13-item physician-rated categorical scale assessing muscle weakness. Each item is assessed on a 4-point scale, where a score of 0 represents no weakness, and a score of 3 represents severe weakness. Higher scores represent greater impairment. The SGI is a 7-point scale on which patients rated their global impression of the effects of the study treatment on their physical well-being. Lower scores on the SGI represent lower perceived benefit with the study treatment.(1) A key secondary efficacy endpoint was the clinical global impression improvement (CGI-I) score, a 7-point scale on which the treating physician rated the global impression of change in clinical symptoms. A higher CGI-I score indicates a perceived worsening of clinical symptoms.(1)

Safety	• Firdapse is contraindicated in patients with:
	  ○ A history of seizures
	  ○ A hypersensitivity to amifampridine or another aminopyridine(1)

REFERENCES

Number	Reference
1	Firdapse Prescribing Information. Catalyst Pharmaceuticals. May 2023.
2	Reference no longer used.
3	National Organization for Rare Disorders (NORD). Rare Disease Database. Lambert-Eaton Myasthenic Syndrome.
4	Nicolle MW. Myasthenia Gravis and Lambert-Eaton Myasthenic Syndrome. Continuum (Minneap Minn) 2016;22(6): 1978-2005.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The prescriber has provided information supporting that the patient has a diagnosis of Lambert Eaton myasthenic syndrome (LEMS) confirmed by at least ONE of the following: (medical records required) A. Decreased amplitude of compound muscle action potential (CMAP) to a single supramaximal stimulus **OR** B. Positive antibody test against voltage-gated calcium channels (VGCC) **AND** 2. If the patient has an FDA approved indication, ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 3. The patient has weakness that interferes with normal function **AND** 4. The patient does NOT have a history of seizures **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months Note: If Quantity Limit applies, please see Quantity Limit criteria **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for an amifampridine containing agent through the plan's Prior Authorization process **AND** 2. The patient has had clinical benefit with an amifampridine containing agent [e.g., improved weakness, improved fatigue, improvement in activities of daily living (ADLs)] **AND** 3. The patient has not developed a history of seizures while using the requested medication **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**

Module	Clinical Criteria for Approval
	5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months Note: If Quantity Limit applies, please see Quantity Limit criteria

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity Limits** for the **Target Agent(s)** will be approved when the requested quantity (dose) does NOT exceed the program quantity limit **Length of Approval:** 6 months for initial 12 months for renewal

Ampyra (dalfampridine)

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Ampyra®* (dalfampridine) Tablet	To improve walking in adult patients with multiple sclerosis (MS). This was demonstrated by an increase in walking speed	*generic equivalent available	1

CLINICAL RATIONALE

Multiple Sclerosis	Multiple sclerosis (MS) is a disorder of the central nervous system (CNS) characterized by demyelization, inflammation, and degenerative changes. Most people with MS experience relapses and remissions of neurological symptoms, particularly early in the disease, and clinical events are usually associated with areas of CNS inflammation. Gradual worsening or progression, with or without subsequent acute attacks of inflammation or radiological activity, may take place early, but usually becomes more prominent over time. While traditionally viewed as a disease solely of CNS white matter, more advanced imaging techniques have demonstrated significant early and ongoing CNS gray matter damage as well.(2) Those diagnosed with MS may have many fluctuating and disabling symptoms (including, but not limited to, fatigue, pain, bladder and bowel issues, sexual dysfunction, movement and coordination problems, visual disturbances, and cognition and emotional changes.(8) There are currently four major types of MS: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS).(2) Many patients with MS develop gait impairment, and some eventually require a cane or wheelchair. Gait impairment in MS can result from a multitude of issues such as spasticity, weakness, fatigue, sensory loss, visual loss, and vestibular dysfunction. Leg weakness and spasticity can result from MS lesions in the descending motor tracts of the brain and spinal cord. Ambulatory imbalance can

	be caused by lesions involving the cerebellar pathways. The International Symposium on Gait and balance in Multiple Sclerosis states that the causes of gait and balance dysfunction in patients with MS are multifactorial and therefore may benefit from a wide range of interventions. Evidence based recommendations from the 2nd International Symposium included balance rehabilitation, self-management, medications, functional electrical stimulation, robotics, sensory augmentation, gait training with error feedback, and fall prevention.(7) There is ample evidence to support the benefits of ongoing treatment for the majority of people with multiple sclerosis, there may be some situations in which clinicians and their patients might consider stopping treatment. Although freedom from subsequent relapse is impossible to guarantee, treatment cessation may be considered in patients who:(2) • Are over 60 years of age • Have experienced a progressive disease course for five years or longer • Have no accumulating T2 lesions or gadolinium enhancing lesions on MRI of the brain or spinal cord after a period of observation over several years. Earlier discontinuation, particularly in patients with active disease, may lead to increased disease activity. Clinical and MRI monitoring for recurrent disease activity is clearly warranted in those patients.(2)
Efficacy	The effectiveness of Ampyra (dalfampridine) was studied in two adequate and well controlled trials involving 540 patients. Patients in these two clinical trials had a mean Kurtzke Expanded Disability Status Scale (EDSS) score of 6. Patient inclusion criteria in both trials included the ability to walk 25 feet in 8 to 45 seconds at baseline. Both trials used a responder analysis as the primary endpoint. Responders were defined as patients who achieved faster walking speeds (measured by a timed 25-foot walk in seconds) in at least three of four visits during the study period compared to their fastest speed during the off-treatment period.(1) A retrospective analysis of a previous trial indicated that treatment responders experienced a 25% improvement in walking speed compared to baseline.(3) An FDA analysis using the entire study group (not just responders) found that neither trial demonstrated statistically significant differences in change in walking speed at visit 6 compared to baseline or average walking speed during the treatment phase of the trial. The FDA calculated that changes in walking speed would improve the 25 foot walk time for dalfampridine patients compared

	to placebo by 0.88 seconds and 0.5 seconds in trials MS-F203 and MS-F204, respectively. FDA analyses found that there was no significant difference between groups in either trial for the SGI score.(4) SGI is a measurement of patient perceived improvement of disease. The FDA analysis did not compare differences in walking endpoints or SGI for the responder group compared to placebo. Evidence is lacking on how to identify patients that are likely to respond to dalfampridine without a trial of the drug. Dalfampridine is approved to improve walking speed in patients with MS and has not been shown to be effective in improving strength in other neurologic conditions (spinal cord injury, etc.). Evidence supports criteria similar to that used in Phase 3 clinical trials which includes patients diagnosed with MS who have difficulty walking as defined by a timed 25 foot walk between 8 and 45 seconds.(5) The Kurtzke Expanded Disability Status Scale (EDSS) quantifies the level of functioning that is used by health care providers diagnosing MS. The EDSS provides a total score on a scale that ranges from 0 to 10. EDSS 1.0 to 4.5 refer to patients with a high degree of ambulatory ability and subsequent levels 5.0 to 9.5 refer to the loss of ambulatory ability. An EDSS score of 7 indicates the patient is unable to walk beyond 5 meters even with aid, essentially restricted to wheelchair.(6)
Safety	Ampyra is contraindicated in:(1) • Patients who have a history of seizures • Patients with moderate to severe renal impairment (CrCl less than 50 mL/min) • Patients with a hypersensitivity to dalfampridine or 4-aminopyridine.

REFERENCES

Number	Reference
1	Ampyra prescribing information. Acorda Therapeutics, Inc. November 2021.
2	Multiple Sclerosis Coalition. The Use of Disease Modifying Therapies in Multiple Sclerosis: Principles and Current Evidence. A Consensus Paper by the Multiple Sclerosis Coalition. June 2019.
3	Goodman AD, Brown TR, Cohen JA, et al. Dose comparison trial of sustained release fampridine in multiple sclerosis. *Neurology* 2008;71:1134-1141.

Number	Reference
4	FDA. Medical review of fampridine. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022250s000_MedR.pdf.
5	Pikoulas TE and Fuller MA. Dalfampridine: A Medication to Improve Walking in Patients with Multiple Sclerosis. *The Annals of Pharmacotherapy* 2012;46:1010-15.
6	U.S. Department of Veterans Affair. Kurtzke Expanded Disability Status Scale. Available at: https://www.va.gov/MS/Professionals/diagnosis/Kurtzke_Expanded_Disability_Status_Scale.asp. Accessed November 2018.
7	Zackowdki KM, Cameron M, Wagner JM. Perspectives in Rehabilitation. 2nd International Symposium on Gait and Balance in Multiple Sclerosis: interventions for gait and balance in MS. Journal of Disability and Rehabilitation. Volume 36,2014 – Issue 13. Pages 1128-1132.
8	MS international federation. About MS - Symptoms. Accessed at MS Symptoms | Multiple Sclerosis (msif.org)

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of multiple sclerosis (MS) AND ALL of the following: 1. ONE of the following: A. The patient will be using a disease modifying agent for the treatment of MS (e.g., Aubagio, Avonex, Bafiertam, Betaseron, Briumvi, Copaxone, Extavia, Gilenya, Glatopa, Kesimpta, Lemtrada, Mavenclad, Mayzent, Ocrevus, Plegridy, Ponvory, Rebif, Rituxan, Tascenso ODT, Tecfidera, Tysabri, Vumerity, Zeposia) in combination with the requested agent **OR** B. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to ALL disease modifying agent drug classes used for the treatment of MS (see MS disease modifying agents drug class table) **AND**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
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2. Information has been provided that the patient has significant limitations attributable to slow ambulation AND
3. The patient is ambulatory with a baseline (prior to therapy with the requested agent) timed 25-foot walk of 8 to 45 seconds AND
4. Information has been provided that the patient has a current EDSS score less than 7 OR
B. The patient has another FDA approved indication for the requested agent and route of administration AND
2. ONE of the following:
A. The patient’s age is within FDA labeling for the requested indication for the requested agent OR
B. The prescriber has provided information in support of using the requested agent for the patient’s age AND
3. The prescriber is a specialist in the area of the patient’s diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent AND
5. If the requested agent is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:
A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
C. The prescriber has provided information to support the use of the requested brand agent over the generic equivalent

<table>
<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Ampyra</td><td>dalfampridine</td></tr>
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Length of Approval: 6 months for MS and 12 months for another FDA approved diagnosis

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Renewal Evaluation
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Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization Review process **AND** 2. ONE of the following: A. The patient has a diagnosis of multiple sclerosis (MS) AND ALL of the following: 1. Information has been provided that the patient has had stabilization or improvement from baseline (before treatment with requested agent) in timed walking speed or EDSS score with the requested agent **AND** 2. The patient is ambulatory **AND** 3. Information has been provided that the patient has a current EDSS score of less than 7 **AND** 4. ONE of the following: A. BOTH of the following: 1. The patient is currently treated with a disease modifying agent for the treatment of MS (e.g., Aubagio, Avonex, Bafiertam, Betaseron, Briumvi, Copaxone, Extavia, Gilenya, Glatopa, Kesimpta, Lemtrada, Mavenclad, Mayzent, Ocrevus, Plegridy, Ponvory, Rebif, Rituxan, Tascenso ODT, Tecfidera, Tysabri, Vumerity, Zeposia) **AND** 2. The patient will continue a disease modifying agent for the treatment of MS in combination with the requested agent **OR** B. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to ALL disease modifying agent drug classes used for the treatment of MS (see MS disease modifying agents drug class table) **OR** B. The patient has another FDA approved indication for the requested agent AND has had stabilization or clinical improvement with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following: A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent **OR** B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent **OR** C. The prescriber has provided information to support the use of the requested brand agent over the generic equivalent

Module	Clinical Criteria for Approval
	<table><tr><th>Brand</th><th>Generic Equivalent</th></tr><tr><td>Ampyra</td><td>dalfampridine</td></tr></table> **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **Length of Approval**: Initial: 6 months for MS and 12 months for another FDA approved diagnosis. Renewal: 12 months

Androgens and Anabolic Steroids

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Androderm® (testosterone) Transdermal patch system	For replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals • Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation Limitations of use: • Safety and efficacy in men with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established • Safety and efficacy in males less than 18 years old have not been established		1
AndroGel® (testosterone) Gel*	For replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis,	*generic available	2,3

Agent(s)	FDA Indication(s)	Notes	Ref#
	vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals • Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation Limitations of use: • Safety and efficacy in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established • Safety and efficacy in males less than 18 years old have not been established • Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure		
Aveed® (testosterone undecanoate) Intramuscular injection solution	Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals • Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation Limitations of use:		20

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Safety and efficacy in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established • Safety and efficacy in males less than 18 years old have not been established		
danazol Capsule*	Endometriosis amenable to hormone management For hereditary angioedema, indicated for the prevention of attacks of angioedema of all types (cutaneous, abdominal, laryngeal) in males and females	*generic available	14
Depo®-Testosterone (testosterone cypionate) Intramuscular injection solution*	For replacement therapy in the male in conditions associated with symptoms of deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome; or orchiectomy • Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation Note: Safety and efficacy in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established	*generic available	18
Fortesta®, Testosterone Gel*	For replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy,	*generic available	5

Agent(s)	FDA Indication(s)	Notes	Ref#
	Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals • Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation Limitations of use: • Safety and efficacy in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established • Safety and efficacy in males less than 18 years old have not been established		
Jatenzo® (testosterone undecanoate) Capsule	Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. • Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation Limitations of use: • Safety and efficacy in males less than 18 years old have not been established.		12

Agent(s)	FDA Indication(s)	Notes	Ref#
Kyzatrex®, Undecatrex™ (testosterone undecanoate) Capsule	Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle stimulating hormone (FSH), luteinizing hormone (LH)) above the normal range • Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low serum testosterone concentrations but have gonadotropins in the normal or low range Limitations of use: • Safety and efficacy in males less than 18 years old have not been established.		7,43
Methitest® (methyltestosterone) Tablet	Androgens are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone in males: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome; or orchiectomy • Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or		11

Agent(s)	FDA Indication(s)	Notes	Ref#
	luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary hypothalamic injury from tumors, trauma, or radiation • Note: Safety and efficacy of methyltestosterone in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established Androgens may be used to stimulate puberty in carefully selected males with clearly delayed puberty Androgens may be used secondarily in women with advancing inoperable metastatic (skeletal) mammary cancer who are 1 to 5 years postmenopausal. This treatment has also been used in premenopausal women with breast cancer who have benefitted from oophorectomy and are considered to have a hormone-responsive tumor.		
methyltestosterone Capsule*	Androgens are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone in males: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome; or orchiectomy • Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary hypothalamic injury from tumors, trauma, or radiation • Note: Safety and efficacy of methyltestosterone in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established	*generic available	10

Agent(s)	FDA Indication(s)	Notes	Ref#
	Androgens may be used to stimulate puberty in carefully selected males with clearly delayed puberty Androgens may be used secondarily in women with advancing inoperable metastatic (skeletal) mammary cancer who are 1 to 5 years postmenopausal. This treatment has also been used in premenopausal women with breast cancer who have benefitted from oophorectomy and are considered to have a hormone-responsive tumor.		
Natesto® (testosterone) Nasal gel	For replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. • Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. Limitations of use: • Safety and efficacy in men with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established • Safety and efficacy in males less than 18 years old have not been established		6

Agent(s)	FDA Indication(s)	Notes	Ref#
Testim® (testosterone) Gel*	For replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals • Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation Limitations of use: • Safety and efficacy in men with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established • Safety and efficacy in males less than 18 years old have not been established • Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure	*generic available	8
Testopel® (testosterone) Pellet	Androgens are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone in males: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsions, orchitis, vanishing testis syndrome; or orchiectomy • Hypogonadotropic hypogonadism (congenital or acquired):		19

Agent(s)	FDA Indication(s)	Notes	Ref#
	gonadotropic luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation • Note: Safety and efficacy in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established Androgens may be used to stimulate puberty in carefully selected males with clearly delayed puberty		
Testosterone Enanthate Intramuscular injection solution	For replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone in males: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, or orchiectomy • Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation • Note: Safety and efficacy in men with age-related hypogonadism have not been established May be used to stimulate puberty in carefully selected males with clearly delayed puberty May be used secondarily in women with advancing inoperable metastatic (skeletal) mammary cancer who are one to five years postmenopausal. This treatment has also been used in premenopausal women with breast cancer who have benefited from oophorectomy and are considered to have a hormone-responsive tumor.		16

Agent(s)	FDA Indication(s)	Notes	Ref#
testosterone Topical solution*	For replacement therapy in males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. • Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. Limitations of use: • Safety and efficacy in men with “age-related hypogonadism” (also referred to as “late-onset hypogonadism”) have not been established • Safety and efficacy in males less than 18 years old have not been established	*generic available	4
Tlando® (testosterone undecanoate) Capsule	Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals • Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone		44

Agent(s)	FDA Indication(s)	Notes	Ref#
	(LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation Limitations of use: • Safety and efficacy in males less than 18 years old have not been established.		
Vogelxo®, Testosterone Gel*	For replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals • Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation Limitations of use: • Safety and efficacy in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established. • Safety and efficacy in males less than 18 years old have not been established. • Topical testosterone products may have different doses, strengths, or application instructions that may result in different systemic exposure.	*generic available	9

Agent(s)	FDA Indication(s)	Notes	Ref#
Xyosted® (testosterone enanthate) Subcutaneous injection solution	Testosterone replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone: • Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchiectomy, Klinefelter's syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range. • Hypogonadotropic hypogonadism (congenital or acquired): gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal or low range. Limitations of Use: • Safety and efficacy in males less than 18 years old have not been established		17

CLINICAL RATIONALE

Testosterone Deficiency	Testosterone is the predominant androgen in males and is involved in a multitude of physiological and biological processes throughout the body.(21) Testosterone deficiency caused by abnormalities at the testicular level is considered primary hypogonadism, while dysfunction of the hypothalamus or the pituitary is considered secondary hypogonadism.(27)

	Patients with testosterone deficiency have consistent low serum total testosterone and/or free testosterone levels. Reference ranges for testosterone levels vary among laboratories and assays due to a lack of standardization of assays, calibrator differences, and differences in the reference populations used.(27) Laboratories often define the normal value of their reference range as being within the 5th and 95th percentile of the sampled population. The American Urological Association (AUA) recommends that clinicians can use an absolute value of a total testosterone level below 300 ng/dL as a reasonable cut-off in support of the diagnosis of low testosterone. Clinicians may use the reference range of the laboratory or the recommended absolute measure to determine if a patient has low testosterone.(21)
	
	The clinical diagnosis of testosterone deficiency is only made when patients have low total testosterone levels combined with symptoms and/or signs. A challenge in making the diagnosis of testosterone deficiency is that many of the symptoms are non-specific and might be related to conditions other than low testosterone. Clinicians should conduct a targeted physical exam for signs that are associated with low testosterone.(21) Signs and symptoms associated with testosterone deficiency include:(21,27)
	
	• Physical symptoms and signs:
	  ○ Reduced energy
	  ○ Reduced endurance
	  ○ Diminished work and/or physical performance
	  ○ Loss of body hair and/or reduced beard growth
	  ○ Very small testes (especially less than 6 ml)
	  ○ Fatigue
	  ○ Reduced lean muscle mass
	  ○ Obesity
	• Cognitive symptoms and signs:
	  ○ Depressive symptoms
	  ○ Cognitive dysfunction
	  ○ Reduced motivation
	  ○ Poor concentration
	  ○ Poor memory
	  ○ Irritability
	• Sexual symptoms and signs:
	  ○ Reduced sex drive
	  ○ Erectile dysfunction
	
	Testosterone therapy is used to raise serum testosterone levels and treat testosterone deficiency. The goal of testosterone therapy is the normalization of

	total testosterone levels combined with improvement in symptoms or signs. The AUA recommends that clinicians use the minimal dosing necessary to drive total testosterone levels to the normal physiologic range, with an absolute value of 450-600 ng/dL being provided. Testosterone levels should be measured every 6-12 months while on testosterone therapy.(21)
Delayed Puberty	Delayed puberty in boys is defined as the absence of testicular growth to at least 4 mL in volume or 2.5 cm in length by 14 years of age. It should also be suspected if pubertal development stops or regresses. The most common cause of delayed puberty is a constitutional delay of growth and puberty (CDGP).(22) CDGP is a non-pathological condition that is an extreme variant in late pubertal timing, and it is usually seen in patients with a family history of delayed puberty.(30) Patients may present with short stature on examination, and a delayed bone age is supportive of the diagnosis.(22,30) Delayed puberty may also be caused by hypo- or hyper-gonadotropic hypogonadism (HH), but differentiating between one of these causes and CDGP can often be clinically challenging due to similar symptoms, signs, and lab results. A diagnosis of CDGP is one of exclusion, and determining the etiology of the patient's delayed puberty is important due to the difference in treatment regimens. Patients with a HH cause need to be treated for their underlying condition, with long term hormone replacement therapy potentially being needed.(30) For boys with CDGP, clinical observation and monitoring for signs of spontaneous puberty is the common approach.(30,31) Testosterone therapy for 3 to 6 months is recommended to initiate puberty for prepubertal boys 14 years of age or older with significant psychological distress (e.g., bullying, low self-esteem).(22,30) Once puberty starts, testosterone administration should be discontinued.(30,31) If puberty is not induced, testosterone therapy can be extended for an additional 3 to 6 months; it may also support a diagnosis of HH. Intramuscular testosterone enanthate or testosterone cypionate at low doses are used most frequently. Transdermal testosterone, subcutaneous testosterone enanthate, and other formulations used for adult testosterone replacement therapy have not been sufficiently studied to support their use for CDGP, and their fixed doses make them inappropriate for this population.(31)
Hereditary Angioedema (HAE)	Hereditary angioedema (HAE) is a rare genetic disease that is caused by a deficiency or dysfunction of C1-inhibitor protein (C1-INH). The disease manifests as angioedema of the skin, the abdomen, and/or the upper respiratory tract. Plasma derived C1-INH is the preferred first line agent for both short-term and long-term prophylactic treatment of HAE. Attenuated androgens (e.g., danazol) have historically been used for preprocedural prophylaxis and long-term

	prophylaxis, but the risk of androgenic and anabolic side effects limit their use, especially long term.(23) For short term prophylaxis prior to a medical, surgical, or dental procedure, danazol may be used for 5 days before and continued 2 to 5 days after the procedure. Danazol may also be used short term prior to a stressful life event that may induce an angioedema attack. Danazol is recommended as second line therapy for long term prophylaxis.(23,28) The use of danazol can be used if first-line medications (e.g., C1-INH, lanadelumab, berotralstat) are not available or if a patient requires oral therapy.(28) The minimal effective dose should be used due to the risk of side effects.(23)
Off Label Use: Chronic Kidney Disease Anemia	The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Anemia in Chronic Kidney Disease recommends not using androgens as an adjuvant to erythropoiesis stimulating agents. They cite the risks of androgen therapy and their uncertain benefit on hemoglobin concentration or clinical outcomes.(29)
Off Label Use: Erectile Dysfunction	The majority of patients who present with erectile dysfunction (ED) have normal testosterone levels.(35) The recommended treatment for these patients is oral phosphodiesterase type 5 (PDE5) inhibitors.(32,36) There is no evidence of benefits in using testosterone therapy for ED in patients with normal testosterone levels, and it is recommended that testosterone therapy not be used.(36) The benefits of testosterone therapy for ED is related to the normalization of testosterone levels in patients with testosterone deficiency (TD), specifically.(36) Therefore, it is recommended that patients with TD and ED be treated with testosterone therapy to get their testosterone levels within normal limits (or greater than 300 ng/dL), and to use a PDE5 inhibitor in addition to testosterone therapy as add-on therapy for ED symptoms.(32)
Off Label Use: Myelofibrosis Associated Anemia	Danazol is a recommended regimen for myelofibrosis (MF) associated anemia in patients with no symptomatic splenomegaly and/or no constitutional symptoms and a serum erythropoietin (EPO) greater than or equal to 500 mU/mL (NCCN 2a recommended use). Patients who were previously treated with a erythropoietin stimulating agent (ESA) for MF associated anemia and had no response, or loss of response, should be managed as a patient with an EPO level greater than or equal to 500 mU/mL.(34)
Off Label Use: Gender Dysphoria / Gender Incongruence	Transgender and gender diverse (TGD) persons may seek support and medically necessary gender-affirming hormone therapy (GAHT) to meet their goals for gender identity and expression.(24) Sex steroids matching the individual's

	affirmed gender are used to achieve and maintain physiologic levels of hormones needed to meet these treatment goals.(24,33) Health care professionals (HCP) assessing TGD people for GAHT should have experience, or be qualified, to assess clinical aspects of gender dysphoria, incongruence, and diversity whenever possible and necessary. They should also be able to identify co-existing mental health or psychosocial concerns and be able to distinguish them from conditions that may be mistaken as gender incongruence. Ideally and where possible, HCPs should work with professionals from different disciplines for consultation, treatment management, and referral, if required. Other members of a multidisciplinary team may include a mental health professional (MHP) or an endocrinologist. The inclusion of a psychologist, psychiatrist, or other MHP is not required. Many TGD people will not require therapy or other forms of mental health care, while others may benefit. Individuals should not be referred for mental health treatment exclusively on the basis of a transgender identity.(24) However, to ensure continuity of care and minimize gaps in accessible care, a HCP without expertise may provide care and support the assessment for GAHT. Due to the importance of GAHT for TGD people, a lack of available experts and resources should not constitute a barrier to care.(24) An informed consent process is adequate for initiating GAHT.(25) Most medications used for GAHT are common and can be safely prescribed by primary care providers (PCP) or other non-specialists, and a specific certification is not required to prescribe them.(24,25) With that, TGD people should be supported to access care with an experienced HCP as soon as possible and should be referred to a MHP if needed.(24) HCPs should be able to assess capacity for the patient to consent to treatment. Consent requires the cognitive capacity to comprehend the nature of the treatment, understand the risks and benefits of a treatment, and the potential negative and positive outcomes. It also requires the ability of the patient to retain that information and use that understanding to make and communicate an informed decision.(24) Most adolescents have the capacity to give informed consent for GAHT by age 16.(33) However, the legal guardian(s) of a minor usually provides the consent for treatment and assent is provided from the minor in a parallel process through communication with the provider.(24) Prior to initiating GAHT, gender incongruence/dysphoria should be documented and sustained over time. The DSM-5 classification of gender dysphoria indicates there should be marked gender incongruence for a duration of at least 6 months. There is minimal evidence to define the length of persistence required for

	treatment in adults. HCPs should give due consideration to the life stage, history, and current circumstances of the adult being assessed, including the nature and consistency of gender incongruence. An abrupt or superficial change in gender identity or lack of persistence is insufficient to initiate GAHT.(24) For adolescents, due to potential shifts in gender-related experiences and the treatment having some irreversible effects, gender diversity/incongruence should have persisted for several years prior to initiating GAHT. A persistent diagnosis requires careful and extended assessments of the young person over time and enables a meaningful decision to be made regarding treatment. Evidence can include a history obtained directly from the adolescent and parents/caregivers when this information is not documented in the medical records.(24) For adults, the following should be met prior to initiating GAHT: • Gender incongruence is marked and sustained(24,33) • Demonstrates capacity to consent for the specific gender-affirming hormone treatment(24,33) • Other possible causes of apparent gender incongruence have been identified and excluded(24) • Mental health and physical/medical conditions that could negatively impact the outcome of treatment have been assessed, with risks and benefits discussed(24,33) • Understands the effects and side effects of gender-affirming hormone treatment, including effects on reproduction, and they have explored reproductive options(24,33) For adolescents, the following should be met prior to initiating GAHT: • The HCP has conducted a comprehensive biopsychosocial assessment, and included mental health and other medical professionals when required(24) • Involvement of parent(s)/guardian(s) in the assessment process, unless their involvement is determined to be harmful to the adolescent or not feasible(24,33) • Gender diversity/incongruence is marked and sustained over time(24,33) • Demonstrates the emotional and cognitive maturity required to provide informed consent/assent for treatment(24,33) • Mental health concerns (if any), physical/medical conditions, or social problems that may interfere with diagnostic clarity, capacity to consent, and gender-affirming medical treatments have been addressed;

	sufficiently so that gender-affirming medical treatment can be provided optimally(24,33)
	• Informed of the effects (including irreversible) and side effects of treatment; including reproductive effects and the potential loss of fertility and the available options to preserve fertility(24,33)
	• Patient is 16 years of age or older(24,33)
	  ○ There may be compelling reasons to initiate GAHT prior to 16 years old, such as avoiding prolonged pubertal suppression due to potential bone health concerns or the psychosocial implications of delaying puberty.(24) However, there is limited information to initiate treatment prior to 13.5 to 14 years of age.(24,33) Providers should compare the physical and psychological benefits and risks of starting treatment versus delaying treatment.(24)
	  ○ It is not recommended to start hormone therapy prior to the onset of endogenous puberty(24,33)
	
	Testosterone is used for the treatment of GAHT in patients seeking masculinizing treatment. Injectable preparations are often used, but transdermal formulations (e.g., gels, creams, patches) and subcutaneous pellets may also be considered.(24,25) Injectable testosterone may be given intramuscularly or subcutaneously.(25,33) Oral dosage forms of testosterone may also be used.(26)
	
	Patients receiving testosterone should be evaluated for physical changes and adverse effects, as well as having serum testosterone levels monitored, every 3 months during the first year of hormone therapy or with dose changes. Once the patient has attained a stable adult maintenance dose, and serum testosterone levels are in the normal physiologic male range, evaluation and monitoring should be conducted once or twice a year.(24,33) Dosing should be adjusted to target serum levels within the normal range for the individual's gender identity.(24)

Safety	AndroGel, Fortesta, Testim, testosterone solution, and Vogelxo carry a boxed warning about secondary exposure to testosterone:(2,3,4,5,8,9) • Virilization has been reported in children who were secondarily exposed to testosterone gel. • Children should avoid contact with unwashed or unclothed application sites in men using testosterone gel. • Healthcare providers should advise patients to strictly adhere to recommended instructions for use.

	Aveed carries a boxed warning concerning serious pulmonary oil microembolism (POME) reactions and anaphylaxis:(20) • Serious POME reactions, involving urge to cough, dyspnea, throat tightening, chest pain, dizziness, and syncope; and episodes of anaphylaxis, including life-threatening reactions, have been reported to occur during or immediately after the administration of testosterone undecanoate injection. These reactions can occur after any injection of testosterone undecanoate during the course of therapy, including after the first dose. • Following each injection of Aveed, observe patients in the healthcare setting for 30 minutes in order to provide appropriate medical treatment in the event of serious POME reactions or anaphylaxis. • Aveed is available only through a restricted program called the Aveed REMS Program. Danazol carries boxed warnings for:(14) • Use of danazol in pregnancy is contraindicated. A sensitive test (e.g., beta subunit test if available) capable of determining early pregnancy is recommended immediately prior to start of therapy. Additionally, a non-hormonal method of contraception should be us ed during therapy. If a patient becomes pregnant while taking danazol, administration of the drug should be discontinued, and the patient should be apprised of the potential risk to the fetus. Exposure to danazol in utero may result in androgenic effects on the female fetus; reports of clitoral hypertrophy, labial fusion, urogenital sinus defect, vaginal atresia, and ambiguous genitalia have been received. • Thromboembolism, thrombotic and thrombophlebitic events including sagittal sinus thrombosis and life-threatening or fatal strokes have been reported. Experience with long-term therapy with danazol is limited. • Peliosis hepatis and benign hepatic adenoma have been observed with long-term use. Peliosis hepatis and hepatic adenoma may be silent until complicated by acute, potentially life-threatening intraabdominal hemorrhage. The physician therefore should be alert to this possibility. Attempts should be made to determine the lowest dose that will provide adequate protection. If the drug was begun at a time of exacerbation of hereditary angioneurotic edema due to trauma, stress or other cause, periodic attempts to decrease or withdraw therapy should be considered. • Danazol has been associated with several cases of benign intracranial hypertension also known as pseudotumor cerebri. Early signs and

	symptoms of benign intracranial hypertension include papilledema, headache, nausea and vomiting, and visual disturbances. Patients with these symptoms should be screened for papilledema and, if present, the patients should be advised to discontinue danazol immediately and be referred to a neurologist for further diagnosis and care. Jatenzo, Kyzatrex, Tlando, Undecatrex, and Xyosted carry a boxed warning for blood pressure increases:(7,12,17,43,44) • Can cause blood pressure (BP) increases that can increase the risk of major adverse cardiovascular events (MACE), including non-fatal myocardial infarction, non-fatal stroke and cardiovascular death. • Before initiating, consider the patient's baseline cardiovascular risk and ensure blood pressure is adequately controlled. • Periodically monitor for and treat new-onset hypertension or exacerbations of pre-existing hypertension and re-evaluate whether the benefits outweigh its risks in patients who develop cardiovascular risk factors or cardiovascular disease on treatment. • Due to this risk, use only for the treatment of men with hypogonadal conditions associated with structural or genetic etiologies. Androderm, Fortesta, Methitest, methyltestosterone capsules, Natesto, Testim, Testopel, testosterone solution, Vogelxo are contraindicated in:(1,4,5,6,8,9,10,11,19) • Men with carcinoma of the breast or known or suspected carcinoma of the prostate • Women who are pregnant AndroGel is contraindicated in:(2,3) • Men with carcinoma of the breast or known or suspected carcinoma of the prostate • Women who are pregnant ○ Pregnant women need to be aware of the potential for transfer of testosterone from men treated with AndroGel Aveed is contraindicated in:(20) • Men with carcinoma of the breast or known or suspected carcinoma of the prostate • Women who are pregnant

	• Men with known hypersensitivity to Aveed or any of its ingredients (testosterone undecanoate, refined castor oil, benzyl benzoate) Danazol is contraindicated in patients with:(14) • Undiagnosed abnormal genital bleeding • Markedly impaired hepatic, renal, or cardiac function • Pregnancy • Breast feeding • Porphyria • Androgen-dependent tumor • Active thrombosis or thromboembolic disease and history of such events • Hypersensitivity to danazol Depo-Testosterone is contraindicated in:(18) • Patients with a known hypersensitivity to the drug • Males with carcinoma of the breast • Males with known or suspected carcinoma of the prostate gland • Women who are pregnant • Patients with serious cardiac, hepatic or renal disease Jatenzo, Kyzatrex, Tlando, and Undecatrex are contraindicated in:(7,12,43,44) • Men with carcinoma of the breast or known or suspected carcinoma of the prostate • Women who are pregnant • Patients with known hypersensitivity to testosterone undecanoate or any ingredients in the product • Men with hypogonadal conditions, such as “age-related hypogonadism”, that are not associated with structural or genetic etiologies Testosterone enanthate is contraindicated in:(16) • Men with carcinoma of the breast or known or suspected carcinoma of the prostate • Women who are or may become pregnant • Patients with a history of hypersensitivity to any of its components Xyosted is contraindicated in:(17)

	• Men with carcinoma of the breast or known or suspected carcinoma of the prostate • Women who are pregnant • Men with hypersensitivity to Xyosted or any of its ingredients (testosterone enanthate and sesame oil) • Men with hypogonadal conditions, such as “age-related hypogonadism”, that are not associated with structural or genetic etiologies

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Prior Authorization with Quantity Limit - Through Generic	**TARGET AGENT(S)** **Androderm** (testosterone patch) **Androgel*** (testosterone gel) **Aveed** (testosterone undecanoate injection solution) **danazol capsule*** **Depo-Testosterone*** (testosterone cypionate injection solution) **Fortesta*** (testosterone gel) **Jatenzo** (testosterone undecanoate capsule) **Kyzatrex** (testosterone undecanoate capsule) **Methitest** (methyltestosterone tablet) **methyltestosterone capsule***

Module	Clinical Criteria for Approval
	Natesto (testosterone nasal gel) **Testim*** (testosterone gel) **Testopel** (testosterone pellet) **Testosterone Enanthate intramuscular injection solution** **testosterone topical solution*** **Tlando** (testosterone undecanoate capsule) **Undecatrex** (testosterone undecanoate capsule) **Vogelxo*** (testosterone gel) **Xyosted** (testosterone enanthate injection solution) * - generic available **Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. If the request is for Androderm, Androgel, Aveed, Fortesta, Jatenzo, Kyzatrex, Natesto, Testim, testosterone topical solution, Tlando, Undecatrex, Vogelxo, or Xyosted, the patient has a diagnosis of ONE of the following: 1. Primary or secondary (hypogonadotropic) hypogonadism **OR** 2. Gender dysphoria/gender incongruence **OR** B. If the request is for Depo-Testosterone or Testopel, the patient has a diagnosis of ONE of the following: 1. Primary or secondary (hypogonadotropic) hypogonadism **OR** 2. Delayed puberty in an adolescent **OR** 3. Gender dysphoria/gender incongruence **OR** C. If the request is for testosterone enanthate intramuscular injection solution, the patient has a diagnosis of ONE of the following: 1. Primary or secondary (hypogonadotropic) hypogonadism **OR** 2. Delayed puberty in an adolescent **OR** 3. Breast cancer **OR** 4. Gender dysphoria/gender incongruence **OR** D. If the request is for danazol, the patient has a diagnosis of ONE of the following: 1. Endometriosis amenable to hormone management **OR** 2. Hereditary angioedema and will be taking for the prevention of attacks **OR** 3. Myelofibrosis associated anemia **OR** E. If the request is for methyltestosterone or Methitest, the patient has a diagnosis of ONE of the following: 1. Primary or secondary (hypogonadotropic) hypogonadism **OR**

Module	Clinical Criteria for Approval
	2. Breast cancer **OR** 3. Delayed puberty in an adolescent **AND** 2. ONE of the following: A. If the request is for primary or secondary hypogonadism, then ONE of the following: 1. The patient is NOT currently receiving testosterone replacement therapy AND meets BOTH of the following: A. The patient has a sign or symptom of hypogonadism **AND** B. The patient has ONE of the following pretreatment levels: 1. Total serum testosterone level below the testing laboratory's normal range or is less than 300 ng/dL **OR** 2. Free serum testosterone level that is below the testing laboratory's normal range **OR** 2. The patient is currently receiving testosterone replacement therapy AND has ONE of the following current levels: A. Total serum testosterone level that is within OR below the testing laboratory's normal range OR is less than 300 ng/dL **OR** B. Free serum testosterone level that is within OR below the testing laboratory's normal range **OR** B. If the request is for gender dysphoria/gender incongruence, then ONE of the following: 1. The patient is an adolescent and ONE of the following: A. The patient is initiating sex hormone treatment AND ALL of the following: 1. A comprehensive biopsychosocial assessment has been conducted by a qualified physician AND the prescriber has consulted with other medical professionals (e.g., mental health professional, endocrinologist) when required **AND** 2. The parents or other caretakers or guardians were involved in the assessment process, unless their involvement has been determined to be harmful to the adolescent or not feasible **AND** 3. A persistent diagnosis of gender dysphoria/gender incongruence has been marked and sustained over time **AND** 4. ONE of the following: A. The patient is 16 years of age or over **OR** B. There is support for initiating therapy prior to 16 years of age **AND**

Module	Clinical Criteria for Approval
	5. The patient has been informed and counseled regarding effects and side effects of sex hormone treatment, including those which are irreversible, and the potential loss of fertility and options available to preserve fertility **AND** 6. The patient has sufficient emotional and cognitive maturity required to provide informed consent/assent for treatment **AND** 7. The patient has provided informed consent/assent for treatment AND, as applicable, the parents or other caretakers or guardians have provided consent to therapy **AND** 8. The patient's coexisting mental health concerns, physical conditions, or social problems that may interfere with diagnosing and/or sex hormone treatment have been addressed to provide optimal treatment **OR** B. The patient is continuing therapy with sex hormone treatment AND the patient is being monitored at least once per year **OR** 2. The patient is an adult AND ONE of the following: A. The patient is initiating sex hormone treatment AND ALL of the following: 1. A persistent diagnosis of gender dysphoria/gender incongruence has been marked and sustained over time **AND** 2. Other possible causes of apparent gender incongruence have been identified and excluded prior to initiation of treatment **AND** 3. The patient has been informed and counseled regarding effects and side effects of sex hormone treatment, including those which are irreversible, and the potential loss of fertility and options available to preserve fertility **AND** 4. The patient has sufficient emotional and cognitive maturity required to provide informed consent for treatment **AND** 5. The patient has provided informed consent for treatment **AND** 6. The patient's coexisting mental health and/or physical conditions that could have a negative impact on sex

Module	Clinical Criteria for Approval
	hormone treatment have been addressed, with risks and benefits discussed, to provide optimal treatment **OR** B. The patient is currently on sex hormone treatment and BOTH of the following: 1. ONE of the following: A. The patient's current testosterone level is ONE of the following: 1. Total serum testosterone level that is within OR below the testing laboratory's normal range for the patient's gender identity OR is less than 300 ng/dL **OR** 2. Free serum testosterone level that is within OR below the testing laboratory's normal range for the patient's gender identity **OR** B. There is support for continuing therapy with the patient's current testosterone level **AND** 2. The patient is being monitored at least once per year **OR** C. If the request is for delayed puberty in an adolescent, then ONE of the following: 1. The patient's sex is male **OR** 2. There is support that the requested agent is medically appropriate for the patient's sex **OR** D. If the request is for breast cancer, then ONE of the following: 1. BOTH of the following: 1. The patient is 1 to 5 years postmenopausal **AND** 2. The patient has inoperable metastatic breast cancer **OR** 2. ALL of the following: 1. The patient is premenopausal **AND** 2. The patient has benefitted from oophorectomy **AND** 3. The patient has a hormone-responsive tumor **OR** E. The request is for endometriosis amenable to hormone management **OR** F. The request is for the prevention of attacks of hereditary angioedema **OR** G. If the request is for myelofibrosis associated anemia, then ONE of the following: 1. The patient has a serum erythropoietin (EPO) greater than or equal to 500 mU/mL **OR** 2. The patient has a serum erythropoietin (EPO) less than 500 mU/mL and had no response or loss of response to an erythropoiesis-stimulating agent (ESA) **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **AND**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>4. If the request is for one of the following brand agents, then ONE of the following:

<table>
<tr><th>Brand Agent(s)</th></tr>
<tr><td>Androderm

Androgel

Aveed

Fortesta, Testosterone gel

Jatenzo

Kyzatrex

Methitest

Natesto

Testim

Testopel

Tlando

Undecatrex

Vogelxo, Testosterone gel

Xyosted</td></tr>
</table>

A. The patient has tried and had an inadequate response to a generic androgen or anabolic steroid agent that is supported for use for the requested indication OR
B. The patient has an intolerance or hypersensitivity to a generic androgen or anabolic steroid agent that is supported for use for the requested indication that is not expected to occur with the brand agent OR</td></tr>
</table>

Module	Clinical Criteria for Approval
	C. The patient has an FDA labeled contraindication to ALL generic androgen or anabolic steroid agents that is supported for use for the requested indication that is not expected to occur with the brand agent **AND** 5. ONE of the following: A. The patient will NOT be using the requested agent in combination with another androgen or anabolic steroid agent for the requested indication **OR** B. There is support for therapy with more than one androgen or anabolic steroid agent **Length of Approval:** 6 months (delayed puberty only), 12 months (all other indications) NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. ONE of the following: A. The patient has a diagnosis of primary or secondary hypogonadism and the patient's current testosterone level is ONE of the following: 1. Total serum testosterone level that is within OR below the testing laboratory's normal range OR is less than 300 ng/dL **OR** 2. Free serum testosterone level that is within OR below the testing laboratory's normal range **OR** B. The patient has a diagnosis of gender dysphoria/gender incongruence AND ONE of the following: 1. If the patient is an adult, then BOTH of the following: A. The patient is being monitored at least once per year **AND** B. ONE of the following: 1. The patient's current testosterone level is ONE of the following: A. Total serum testosterone level that is within OR below the testing laboratory's normal range for the patient's gender identity OR is less than 300 ng/dL **OR**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
B. Free serum testosterone level that is within OR below the testing laboratory's normal range for the patient's gender identity OR
2. There is support for continuing therapy with the patient’s current testosterone level OR
2. If the patient is an adolescent, the patient is being monitored at least once per year OR
C. The patient has a diagnosis other than primary or secondary hypogonadism or gender dysphoria/gender incongruence AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent AND
5. If the request is for one of the following brand agents, then ONE of the following:
<table>
<tr><th>Brand Agent(s)</th></tr>
<tr><td>Androderm

Androgel

Aveed

Fortesta, Testosterone gel

Jatenzo

Kyzatrex

Methitest

Natesto

Testim

Testopel

Tlando

Undecatrex</td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval
	Vogelxo, Testosterone gel Xyosted A. The patient has tried and had an inadequate response to a generic androgen or anabolic steroid agent that is supported for use for the requested indication **OR** B. The patient has an intolerance or hypersensitivity to a generic androgen or anabolic steroid agent that is supported for use for the requested indication that is not expected to occur with the brand agent **OR** C. The patient has an FDA labeled contraindication to ALL generic androgen or anabolic steroid agents that is supported for use for the requested indication that is not expected to occur with the brand agent **AND** 6. ONE of the following: 1. The patient will NOT be using the requested agent in combination with another androgen or anabolic steroid agent for the requested indication **OR** 2. There is support for therapy with more than one androgen or anabolic steroid agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Ops Set Up	Validation Options	Other Explanation
Prior Authorization with Quantity Limit - Through Generic	Validation: Apply Baseline and go to Validation Options	Contraind., intolerance, or hypersensitivity to prereq.;Other (see Other explanation field);Prerequisites	*Review info: There is support that the requested agent is medically appropriate for the patient's sex *Gender dysphoria/gender incongruence: - For adolescents, verify patient age (greater than/less than 16 years old)

Module	Ops Set Up	Validation Options	Other Explanation
			- Review info: Support for initiating therapy if adolescent is less than 16 years old *Review info: Support of therapy with more than one androgen or anabolic steroid agent *Review info: Support of continuing therapy with the patient's testosterone level

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Anti-COVID19

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Lagevrio™ (molnupiravir) Capsule	Emergency Use Authorization (EUA) for the treatment of mild-to-moderate COVID-19 in adults: • Who are at high risk for progression to severe COVID-19, including hospitalization or death, and for • Whom alternative COVID-19 treatment options authorized by FDA are not accessible or clinically appropriate Limitations of Authorized Use: • Not authorized for use in patients less than 18 years of age • Not authorized for initiation of treatment in patients requiring hospitalization due to COVID-19. Benefit of treatment with Lagevrio has not been observed in subjects when treatment was initiated after hospitalization due to COVID-19 • Not authorized for use longer than 5 consecutive days • Not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19		1
Paxlovid™ (nirmatreivir/ritonavir) Tablet	Treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalization or death Limitations of Use:		2,6

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Paxlovid is not approved for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19 Paxlovid is approved through an Emergency Use Authorization (EUA) for the treatment of mild-to-moderate COVID-19 in pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death Limitations of Authorized Use: • Paxlovid is not authorized for initiation of treatment in patients requiring hospitalization due to severe or critical COVID-19 • Paxlovid is not authorized for pre-exposure or post-exposure prophylaxis for prevention of COVID-19 • Paxlovid is not authorized for use longer than 5 consecutive days		

CLINICAL RATIONALE

COVID-19	Data currently indicates that prior infection with COVID-19 does provide some protection from reinfection. Some studies find that prior infection reduces the risk of infection by 80-85% for 6-7 months.(3,4) Others find that reinfections are rare events and that persons there is minimal risk of reinfection for at least 8 months after the primary infection.(5)
Safety	Molnupiravir has no FDA labeled contraindications for use based on the limited available data on the emergency use molnupiravir authorized under the EUA.(1) Nirmatrelvir tablets; ritonavir tablets are contraindicated in the following:(2,6) • History of clinically significant hypersensitivity reactions to the active ingredients (nirmatrelvir or ritonavir) or any other components

	• Co-administration with drugs highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions • Co-administration with potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance Nirmatrelvir tablets; ritonavir tablets have a boxed warning:(2,6) • Paxlovid includes ritonavir, a strong CYP3A inhibitor, which may lead to greater exposure of certain concomitant medications, resulting in potentially severe, life-threatening, or fatal events • Prior to prescribing Paxlovid: 1) review all medication taken by the patient to assess potential drug-drug interactions with strong CYP3A inhibitor like Paxlovid and 2) determine if concomitant medications require and dose adjustment, interruption, and/or additional monitoring • Consider the benefit of Paxlovid treatment in reducing hospitalization and death, and whether the risk of potential drug-drug interactions for an individual patient can be appropriately managed

REFERENCES

Number	Reference
1	Lagevrio Fact Sheet for Healthcare Providers: Emergency Use Authorization for Lagevrio. Merck Sharp & Dohme LLC. October 2023.
2	Paxlovid Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid. Pfizer Labs. November 2023. https://labeling.pfizer.com/ShowLabeling.aspx?id=16474&format=pdf.
3	Hall VJ, Foulkes S, Charlett A, et al. SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN). Lancet. 2021;397(10283):1459. Epub 2021 Apr 9.
4	Hansen CH, Michlmayr D, Gubbels SM, et al. Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. Lancet. 2021;397(10280):1204. Epub 2021 Mar 17.

Number	Reference
5	Leidi A, Koegler F, Dumont R, et al. SEROCoV-POP study group, Risk of Reinfection After Seroconversion to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): A Population-based Propensity-score Matched Cohort Study. *Clinical Infectious Diseases*, February 2022, Pages 622-629, https://doi.org/10.1093/cid/ciab495
6	Paxlovid prescribing information. Pfizer Laboratories Division of Pfizer Inc. May 2023.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ALL of the following are met: 1. The patient is using the requested agent for a COVID-19 reinfection **AND** 2. The patient's age is within FDA labeling OR Emergency Use Authorization (EUA) for the requested indication for the requested agent **AND** 3. The requested agent is NOT being used to extend treatment beyond the maximum FDA labeling OR EUA treatment regimen for the requested indication **AND** 4. The patient will NOT be using the requested agent in combination with another agent in this program for the requested indication **AND** 5. The requested quantity (dose) does NOT exceed the maximum FDA labeling OR EUA dosing for the requested indication **Length of Approval:** 1 additional course of therapy for 1 month

Antidepressant

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Aplenzin® (bupropion extended release) Tablet	Treatment of: - Major Depressive Disorder (MDD) - Seasonal Affective Disorder (SAFD)		22
Auvelity® (dextromethorphan hbr-bupropion hcl tab er) Tablet	Treatment of Major Depressive Disorder (MDD) in adults		29
Celexa® (citalopram)* Tablet Oral solution	Treatment of depression	*generic available	1, 2
Citalopram Capsule	Treatment of Major Depressive Disorder (MDD) in adults		4
Cymbalta® (duloxetine delayed release) Capsule*	Treatment of: - Major Depressive Disorder (MDD) - Generalized Anxiety Disorder (GAD) in adults and pediatric patients 7 years of age and older - Diabetic Peripheral Neuropathic Pain (DPNP) in adults	*generic available	13

Agent(s)	FDA Indication(s)	Notes	Ref#
	- Fibromyalgia (FM) in adults and pediatric patients 13 years of age and older - Chronic Musculoskeletal Pain (CMP) in adults		
Desvenlafaxine ER Tablet	Treatment of Major Depressive Disorder (MDD)		18
Drizalma Sprinkle™ (duloxetine DR) Capsule	Treatment of: -Major Depressive Disorder (MDD) in adults -Generalized Anxiety Disorder (GAD) in adults and pediatric patients ages 7 years of age and older -Diabetic Peripheral Neuropathic Pain (DPNP) in adults -Fibromyalgia (FM) in adults -Chronic Musculoskeletal Pain in adults		5
Effexor XR® (venlafaxine extended release) Capsule*	Treatment of: - Major Depressive Disorder (MDD) - Panic Disorder (MDD) - Generalized Anxiety Disorder (GAD) - Social Anxiety Disorder (SAD)	*generic available	16
Fetzima® (levomilnacipran ER) Capsule	Treatment of Major Depressive Disorder (MDD) in adults Limitation of Use: Fetzima is not approved for the management of fibromyalgia. The efficacy and safety of Fetzima for the management of fibromyalgia have not been established.		17
Fluoxetine 60 mg Tablet*	Treatment of: - Major Depressive Disorder (MDD) - Obsessive Compulsive Disorder (OCD) - Bulimia Nervosa	*generic available	3

Agent(s)	FDA Indication(s)	Notes	Ref#
	- Panic Disorder (PD), with or without agoraphobia		
Fluoxetine Delayed Release Capsule	Acute and maintenance treatment of Major Depressive Disorder (MDD)		10
Prozac® (fluoxetine)* Tablet Capsule Oral solution	Treatment of: - Acute and maintenance treatment of Major Depressive Disorder (MDD) - Acute and maintenance treatment of Obsessive Compulsive Disorder (OCD) - Acute and maintenance treatment of Bulimia Nervosa - Acute treatment of Panic Disorder (PD), with or without agoraphobia	*generic available	11
Forfivo XL® (bupropion extended release) Tablet	Treatment of Major Depressive Disorder (MDD)		23
Lexapro® (escitalopram)* Tablet Oral suspension	Treatment of: - Major Depressive Disorder (MDD) in adults and pediatric patients 12 years of age and older - Generalized Anxiety Disorder (GAD) in adults and pediatric patients 12 years of age and older	*generic available	6
Paxil® (paroxetine)* Tablet Oral suspension	Treatment of: - Major Depressive Disorder (MDD) - Obsessive Compulsive Disorder (OCD)	*generic available	7

Agent(s)	FDA Indication(s)	Notes	Ref#
	- Panic Disorder (PD) - Generalized Anxiety Disorder (GAD) - Social Anxiety Disorder (SAD) - Post-Traumatic Stress Disorder (PTSD)		
Paxil CR® (paroxetine extended release) Tablet*	Treatment of: - Major Depressive Disorder (MDD) - Panic Disorder (PD) - Social Anxiety Disorder (SAD) - Premenstrual Dysphoric Disorder (PMDD)	*generic available	8
Pexeva® (paroxetine mesylate) Tablet	Treatment of: - Major Depressive Disorder (MDD) - Obsessive Compulsive Disorder (OCD) - Panic Disorder (PD) - Generalized Anxiety Disorder (GAD)		9
Pristiq® (desvenlafaxine succinate extended release) Tablet*	Treatment of Major Depressive Disorder (MDD)	*generic available	20
Remeron SolTab® (mirtazapine ODT) Orally disintegrating tablet*	Treatment of Major Depressive Disorder (MDD)	*generic available	25

Agent(s)	FDA Indication(s)	Notes	Ref#
Remeron® (mirtazapine) Tablet*	Treatment of Major Depressive Disorder (MDD)	*generic available	25
Sertraline Capsule	Treatment of: - Major depressive disorder (MDD) in adults - Obsessive-compulsive disorder (OCD) in adults and pediatric patients 6 years and older		24
Trintellex® (vortioxetine) Tablet	Treatment of Major Depressive Disorder (MDD)		27
Venlafaxine besylate ER Tablet	Treatment of: - Major Depressive Disorder (MDD) - Social Anxiety Disorder (SAD)		21
Viibryd® (vilazodone) Tablet*	Treatment of Major Depressive Disorder (MDD)	*generic available	28
Wellbutrin SR® (bupropion sustained release) Tablet*	Treatment of Major Depressive Disorder (MDD)	*generic available	30
Wellbutrin XL® (bupropion extended release)	Treatment of: - Major Depressive Disorder (MDD) - Seasonal Affective Disorder (SAFD)	*generic available	31

Agent(s)	FDA Indication(s)	Notes	Ref#
Tablet*			
Zoloft® (sertraline)* Tablet Oral concentrate	Treatment of: - Major Depressive Disorder (MDD) - Obsessive Compulsive Disorder (OCD - Panic disorder (PD) - Post-traumatic stress disorder (PTSD) - Social anxiety disorder (SAD) - Premenstrual dysphoric disorder (PMDD)	*generic available	12

CLINICAL RATIONALE

Depression	Selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, mirtazapine, and several newer agents are typically used as first-line medications because their safety and tolerability may be preferable to patients and clinicians compared to those of tricyclic antidepressants (TCAs) and monoamine oxidase (MAO) inhibitors(32). Many clinical features and medication characteristics influence the choice of a first-line antidepressant. There are no absolutes, and relative differences between medications are small, hence, selecting an antidepressant involves an individualized needs assessment for each patient(33). No antidepressant has been clearly shown to be superior to another. All FDA-approved antidepressant medications should be considered potentially appropriate for first-line treatment(32).
Anxiety Disorders	Guidelines for treatment of anxiety include several anxiety-related conditions: generalized anxiety disorder (GAD), panic disorder (PD), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), and social anxiety disorder (SAD). SSRIs are generally considered first-line therapy for GAD and PD. In the treatment of PD, TCAs are as effective as SSRIs, but adverse effects may limit the use of TCAs in some patients. Extended-release venlafaxine is effective and well tolerated for GAD and PD, whereas duloxetine has been adequately evaluated only for GAD. Due to the typical delay in onset of action, medications should not be considered ineffective until they are titrated to the

	high end of the dose range and continued for at least four weeks. Once symptoms have improved, medications should be used for 12 months before tapering to limit relapse. Some patients will require longer treatment(34). OCD has a highly selective response to serotonergic medications. SSRIs are preferred for initial therapy. There is insufficient evidence to show that one SSRI is superior, and the choice should be individualized, taking into account potential drug interactions and tolerability. Dosage should be increased over four to six weeks until maximum dose is achieved. Trial of therapy should continue for eight to 12 weeks, with at least four to six weeks at the maximum tolerable dosage. It usually takes at least four to six weeks for patients to note any significant improvement in symptoms; it may take 10 weeks or longer for some. If successful, medication should be continued for at least one to two years, if not indefinitely(35). Among adult patients with PTSD, fluoxetine, paroxetine, sertraline, and venlafaxine are appropriate choices, with none showing improved efficacy over the others(36). For SAD, SSRIs and SNRIs venlafaxine are the clear first-line pharmacotherapy treatment based on demonstrated efficacy in randomized controlled trials and meta-analyses. Medications in these classes that have been FDA-approved in the U.S. are paroxetine (immediate-release and controlled release), sertraline, fluvoxamine controlled release, and venlafaxine extended release. Other medications in these classes with evidence of efficacy from randomized controlled trials include citalopram, escitalopram, and vilazodone. Fluoxetine has had mixed results in randomized controlled trials. SNRIs should be used with caution in patients at risk for suicide due to greater toxicity in overdose. No individual medication within this class has been consistently shown to be superior to another in this class(37).
Neuropathic Pain	First-line treatment for neuropathic pain include TCAs, gabapentin, pregabalin, and SNRI antidepressants (duloxetine [most studied], venlafaxine) as first-line therapies(38). For patients with diabetic neuropathy, only two medications, pregabalin and duloxetine, have been approved by the FDA. However, in addition to those two medications, gabapentin and amitriptyline are considered first-line therapy. SNRIs such as venlafaxine and desvenlafaxine are considered second-line therapy. SSRIs such as citalopram, paroxetine, and escitalopram are considered third-line therapy(39).
Fibromyalgia	Pharmaceutical therapy recommendations depend on the source of the guideline. Guidelines are available from the European League Against Rheumatism (EULAR-2016), the Canadian Pain Society (2012) and the Association of the Scientific Medical Societies in Germany (AWMF-2012). Recommendations from these guidelines include amitriptyline, pregabalin, gabapentin, SNRIs (including duloxetine and milnacipran), and SSRIs. Amitriptyline, pregabalin, and duloxetine are used most commonly(40).

Chronic Musculoskeletal Pain	Antidepressants are options for the treatment of chronic pain. Meta-analyses of randomized controlled trials indicate that TCAs and SNRIs provide effective pain relief for a variety of chronic pain etiologies(41). Duloxetine is FDA approved for chronic musculoskeletal pain(13).
Safety	All of the above listed agents have had a black box warning issued by the FDA. The warning concerns suicidal thoughts and behaviors. Since there are small differences between the warnings, they are not listed here. Please see the respective agent's prescribing information for the warning(1-14,16-18,20-31).

REFERENCES

Number	Reference
1	Celexa prescribing information. Allergan USA, Inc. August 2023.
2	Citalopram solution prescribing information. Aurobindo Pharma Limited. August 2023.
3	Fluoxetine 60 mg tablet prescribing information. Nivagen Pharmaceuticals, Inc. June 2021.
4	Citalopram capsule prescribing information. Almatica Pharma, LLC. August 2023.
5	Drizalma Sprinkle prescribing information. Sun Pharmaceutical Industries Limited. July 2021.
6	Lexapro prescribing information. AbbVie, Inc. August 2023.
7	Paxil prescribing information. GlaxoSmithKline. August 2023.
8	Paxil CR prescribing information. Apotex Corp. August 2023.
9	Pexeva prescribing information. Sebela Pharmaceuticals, Inc. August 2023.
10	Fluoxetine delayed release capsule prescribing information. Dr. Reddy's Laboratories Limited. July 2023.
11	Prozac prescribing information. Eli Lilly and Company. August 2023.
12	Zoloft prescribing information. Pfizer, Inc. August 2023.

Number	Reference
13	Cymbalta prescribing information. Eli Lilly and Company. August 2023.
14	Reference No Longer Used
15	Reference No Longer Used
16	Effexor XR prescribing information. Pfizer, Inc. August 2023.
17	Fetzima prescribing information. Allergan USA, Inc. August 2023.
18	Desvenlafaxine ER prescribing information. Alembic Pharms LTC. September 2021.
19	Reference No Longer Used
20	Pristiq prescribing information. Pfizer, Inc. August 2023.
21	Venlafaxine besylate ER tablets prescribing information. Almatica Pharma LLC. March 2022.
22	Aplenzin prescribing information. Valeant Pharmaceuticals North America, LLC. March 2022.
23	Forfivo prescribing information. Almatica Pharma, Inc. December 2019.
24	Sertraline prescribing information. Almatica Pharma LLC. October 2021.
25	Remeron prescribing information. Merck & Co, Inc. November 2021.
26	Remeron SolTab prescribing information. Merck & Co, Inc. November 2021.
27	Trintellix prescribing information. Takeda Pharmaceuticals America, Inc. August 2023.
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ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
58060090000130	Zurzuvae	zuranolone cap	30 MG	*Quantity limit is cumulative across all strengths. 30 mg will be limited to a maximum of 14 per 365.			
580600900001	Zurzuvae 20 MG, Zurzuvae 25 MG	zuranolone cap 20 MG, zuranolone cap 25 MG	20 MG ; 25 MG ; 30 MG	*Quantity limit is cumulative for the 20mg and 25 mg strengths.		11-17-2023	

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Antiemetic

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Akynzeo® (netupitant/palonosetron) Capsule	• In combination with dexamethasone in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy		1
Anzemet® (dolasetron) Tablet	• Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy, including initial and repeat courses in adults and children 2 years of age and older		2

Emend®
 	
(aprepitant)
 	
Capsule*
 	
Oral suspension
	Emend capsules
	
	• In combination with other antiemetic agents, in patients 12 years of age and older for the prevention of:
	  ○ Acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy (HEC) including high-dose cisplatin
	  ○ Nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)
	
	Emend oral suspension
		*generics available	3

Agent(s)	FDA Indication(s)	Notes	Ref#

	• In combination with other antiemetic agents, in patients 6 months of age and older for the prevention of:
	  ○ Acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin
	  ○ Nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC)
	
	Limitations of use:
	
	• Emend has not been studied for treatment of established nausea and vomiting
	• Chronic continuous administration of Emend is not recommended		

granisetron** Tablet	• Prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high dose cisplatin • Prevention of nausea and/or vomiting associated with radiotherapy	**available as generic only	4
ondansetron** Tablet Oral disintegrating tablet Oral solution	• Prevention of nausea and vomiting associated with highly emetogenic cancer chemotherapy, including cisplatin greater than or equal to 50 mg/m^2 • Prevention of nausea and/or vomiting associated with initial and repeat courses of moderately emetogenic cancer therapy • Prevention of nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen	** available as generic only	7, 15

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Prevention of postoperative nausea and/or vomiting		
Sancuso® (ganisetron) Transdermal patch	• Prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy for up to 5 consecutive days		5
Varubi® (rolapitant) Tablet	• Used in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy		6

CLINICAL RATIONALE

Guidelines	Multiple randomized clinical trials along with current guidelines in antiemesis demonstrate that granisetron (oral and injectable), ondansetron (oral and injectable), palonosetron (injectable), and dolasetron (oral) are largely therapeutically equivalent and considered first line treatment for chemotherapy induced nausea and vomiting (CINV), radiation induced nausea and vomiting (RINV) and postoperative nausea and vomiting (PONV) and are associated with relatively few mild adverse events.(9-11)
Chemotherapy and Radiation Therapy Induced Nausea and Vomiting	Nausea and vomiting caused by anticancer agents and/or radiation therapy (RT) can have significant impact on a patient's quality of life, leading to poor compliance with further anticancer agents and/or RT. In addition, nausea and/or vomiting can result in dehydration, metabolic imbalances, degeneration of self-care and functional ability, nutrient depletion, anorexia, decline of the patient's performance status and mental status, wound dehiscence, esophageal tears, and withdrawal from potentially useful or curative anticancer treatment.(10) The incidence and severity of nausea and/or vomiting in patients receiving anticancer agents and/or RT are affected by several factors including specific chemotherapy agents, dose, route of administration, schedule of administration,

	radiation target, and patient variability (age, sex, prior chemotherapy, history of alcohol use, etc.). In highly emetogenic regimens more than 90% of patients will experience episodes of vomiting but only about 30% will do so when given antiemetic prophylactic therapy.(10) Vomiting is triggered by afferent impulses to the vomiting center from the chemoreceptor trigger zone, pharynx and gastrointestinal tract (GI), and cerebral cortex. The principal chemoreceptors involved in the emetic response are the serotonin and dopamine receptors. Additional neuroreceptors stimulated include acetylcholine, corticosteroid, histamine, cannabinoid, opioid, and neurokinin-1 receptors. Due to the variety of receptors involved and no final common pathway for emesis identified, multiple agents are used to block different pathways to provide a synergistic effect in an antiemesis prophylactic regimen.(10) There are several identified classes of CINV including acute onset (typically occurs within the first few minutes to hours after chemotherapy administration), delayed onset (occurs more than 24 hours after chemotherapy dosing), anticipatory (occurs prior to chemotherapy administration and is considered a conditioned response), breakthrough (occurs despite prophylactic treatment and requires “rescue” antiemetic agents), and refractory (occurs during subsequent chemotherapy treatment cycles despite prophylactic and rescue therapy).(10) National Comprehensive Cancer Network (NCCN) Guidelines recommend antiemetic therapy begins prior to chemotherapy and continues for the same length of time as the duration of the emetic activity of the drug given. The frequency of chemotherapy induced emesis depends mostly on the potential for the regimen to cause nausea and vomiting. Many chemotherapy regimens have been categorized by their potential to cause emesis. The classification (i.e., high, moderate, low, minimal) is based on the percentage of patients that experience acute emesis. High emetogenic risk is defined as 90% or more of patients, moderate risk has 30%-90% of patients, low risk is between 10% and 30% of patients, and minimal risk is less than 10% of patients experience acute emesis.(10) The American Society of Clinical Oncology (ASCO) Practice Guidelines for Antiemetics in Oncology recommends that for patients who receive high-risk radiation therapy, patients receive a 5-HT3 antagonist before each radiation fraction and at least 24 hours after completing radiation therapy. Patients should also be given a five-day course of dexamethasone during fractions one to five.(9)

NCCN recommends starting pretreatment for each day of radiation therapy treatment with either granisetron or ondansetron, with or without dexamethasone.(10)

NCCN suggests when a serotonin (5-HT3) antagonist is used as part of an antiemetic regimen that does not include an NK-1 antagonist, either palonosetron or granisetron extended-release injection is the preferred 5-HT3 antagonist compared to the other 5-HT3 antagonists [i.e., ondansetron, granisetron (tablets, intravenous injection), dolasetron], due to longer half-life and prolonged inhibition of the 5-HT3 receptor.(10)

NCCN and ASCO recommend the following for CINV and RINV:(9-10)

Emetic Risk	Antiemetic Therapy
IV Chemotherapy Acute and Delayed Emesis Prevention	
High Emetic Risk	olanzapine + NK-1RA + 5-HT3 + DEX (preferred)
	olanzapine + palonosetron IV +DEX
	NK-1RA + 5-HT3 + DEX
Moderate Emetic Risk	5-HT3 + DEX
	NK-1RA + 5-HT3 + DEX
	olanzapine + palonosetron IV +DEX
Low Emetic Risk	DEX
	metoclopramide
	prochlorperazine
	5-HT3 (excluding palonosetron IV)
Minimal Emetic Risk	No routine prophylaxis
Oral Chemotherapy Acute and Delayed Emesis Prevention	
High to Moderate Emetic Risk	Oral 5-HT3
Low to Minimal Emetic Risk (PRN recommended)	Oral 5-HT3
	metoclopramide
	prochlorperazine
Breakthrough Treatment	
Breakthrough Treatment	olanzapine (atypical antipsychotic)

	Add one agent from a different drug class to the current regimen	(preferred)
		dolasetron, granisetron, ondansetron (5-HT3)
		lorazepam (benzodiazepine)
		dronabinol, nabilone (cannabinoid)
		DEX (steroid)
		prochlorperazine, promethazine (phenothiazine)
		haloperidol, metoclopramide, scopolamine patch (other)
	Radiation-induced	
	Radiation therapy – upper abdomen/localized sites	Oral granisetron ± DEX
		Oral ondansetron ± DEX
	Total body irradiation	Oral granisetron ± DEX
		Oral ondansetron ± DEX
	Chemotherapy and radiation therapy	See emesis prevention for chemotherapy-induced nausea/vomiting
	Pediatric patients	
	High emetic risk	5-HT3 + DEX + aprepitant
		5-HT3 + DEX + fosaprepitant
		5-HT3 + DEX
		palonosetron + aprepitant
		palonosetron + fosaprepitant
	Moderate emetic risk	5-HT3 +DEX
		5-HT3 +aprepitant
		5HT-3 + fosaprepitant
	Low emetic risk	ondansetron
		granisetron
	Minimal emetic risk	Should not be offered routine antiemetic prophylaxis

NK-1RA (aprepitant, fosaprepitant, netupitant, rolapitant) = neurokinin 1 antagonist; 5-HT3 = Serotonin 5-HT3 antagonist (dolasetron, granisetron, ondansetron, palonosetron IV); DEX = dexamethasone

In a comparative clinical trial, the granisetron transdermal patch was shown to be non-inferior to oral granisetron in the prevention of nausea and vomiting.(4) The granisetron transdermal patch must be applied 24-48 hours

	before the start of chemotherapy. Patients often have blood counts tested on the day of chemotherapy and if they do not qualify for chemotherapy that day, the patch may be wasted. The manufacturer of the granisetron patch does provide free replacement patches to patients that waste one.(5)
Postoperative Nausea and Vomiting	Nausea and vomiting are two of the most common adverse events in the postoperative period with an estimated incidence of 30% in the general surgical population and as high as 80% in high risk patients. Unresolved postoperative nausea and vomiting (PONV) is a highly distressing experience and may result in prolonged post anesthesia care unit stay and unanticipated hospital admission that leads to a significant increase in overall health care costs. The goal of PONV prophylaxis is to decrease the incidence of PONV, patient-related distress, and health-care costs.(11) Optimal management of PONV is a complex process. There are numerous antiemetics with varying pharmacokinetics, efficacy, and side-effect profiles, thus the choice of an antiemetic will depend on the clinical context. The benefit of PONV prophylaxis also needs to be balanced with the risk of adverse effects. At an institutional level, the management of PONV is also influenced by factors such as cost-effectiveness, drug availability, and drug formulary decisions.(11) The Society for Ambulatory Anesthesiology has published Consensus Guidelines for the management of postoperative nausea and vomiting. The goals of these guidelines include:(11) • Identification of reliable predictors of PONV risks in adults and postoperative vomiting in children • Establishment of interventions which reduce baseline risks for PONV • Identify the most effective antiemetic single therapy and combination therapy regimens for PONV prophylaxis • Evaluation of the efficacy of PONV and post-discharge nausea and vomiting (PDNV) treatment with or without prior PONV prophylaxis • Determination of the optimal dosing and timing of antiemetic prophylaxis • Appraisal of the cost-effectiveness of PONV management strategies • Creating an algorithm to summarize the risk stratification, risk reduction, prophylaxis, and treatment of PONV • Evaluating the management of PONV recovery pathways • Proposal of a research agenda for future studies Risk for PONV in adults can be identified using an assessment called Apfel's simplified risk score for identification of high-risk patients. Patients are given 1 point for each of the following when met:(11)

	• Female gender • Non-smoker • History of PONV and/or motion sickness • Postoperative opioids A score of 0, 1, 2, 3, and 4 correlates with an approximate risk of PONV of 10%, 20%, 40%, 60% and 80% respectively. Patients with a score of 0-1 are classified as low risk, a score of 2 is medium risk, and a score of 3-4 indicates high risk.(11) Risk for PDNV in adults can also be assessed using an assessment also by Apfel et al. Patients are given 1 point for each of the following when met:(11) • Female gender • History of PONV • Age less than 50 • Use of opioids in postanesthesia care unit (PACU) • Nausea in PACU A score of 0, 1, 2, 3, 4, or 5 correlates with an approximate risk of PDNV of 10%, 20%, 30%, 50%, 60%, and 80% respectively.(11) The risk factors for POV/PONV in children are different from those in adults. Pediatric patients are evaluated using a Simplified Risk Score from Eberhart et al. Similar to the adult risk factor assessments, patients are given 1 point for each risk factor met.(11) • Surgery greater than or equal to 30 minutes • Age greater than or equal to 3 years • Strabismus surgery • History of POV or family history of PONV A score of 0, 1, 2, 3, or 4 correlates with an approximate risk of POV of 10%, 10%, 30%, 50%, and 70% respectively.(11) The guidelines recommend the use of multimodal prophylaxis in patients with one or more risk factors for PONV. Patients with 1-2 risk factors for PONV should receive 2 agents for prophylaxis of PONV and patients with greater than 2 risk factors should receive 3-4 agents for prophylaxis. Ondansetron is the most commonly used and studied 5-HT_3 receptor antagonist and is considered the gold standard in PONV management.(11)

	There is not sufficient evidence for the guidelines to guide the clinician to select the most effective individual antiemetic over other combination therapies with the exception of using agents from a different pharmacologic class. Recommended agents for adults and children (listed in alphabetical order) are the following: (Please note: Not all products are available in the United States and not all products are FDA labeled for PONV)(11) Adults • Amisulpride (IV) • Aprepitant (oral) • Casopitant (oral) • Dexamethasone (IV) • Dimenhydrinate (IV) • Dolasetron (IV) • Droperidol (IV) • Ephedrine (IM) • Granisetron (IV) • Haloperidol (IM/IV) • Methylprednisolone (IV) • Metoclopramide (oral) • Ondansetron (IV or oral disintegrating tablet) • Palonosetron (IV) • Perphenazine (IV) • Promethazine (oral) • Ramosetron (IV) • Rolapitant (oral) • Scopolamine (transdermal patch) • Tropisetron (IV) Pediatrics • Aprepitant (IV) • Dexamethasone (IV) • Dimenhydrinate (IV) • Dolasetron (IV) • Droperidol (IV) • Granisetron (IV) • Ondansetron (IV) • Palonosetron (IV) • Tropisetron (IV)

Nausea and Vomiting of Pregnancy(12)	American College of Obstetricians and Gynecologists (ACOG, 2018) recommends the following for nausea and vomiting during pregnancy:(12) • Taking prenatal vitamins for one month before conception may reduce the incidence and severity of nausea and vomiting of pregnancy • Treatment of nausea and vomiting of pregnancy with vitamin B6 or vitamin B6 plus doxylamine is safe and effective and should be considered first-line pharmacotherapy. Medications for which there are some safety data and evidence of efficacy include anticholinergics and metoclopramide. Evidence is limited on the safety or efficacy of the 5-HT3 inhibitors (e.g., ondansetron) for nausea and vomiting of pregnancy; however, because of their effectiveness in reducing chemotherapy-induced emesis, their use appears to be increasing.

Safety	• **Akynzeo** (netupitant and palonosetron) has no FDA labeled contraindications(1)
	• **Anzemet** (dolasetron mesylate) is contraindicated in:(2)
	  ○ Patients known to have hypersensitivity to the drug
	• **Emend** (aprepitant) is contraindicated in:(3)
	  ○ Known hypersensitivity to any component of this drug
	  ○ Concurrent use with pimozide
	• **Granisetron** is contraindicated in:(4)
	  ○ Patients with known hypersensitivity to the drug or any of its components
	• **Sancuso** (granisetron) is contraindicated in:(5)
	  ○ Known hypersensitivity to granisetron or to any of the components of the transdermal system
	• **Varubi** (rolapitant) is contraindicated in:(6)
	  ○ Use with CYP2D6 substrates with narrow therapeutic index (e.g., thioridazine and pimozide)
	  ○ Pediatric patients less than two years of age because of irreversible impairment of sexual development and fertility in juvenile rats
	• **ondansetron** is contraindicated in:(7,15)
	  ○ Patients known to have hypersensitivity (e.g., anaphylaxis) to ondansetron or any components of the formulation
	  ○ Concomitant use of apomorphine

REFERENCES

Number	Reference
1	Akynzeo prescribing information. Helsinn Therapeutics, Inc. December 2023.
2	Anzemet prescribing information. Validus Pharmaceuticals, LLC. December 2023.
3	Emend prescribing information. Merck, Sharp & Dohme, LLC. December 2023.
4	Granisetron (tablets) prescribing information. Natco Pharma Limited. October 2019.
5	Sancuso prescribing information. Kyowa Kirin, Inc. August 2023.
6	Varubi prescribing information. TerSera Therapeutics, LLC. August 2020.
7	Ondansetron solution prescribing information. Hikma Pharmaceuticals USA Inc. October 2021.
8	Reference no longer used
9	Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: ASCO Guideline Update. J Clin Oncol 2020 38:24/,2782-2797
10	National Comprehensive Cancer Network (NCCN). Antiemesis Guidelines. Version 1.2024.
11	Gan TJ, Belani KG, Bergese S, et al. Fourth Consensus Guidelines for the Management of Postoperative Nausea and Vomiting. International Anesthesia Research Society. August 2020. Volume 131. Number 2.
12	American College of Obstetrician and Gynecologists (ACOG). ACOG Practice Bulletin: Nausea and Vomiting of Pregnancy. Obstet Gynecol. 2018;131(1):e15-e29.
13	Reference no longer used
14	Reference no longer used
15	Ondansetron tablets/orally disintegrating tablets prescribing information. Glenmark Pharmaceuticals Inc, USA. November 2021.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Akynzeo, Emend, Varubi QL	**Quantity limit for Akynzeo, Emend, or Varubi** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The patient has cancer chemotherapy related nausea and vomiting and the patient will be receiving chemotherapy more than 7 days per month **OR** 3. There is support for the use of the requested agent for the requested diagnosis and quantity **Length of Approval:** 12 months
Anzemet, granisetron, ondansetron/ ondansetron ODT QL	**Quantity limit for Anzemet, granisetron, or ondansetron/ondansetron ODT** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The patient has cancer chemotherapy related nausea and vomiting and will be receiving chemotherapy more than 7 days per month **OR** 3. The patient has delayed emesis in highly emetogenic chemotherapy **OR** 4. The patient has hyperemesis gravidarum **OR** 5. The patient has radiation therapy induced nausea and vomiting for radiation treatment that extends beyond 7 days per month **OR** 6. There is support for the use of the requested agent for the requested diagnosis and quantity **Length of Approval**: 12 months
Sancuso QL	**Quantity limit for Sancuso** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The patient has cancer chemotherapy related nausea and vomiting and will be receiving chemotherapy more than 14 days per month **OR** 3. There is support for the use of the requested agent for the requested diagnosis and quantity **Length of Approval:** 12 months

Antifungals

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Brexafemme® (ibrexafungerp) Tablets	Treatment in adult and post-menarchal pediatric females for: • Vulvovaginal candidiasis (VVC) • Reduction in the incidence of recurrent vulvovaginal candidiasis (RVVC)		14
Cresemba® (isavuconazonium) Capsule Injection	Treatment of invasive aspergillosis and invasive mucormycosis as follows: • Injection: adults and pediatric patients 1 year of age and older • Capsules: adults and pediatric patients 6 years of age and older who weigh 16 kilograms and greater		1
Noxafil® (posaconazole) Delayed-release (DR) tablet* Intravenous injection* Oral suspension* PowderMix for DR oral suspension	Oral Suspension: treatment of oropharyngeal candidiasis including oropharyngeal candidiasis refractory to itraconazole or fluconazole in adults and pediatric patients 13 years of age and older. Injection and delayed-release (DR) tablets: treatment of invasive aspergillosis in adults and pediatric patients 13 years of age and older. Prophylaxis of invasive *Aspergillus* and *Candida* infections in patients who are at high risk of developing these infections due to being severely immunocompromised, such as hematopoietic stem cell transplant (HSCT) recipients with graft-versus-host disease (GVHD) or those with hematologic malignancies	*generic available	2

Agent(s)	FDA Indication(s)	Notes	Ref#
	with prolonged neutropenia from chemotherapy as follows: • Injection: adults and pediatric patients 2 years of age and older • DR tablets: adults and pediatric patients 2 years of age and older who weigh greater than 40 kg • Oral suspension: adults and pediatric patients 13 years of age and older • PowderMix for DR oral suspension: pediatric patients 2 years of age and older who weigh 40 kg or less		
Vfend®, Voriconazole (voriconazole)* Intravenous injection Oral suspension Tablet	Treatment of adults and pediatric patients 2 years of age and older with: • Invasive aspergillosis • Candidemia in non-neutropenics and other deep tissue *Candida* infections • Esophageal candidiasis • Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species, including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy	*generic available	3
Vivjoa® (oteseconazole) Capsule	Reduce the incidence of recurrent vulvovaginal candidiasis (RVVC) in females with a history of RVVC who are NOT of reproductive potential		17

CLINICAL RATIONALE

Invasive Aspergillosis	IDSA Guidelines recommend primary treatment with voriconazole for invasive aspergillosis. Alternative therapies include liposomal amphotericin B, isavuconazole, or other lipid formulations of amphotericin B. An individualized approach should be used for refractory or progressive aspergillosis (salvage

	therapy) that include lipid formulations of amphotericin B, micafungin, caspofungin, posaconazole, or itraconazole.(5) Solid organ transplant (SOT) patients have a significant risk of invasive fungal diseases (IFD) caused mainly by Candida, Aspergillus, and Cryptococcus with invasive candidiasis being the most frequent infection. Correct identification of patients at increased risk of fungal infection is key to IFD prevention. The selection of universal prophylaxis vs. targeted prophylaxis is based on the type of transplant. Choice of prophylaxis must consider the effectiveness, safety, side-effects, and drug interactions of the antifungal selected.(9) The 2013 guidelines from the American Society of Transplantation recommend amphotericin B, itraconazole, fluconazole, voriconazole, posaconazole, and/or an echinocandin, depending on the specific situation.(11,12) Patients undergoing hematopoietic stem cell transplants (HSCT) are at an increased risk of infection with infection being the primary cause of death in 8% of autologous HSCT patients and 17%-20% of allogeneic HCT recipients. Risk factors for fungal infection in this population includes mucositis, neutropenia, and graft versus host disease (GVHD). Additionally, allogeneic transplant recipients are at a significantly higher risk for fungal infection than those receiving autologous marrow stem cells. Guidelines recommend fluconazole as the drug of choice for the prophylaxis of invasive candidiasis though there is increasing resistance to fluconazole.(13) IDSA recommends prophylaxis for invasive aspergillosis (IA) with posaconazole as a first-line treatment during prolonged neutropenia for those who are at high risk, followed by voriconazole and/or micafungin. Itraconazole is noted to be effective, but therapy may be limited by absorption and tolerability. Patients at high risk for IA include those with prolonged neutropenia, allogeneic HSCT recipients, SOT (with lung transplant recipients having the highest risk), patients receiving corticosteroids, those with advanced AIDS, and those with chronic granulomatous disease. In patients with hematologic malignancies, myelodysplastic syndrome (MDS), and other diseases associated with marrow failures (e.g., aplastic anemia), the intensity and duration of neutropenia predicts the risk of IA. Patients with refractory or relapsed acute leukemia treated with reinduction regimens are at particularly high risk for IA and other mold infections. The IDSA guidelines for antifungal prophylaxis recommend a systemic triazole such as voriconazole or itraconazole after lung transplant over amphotericin B. IDSA recommends posaconazole for prophylaxis against aspergillus in HSCT recipients with GVHD at high risk.(5)

Esophageal candidiasis and candidemia	Infectious Diseases Society of America (IDSA) Guidelines note that systemic antifungal therapy is always required and they recommend fluconazole as the first-line oral therapy for esophageal candidiasis and candidemia in nonneutropenic patients. For patients with fluconazole-refractory disease, itraconazole or voriconazole is recommended. Guidelines note that voriconazole is as efficacious as fluconazole in the treatment of fluconazole-refractory mucosal candidiasis. While voriconazole has demonstrated effectiveness for both mucosal and invasive candidiasis, it offers little advantage over fluconazole as initial therapy for candidemia. Its clinical use has been primarily for step-down oral therapy in select patients with candidemia due to C. krusei.(4)
Oropharyngeal candidiasis	First-line therapy recommendation for oropharyngeal candidiasis from IDSA Guidelines includes clotrimazole troches or nystatin suspension for mild disease. For moderate to severe disease, oral fluconazole shows high-quality evidence and is given a strong recommendation. For fluconazole-refractory disease, itraconazole, posaconazole, voriconazole, or amphotericin B are recommended.(4)
Vulvovaginal candidiasis	IDSA Guidelines recommend as first-line therapy for the treatment of uncomplicated vulvovaginal candidiasis (VVC) any topical antifungal agent (with no one agent superior to another) or a single oral dose of fluconazole 150 mg. In severe cases, the recommendation is fluconazole 150mg given every 72 hours for a total of 2 or 3 doses.(4) IDSA defines VVC as recurrent when at there at least four episodes of symptomatic infection within one year. For recurring vulvovaginal candidiasis (RVVC), 10 to 14 days of induction therapy with a topical agent or oral fluconazole, followed by fluconazole 150 mg weekly for 6 months is recommended. For *C. glabrata* vulvovaginitis that is unresponsive to oral azoles, topical intravaginal boric acid capsules or nystatin intravaginal suppositories have a strong recommendation but the quality of evidence is low.(4) Newer agents, Brexafemme and Vivjoa, do not have current IDSA guideline recommendations for treatment of RVVC. Patients who may benefit from with Brexafemme or Vivjoa, include those who are allergic to fluconazole and other triazoles, do not tolerate fluconazole or other triazoles, and/or have candida infections that are resistant to fluconazole.(16,17) *Efficacy* Brexafemme is FDA labeled and was evaluated for use in post-menarchal

	females with vulvovaginal candidiasis (VVC) in two randomized placebo-controlled clinical trials (Trial 1, NCT03734991 and Trial 2, NCT03987620). The trials had a similar design and were conducted to evaluate the safety and efficacy of a single day of Brexafemme 600 mg (two 150 mg tablets per dose, administered 12 hours apart) for the treatment of VVC. In both trials, statistically significantly greater percentages of patients experienced a complete clinical response at TOC, negative culture at TOC, and complete clinical response at follow-up treatment with Brexafemme compared to placebo.(14) Brexafemme is FDA labeled for use in post-menarchal females with RVVC. A randomized placebo-controlled clinical trial (Trial 3, NCT04029116) was conducted to evaluate the safety and efficacy of Brexafemme 300 mg (two 150 mg tablets) administered approximately 12 hours apart for one day, for a total daily dosage of 600 mg (four 150 mg tablets) administered once monthly for six months. Non-pregnant post-menarchal females presenting with a symptomatic VVC episode and a history of RVVC (at least 3 episodes of VVC in the previous 12 months) were eligible. Patients were randomized at a 1:1 ratio to receive double-blind Brexafemme or placebo administered as a single-day treatment repeated every 4 weeks for a total of 6 single-day treatments. Study visits included the test of cure (TOC) at Week 24 (4 weeks after the last dose) and a follow-up visit at Week 36. Clinical Success at Week 24 and 36 was greater for Brexafemme compared to placebo.(14) Vivjoa is FDA labeled to reduce the incidence of RVVC in females with a history of RVVC who are NOT of reproductive potential. A total of 656 adults and post-menarchal pediatric females with RVVC (defined as greater than or equal to 3 episodes of vulvovaginal candidiasis (VVC) in a 12-month period. Both trials consisted of two phases: an open-label induction phase and an 11-week maintenance phase. Patients received three sequential doses of 150 mg of fluconazole on Days, 1, 4 and 7 during the induction phase. Patients returned 14 days after the first dose of fluconazole and if the acute VVC episode was resolved (signs and symptoms score < 3) they were randomized (2:1) to receive either 150 mg of Vivjoa or placebo for 7 days followed by 11 weekly doses in the maintenance phase. Vivjoa was superior to placebo in patients through Week 48, with acute VVC episodes, or who took medication known to treat VVC during the Maintenance Phase through Week 48.(17) A third trial, was a randomized, double-blind trial evaluating the efficacy and safety of Vivjoa versus fluconazole and placebo in adults and post-menarchal pediatric females with RVVC. During the induction phase, patients received 1050 mg of Vivjoa over two days (4x150mg) on Day 1 and (3x150mg) on Day 2 or three sequential doses of 150 mg of fluconazole on Days, 1, 4 and 7. Patients returned 14 days after the first

	dose and moved to the maintenance phase if the acute VVC episode was resolved. During the maintenance phase, patients received 150 mg Vivjoa weekly or placebo weekly for 11 weeks with an additional post randomization phase through Week 50. Vivjoa was superior to fluconazole/placebo in all groups of patients.(17)
Rare fungal infections	The European Confederation of Medical Mycology (ECMM) together with the Mycoses Study Group Education & Research Consortium brought together authors from 33 countries to publish a global guideline for the diagnosis and management of mucormycosis. Mucormycosis is a difficult to diagnose rare disease with high morbidity and mortality. Diagnosis of mucormycosis is recommended using biopsy, direct microscopy, histopathology, culture and molecular-based methods. First-line treatment with high-dose liposomal amphotericin is strongly supported across all patterns of organ involvement. Isavuconazole is recommended with moderate strength for the first-line treatment of mucormycosis. The group marginally supports use of posaconazole oral suspension, and moderately supports posaconazole delayed release tablets and infusion for first-line treatment. (6) Isavuconazonium has shown activity against Mucorales such as *Rhizopus oryzae* and *Mucormycetes* species.(1) *Scedosporium* species are typically resistant to polyenes (amphotericin B) as well as to fluconazole and has shown reduced susceptibility to echinocandins (micafungin, casprofungin, and anidulafungin). The high degrees of intrinsic antifungal resistance among this species make these infections difficult to manage. Most international guidelines recommend voriconazole as first-line therapy; however, antifungal combination therapy has emerged as a promising option because therapeutic effect can be achieved at lower concentrations thereby reducing toxic side effects, improving safety and tolerability, and shortening the therapeutic effect while potentially preventing treatment failure. *Fusarium* are some of the more difficult fungi to treat because they often display high levels of resistance to existing antifungal agents. Itraconazole, voriconazole, isavuconazole, posaconazole and amphotericin B are all treatment possibilities based on in-vitro data with variable susceptibility.(7)
Safety	Brexafemme is contraindicated in:(14) • Pregnancy • Patients with hypersensitivity to ibrexafungerp Cresemba is contraindicated in the following:(1) • Patients with known hypersensitivity to isavuconazonium

	• Coadministration with string CYP3A4 inhibitors, such as ketoconazole or high-dose ritonavir
	• Coadministration with strong CYP3A4 inducers, such as rifampin, carbamazepine, St. John's wort, or long acting barbiturates
	• Patients with familial short QT syndrome
	
	Noxafil is contraindicated in:(2)
	
	• Patients with known hypersensitivity to posaconazole or other azole antifungal agents
	• Concomitant administration with:
	  ○ Sirolimus
	  ○ CYP3A4 substrates that prolong the QT interval (pimozide, quinidine)
	  ○ HMG-CoA reductase inhibitors primarily metabolized through CYP3A4 (atorvastatin, lovastatin, simvastatin)
	
	Vfend is contraindicated in:(3)
	
	• Patients with known hypersensitivity to voriconazole or its excipients
	• Concomitant administration with:
	  ○ pimozide, quinidine or ivabradine because of increased plasma concentrations of these drugs that can lead to QT prolongation or rare occurrences of torsade de pointes
	  ○ Sirolimus significantly increases sirolimus concentrations
	  ○ Rifampin, carbamazepine, long-acting barbiturates, rifabutin, ergot alkaloids, and St John's Wort due to risk of loss of efficacy
	  ○ Efavirenz doses of 400 mg every 24 hours or higher due to risk of loss of efficacy
	  ○ Ritonavir, high-dose (400 mg every 12 hours) due to risk of loss of efficacy
	  ○ naloxegol, tolvaptan, and lurasidone due to risk of adverse reactions
	  ○ venetoclax at initiation and during the ramp-up phase is contraindicated in patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) due to the potential for increased risk of tumor lysis syndrome
	
	Vivjoa is contraindicated in:(17)
	
	• Females of reproductive potential
	• Pregnant and lactating women

	• Hypersensitivity to oteseconazole

REFERENCES

Number	Reference
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2	Noxafil prescribing information. Merck & Co., Inc. September 2022.
3	Vfend prescribing information. Pfizer. October 2022.
4	Pappas PG, Kauffman CA, Andes DR, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 update by the Infectious Diseases Society of America. *Clinical Infectious Diseases/Clinical Infectious Diseases (Online University of Chicago Press)*. 2015;62(4):e1-e50. doi:10.1093/cid/civ933
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7	McCarthy MW, Katragkou A, Iosifidis E, Roilides E, Walsh TJ. Recent advances in the treatment of scedosporiosis and fusariosis. *Journal of Fungi*. 2018;4(2):73. doi:10.3390/jof4020073
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12	Singh NM, Husain S. Aspergillosis in solid organ transplantation. *American Journal of Transplantation*. 2013;13:228-241. doi:10.1111/ajt.12115
13	Tomblyn M, Chiller T, Einsele H, et al. Guidelines for Preventing Infectious Complications among Hematopoietic Cell Transplantation Recipients: A Global Perspective. *Biology of Blood and Marrow Transplantation*. 2009;15(10):1143-1238. doi:10.1016/j.bbmt.2009.06.019
14	Brexafemme prescribing information. Scynexis, Inc. November 2022.
15	Reference no longer used
16	Martens MG, Maximos B, Degenhardt T, et al. Phase 3 study evaluating the safety and efficacy of oteseconazole in the treatment of recurrent vulvovaginal candidiasis and acute vulvovaginal candidiasis infections. *American Journal of Obstetrics and Gynecology*. 2022;227(6):880.e1-880.e11. doi:10.1016/j.ajog.2022.07.023
17	Vivjoa prescribing information. Mycovia Pharmaceuticals, Inc. April 2022.
18	Reference no longer used

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Brexafemme	**Brexafemme (ibrexafungerp)** will be approved when BOTH of the following are met 1. ONE of the following: A. BOTH of the following: 1. The patient is an adult or a post-menarchal pediatric patient AND ONE of the following: A. The patient has a diagnosis of vulvovaginal candidiasis (VVC) **OR** B. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The patient is using the requested agent to reduce the incidence of recurrent vulvovaginal candidiasis (RVVC) **AND** 2. The patient has experienced greater than or equal to 4 episodes of VVC within a 12 month period **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to fluconazole **OR** B. The patient has an intolerance or hypersensitivity to fluconazole **OR** C. The patient has an FDA labeled contraindication to fluconazole **OR** B. The patient has another FDA labeled indication for the requested agent and route of administration **OR** C. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence **Length of Approval:** VVC - 3 months, RVVC - 6 months, all other indications - 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
Cresemba	**Initial Evaluation** **Cresemba (isavuconazole)** will be approved when BOTH of the following are met: 1. ONE of the following: A. The patient has a diagnosis of invasive aspergillosis **OR** B. The patient has a diagnosis of invasive mucormycosis **OR** C. The patient has another FDA labeled indication for the requested agent and route of administration **OR** D. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence **Length of Approval:** 6 months

Module	Clinical Criteria for Approval
	Renewal Evaluation **Cresemba (isavuconazole)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization review process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. ONE of the following: A. BOTH of the following: 1. The patient has a diagnosis of invasive aspergillosis or invasive mucormycosis **AND** 2. The patient has continued indicators of active disease (e.g., biomarkers in serum assay, biopsy, microbiologic culture, radiographic evidence) **OR** B. BOTH of the following: 1. The patient has a diagnosis other than invasive aspergillosis or invasive mucormycosis **AND** 2. There is support for continued use of the requested agent for the requested indication **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence **Length of Approval:** 6 months
Noxafil	**Initial Evaluation** **Noxafil (posaconazole)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of oropharyngeal candidiasis AND ONE of the following: 1. The patient has tried and had an inadequate response to itraconazole or fluconazole **OR** 2. The patient has an intolerance or hypersensitivity to itraconazole or fluconazole **OR** 3. The patient has an FDA labeled contraindication to BOTH fluconazole AND itraconazole **OR** B. BOTH of the following: 1. The requested agent is prescribed for prophylaxis of invasive Aspergillus or Candida **AND**

Module	Clinical Criteria for Approval
	2. The patient is severely immunocompromised (e.g., hematopoietic stem cell transplant [HSCT] recipient, a hematologic malignancy with prolonged neutropenia from chemotherapy), or is a high-risk solid organ (e.g., lung, heart, kidney, liver, pancreas, small bowel) transplant recipient **OR** C. The patient has a diagnosis of invasive aspergillosis AND ONE of the following: 1. The patient has tried and had an inadequate response to voriconazole, amphotericin B, or isavuconazole **OR** 2. The patient has an intolerance or hypersensitivity to voriconazole, amphotericin B, or isavuconazole **OR** 3. The patient has an FDA labeled contraindication to voriconazole, amphotericin B, AND isavuconazole **OR** D. The patient has another FDA labeled indication for the requested agent and route of administration **OR** E. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence **Length of Approval:** oropharyngeal candidiasis - 1 month, all other indications - 6 months **Renewal Evaluation** **Noxafil (posaconazole)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization review process [Note: patients not previously approved for the requested agent will require initial evaluation review]. (A diagnosis of oropharyngeal candidiasis must go through initial criteria) **AND** 2. ONE of the following: A. BOTH of the following: 1. The requested agent is being prescribed for prophylaxis of invasive Aspergillus or Candida **AND**

Module	Clinical Criteria for Approval
	2. The patient continues to be severely immunocompromised (e.g., HSCT recipient, a hematologic malignancy with prolonged neutropenia from chemotherapy), or is a high-risk solid organ (e.g., lung, heart, kidney, liver, pancreas, small bowel) transplant recipient **OR** B. BOTH of the following: 1. The patient has a diagnosis of invasive aspergillosis **AND** 2. The patient has continued indicators of active disease (e.g., biomarkers in serum assay, biopsy, microbiologic cultures, radiographic evidence) **OR** C. BOTH of the following: 1. The patient has a diagnosis other than invasive aspergillosis or prophylaxis of invasive Aspergillus or Candida **AND** 2. There is support for continued use of the requested agent for the requested indication **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence **Length of Approval:** 6 months
Vfend	**Initial Evaluation** **Vfend (voriconazole)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of invasive aspergillosis **OR** B. BOTH of the following: 1. The requested agent is being prescribed for prophylaxis of invasive Aspergillus or Candida **AND** 2. The patient is severely immunocompromised (e.g., hematopoietic stem cell transplant (HSCT) recipient, a hematologic malignancy with prolonged neutropenia from chemotherapy), or is a high-risk solid organ (e.g., lung, heart, kidney, liver, pancreas, small bowel) transplant recipient **OR** C. The patient has a diagnosis of esophageal candidiasis, candidemia, or other deep tissue Candida infection AND ONE of the following: 1. The patient has tried and had an inadequate response to fluconazole **OR** 2. The patient has an intolerance or hypersensitivity to fluconazole **OR** 3. The patient has an FDA labeled contraindication to fluconazole **OR** D. The patient has a serious infection caused by Scedosporium or Fusarium species **OR**

Module	Clinical Criteria for Approval
	E. The patient has another FDA labeled indication for the requested agent and route of administration **OR** F. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence **Length of Approval:** esophageal candidiasis - 1 month, all other indications - 6 months **Renewal Evaluation** **Vfend (voriconazole)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization review process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. ONE of the following: A. BOTH of the following: 1. The patient has a diagnosis of invasive aspergillosis; serious infection caused by Scedosporium or Fusarium species; esophageal candidiasis, candidemia, or other deep tissue Candida infection **AND** 2. The patient has continued indicators of active disease (e.g., biomarkers in serum assay, biopsy, microbiologic cultures, radiographic evidence) **OR** B. BOTH of the following: 1. The requested agent is being prescribed for prophylaxis of invasive Aspergillus or Candida **AND** 2. The patient is severely immunocompromised (e.g., HSCT recipient, a hematologic malignancy with prolonged neutropenia from chemotherapy), or is a high-risk solid organ (e.g., lung, heart, kidney, liver, pancreas, small bowel) transplant recipient **OR** C. BOTH of the following: 1. The patient has a diagnosis other than invasive aspergillosis; prophylaxis of invasive Aspergillus or Candida; serious infection caused by

Module	Clinical Criteria for Approval
	Scedosporium or Fusarium species; esophageal candidiasis, candidemia, or other deep tissue Candida infection **AND** 2. There is support for continued use of the requested agent for the intended diagnosis **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence **Length of Approval:** esophageal candidiasis - 1 month, all other indications - 6 months
Vivjoa	**Vivjoa (oteseconazole)** will be approved when BOTH of the following are met: 1. ONE of the following: A. ALL of the following: 1. The patient has a diagnosis of recurrent vulvovaginal candidiasis (RVVC) **AND** 2. The patient has experienced greater than or equal to 2 episodes of VVC within a 12 month period **AND** 3. ONE of the following: A. The patient will be using fluconazole in combination with the requested agent **OR** B. The patient has tried and had an inadequate response to fluconazole **OR** C. The patient has an intolerance or hypersensitivity to fluconazole **OR** D. The patient has an FDA labeled contraindication to fluconazole **OR** B. The patient has another FDA labeled indication for the requested agent and route of administration **OR** C. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence **Length of Approval:** RVVC - 4 months, all other indications - 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Anti-Influenza Agents

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#

Relenza
 	
(zanamivir)
 	
Oral inhalation powder
	Treatment of uncomplicated acute illness due to influenza type A and B infections in adults and pediatric patients aged 7 years and older who have been symptomatic for no more than 2 days
	
	Prophylaxis of influenza in patients aged 5 years and older
	
	Important limitations on use of zanamivir:
	
	• Not a substitute for annual influenza vaccination
	• Consider available information on influenza susceptibility patterns and treatment effects when deciding whether to use zanamivir
	• Not recommended for treatment or prophylaxis of influenza in:
	  ○ Individuals with underlying airways disease
	• Not proven effective for:
	  ○ Treatment in individuals with underlying airways disease
	  ○ Prophylaxis in nursing home settings
			1

Tamiflu® (oseltamivir)* Capsule Oral suspension	Treatment of acute, uncomplicated influenza A and B in patients 2 weeks of age and older who have been symptomatic for no more than 48 hours Prophylaxis of influenza A and B in patients 1 year and older. Important limitations of use: • Not a substitute for annual influenza vaccination • Consider available information on influenza susceptibility patterns and treatment effects when deciding whether to use oseltamivir	*generic available	2

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Not recommended for patients with end-stage renal disease not undergoing dialysis		
Xofluza® (baloxavir marboxil) Tablet Oral suspension	Treatment of acute uncomplicated influenza in patients 5 years of age and older who have been symptomatic for no more than 48 hours and who are otherwise healthy or at high risk of developing influenza-related complications Post-exposure prophylaxis of influenza in persons 5 years of age and older following contact with an individual who has influenza Limitations of use: • Consider available information on drug susceptibility patterns for circulating virus strains when deciding whether to use baloxavir		4

CLINICAL RATIONALE

Guidelines	**Influenza** Antiviral treatment is recommended by the Centers for Disease Control and Prevention (CDC) as early as possible for any patient with confirmed or suspected influenza who: is hospitalized, has severe, complicated, or progressive illness, or is at higher risk for influenza complications. Antiviral treatment also can be considered for any previously healthy, symptomatic outpatient not at high risk for influenza complications, who is diagnosed with confirmed or suspected influenza, on the basis of clinical judgement, if treatment can be initiated within 48 hours of illness onset. Recommended duration for antiviral treatment is 5 days for oral oseltamivir or inhaled zanamivir. For the treatment of uncomplicated influenza with intravenous peramivir or oral baloxavir, a single dose is recommended. Longer daily dosing (oral oseltamivir or intravenous peramivir) can be considered for patients who remain severely ill after 5 days of treatment.(5)

	The CDC does not recommend widespread or routine use of antiviral medications for chemoprophylaxis except as one of multiple interventions to control institutional influenza outbreaks. Routine use of post-exposure chemoprophylaxis is not recommended; one reason for this is to avoid sub-therapeutic treatment dosing if infection is already established, although the possibility of whether antiviral resistant viruses could emerge is unknown. Antiviral medications can be considered for chemoprophylaxis to prevent influenza in certain situations, such as: prevention in people at high risk to influenza complications during the first two weeks following vaccination after exposure to a person with influenza, prevention for people at high risk for complications from influenza who cannot receive influenza vaccine due to a contraindication after exposure to a person with influenza, and prevention for people with severe immune deficiencies or others who might not respond to influenza vaccination, such as people receiving immunosuppressive medications, after exposure to a person with influenza. To be effective as chemoprophylaxis, an antiviral medication must be taken each day for the duration of potential exposure to a person with influenza and continued for 7 days after the last known exposure. For persons taking antiviral chemoprophylaxis after inactivated influenza vaccination, the recommended duration is until immunity after vaccination develops (antibody development after vaccination takes about two weeks in adults and can take longer in children depending on age and vaccination history). For control of outbreaks in institutional settings (e.g., long-term care facilities for elderly people and children) and hospitals, CDC recommends antiviral chemoprophylaxis with oral oseltamivir or inhaled zanamivir for a minimum of 2 weeks and continuing up to 1 week after the last known case was identified. Antiviral chemoprophylaxis is recommended for all residents, including those who have received influenza vaccination. Baloxavir is approved for post-exposure prophylaxis (single-dose) of influenza in persons aged 5 years and older.(3) **COVID-19 (SARS-CoV-2) and Influenza** During periods of community co-circulation of influenza viruses and SARS-CoV-2, empiric antiviral treatment of influenza is recommended as soon as possible for the following priority groups: hospitalized patients with respiratory illness, outpatients with severe, complicated, or progressive respiratory illness, and outpatients at higher risk for influenza complications who present with any acute respiratory illness symptoms (with or without fever). Patients who require hospitalization and are suspected of having either or both viral infections should receive influenza antiviral treatment with oseltamivir as soon as possible without waiting for influenza testing results. Treatment for influenza is the same for all patients regardless of SARS-CoV-2 coinfection. Clinicians can consider starting

	early (less than or equal to 48 hours after illness onset) empiric antiviral treatment of non-high-risk outpatients with suspected influenza based upon clinical judgement. SARS-CoV-2 and other etiologies of influenza-like illness should also be considered.(5)
Safety	Zanamivir is contraindicated in patients with history of allergic reaction to any ingredient of Relenza, including milk proteins.(1)

REFERENCES

Number	Reference
1	Relenza prescribing information. GlaxoSmithKline. October 2021.
2	Tamiflu prescribing information. Gilead Sciences, Inc. August 2019.
3	Influenza Antiviral Medications: Summary for Clinicians. Center for Disease Control and Prevention. December 8, 2023. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm
4	Xofluza prescribing information. Genentech USA, Inc. March 2024.
5	Influenza and COVID-19. Center for Disease Control and Prevention. December 20, 2023. Available at: https://www.covid19treatmentguidelines.nih.gov/special-populations/influenza/

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when **BOTH** of the following are met: 1. ONE of the following: A. The patient requires additional courses of therapy due to additional episodes of acute influenza infection **OR** B. The patient requires additional courses or increased duration of therapy for prophylaxis after exposure to an influenza infected person **AND** 2. ONE of the following: A. There is no shortage of the requested agent and ONE of the following: 1. ALL of the following:

Module	Clinical Criteria for Approval
	A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support of therapy with a higher dose for the requested indication **OR** B. There is a shortage of the requested agent and ONE of the following: 1. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support of therapy with a higher dose for the requested indication **Length of Approval:** up to 4 months

Antiretroviral Quantity Limit

Quantity Limit

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Arikayce

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Arikayce® (amikacin liposome inhalation suspension) Oral inhalation	Indicated in adults, who have limited or no alternative treatment options, for the treatment of Mycobacterium avium complex (MAC) lung disease as part of a combination antibacterial drug regimen in patients who do not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy Limitations of Use: Arikayce has been studied only in patients with refractory MAC lung disease, defined as patients who did not achieve negative sputum cultures after a minimum of 6 consecutive months of a multidrug background regimen therapy. The use of Arikayce is not recommended for patients with non-refractory MAC lung disease.		1

CLINICAL RATIONALE

Nontuberculous Mycobacteria (NTM) Lung Disease	Nontuberculous mycobacteria (NTM) species are mycobacterial organisms other than those belonging to the *Mycobacterium tuberculosis* complex. NTM are free-living organisms, ubiquitous in soil and water worldwide. The most common species of NTM is *Mycobacterium avium* complex (MAC) which causes pulmonary disease. MAC lung disease causes progressive inflammatory lung damage which often occurs in the context of preexisting lung disease (e.g., chronic obstructive pulmonary disease [COPD], bronchiectasis, cystic fibrosis, previous tuberculosis). As a result, the clinical manifestations of NTM lung disease (e.g., cough, fatigue, malaise, fever, weight loss, dyspnea, hemoptysis, chest discomfort) are often similar to those of the underlying disease and complicate evaluation and diagnosis of NTM pulmonary disease.(3,4,5)

	Diagnosis of NTM lung disease, jointly established by the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA), includes the following:(3,4,8)
	
	• Clinical findings (ALL required)
	  ○ Pulmonary or systemic symptoms AND
	  ○ Nodular or cavitary opacities on chest radiograph OR a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules AND
	  ○ Appropriate exclusion of other diagnoses
	• Microbiologic findings (only ONE is required)
	  ○ Positive culture results from at least two separate expectorated sputum samples
	  ○ Positive culture result from at least one bronchial wash or lavage
	  ○ Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or acid-fast bacilli [AFB]) and positive culture for NTM; OR biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM
	
	Drug therapy for MAC disease involves multiple drugs; therefore, the risk of adverse drug reactions and/or toxicities is relatively high. In addition, the choice of therapeutic regimen for a specific patient depends on (but is not limited to) the goals of therapy, comorbidities, and whether the patient has failed prior drug therapy. For these reasons, the treatment of MAC disease is best accomplished by physicians experienced in the treatment of mycobacterial diseases.(3,4) Initial treatment regimen for MAC contains a three-drug regimen consisting of a macrolide (azithromycin or clarithromycin), a rifamycin (rifampin, rifabutin), and ethambutol. For patients who have severe nodular bronchiectatic disease or fibrocavitary disease, rapidly growing mycobacteria, or have failed conventional treatments, a parenteral aminoglycoside (streptomycin or amikacin) is also often used as a 4th agent for 2-4 months.(2,3,4,6,8) Nebulized amikacin may be considered in place of an injectable aminoglycoside when parenteral administration is impractical or contraindicated.(2,4,6) If sputum cultures have not converted to negative after 6 months of guideline-based treatment, nebulized amikacin should be used as part of the continuation treatment regimen.(3) For patients with less severe disease, or those who are intolerant to the three-drug regimen, a two-drug regimen with a macrolide and ethambutol may be appropriate. However, there are concerns that a two-drug regimen might promote the emergence of macrolide-resistant MAC isolates.(2,3)

	The goals of therapy include symptomatic, radiographic, and microbiologic improvement. The primary microbiologic treatment endpoint for MAC lung disease is the conversion of sputum cultures to negative. Therefore, AFB smears and cultures of sputum should be obtained every 1-2 months during therapy to assess patient response; once sustained conversion (repeat negative cultures) has been documented, sputum cultures can be obtained less frequently.(2,3,8) Patients should show clinical improvement within 3 to 6 months and should convert their sputum to negative within 12 months on macrolide-containing regimens.(2,3,4) Studies suggest that culture-negative status for 12 months consecutively while receiving a clarithromycin- or azithromycin-containing regimen is adequate for most patients.(3,4,8) Genotyping studies support 12 months of culture-negative sputum as a reasonable treatment endpoint because new positive sputum cultures for MAC after initial sputum conversion and culture negativity for 10 to 12 months are usually due to reinfection (new MAC genotype) rather than disease relapse.(3) Less emphasis is placed on symptomatic and radiographic improvement because, while important, underlying concomitant disease progression or exacerbation may complicate assessment.(2,3) There is no currently widely accepted definition for treatment failure, although most experts define is as the failure to achieve culture conversion after 6 to 12 months of therapy.(2,3,4) Patients with treatment failure warrant evaluation for adherence to the drug regimen, assessment of serum drug concentrations, and susceptibility testing to macrolides and other drugs that may be needed for treatment. Once treatment failure has occurred, other interventions that should be considered include administration of an inhaled aminoglycoside and/or resectional surgery.(2,4) For patients with colonization by more than one organism, for example a cystic fibrosis patient with a Pseudomonal infection as well as MAC, 2007 ATS/IDSA guidelines state that it is important that nonmycobacterial pathogens be maximally treated before initiating specific antimycobacterial treatment, given the overlapping spectrum of antimycobacterial drugs for common CF pathogens, to facilitate assessment of the clinical response to antimycobacterial treatment.(10)
Efficacy	In an open-label, randomized, multi-center trial in patients with refractory MAC lung disease [as confirmed by at least 2 positive sputum culture results after a minimum duration of 6 consecutive months of guidelines-based background regimen therapy (GBT)], patients were randomized to either Arikayce plus background regimen (ALIS + GBT) or background regimen alone (GBT). The primary endpoint was culture conversion, defined as three consecutive monthly MAC-negative sputum cultures by Month 6. Culture conversion was achieved by

	65 of 224 patients (29.0%) with ALIS + GBT and 10 of 112 (8.9%) with GBT alone (odds ratio, 4.22; 95% confidence interval, 2.08–8.57; p less than 0.001).(1,7) Patients with culture conversion by month 6 continued treatment for 12 months after the time of conversion. Of the 65 enrolled patients on ALIS + GBT therapy, 63% (41/65) remained culture negative after 12 months of subsequent treatment; 63% (41/65) of patients also remained culture negative 3 months off all antibiotics.(9)
Safety	Arikayce has a boxed warning due to an increased risk of respiratory adverse reactions including hypersensitivity pneumonitis, hemoptysis, bronchospasm, exacerbation of underlying pulmonary disease that have led to hospitalizations in some cases.(1)

REFERENCES

Number	Reference
1	Arikayce prescribing information. Insmed Incorporated. February 2023.
2	Kasperbauer S, Daley CL, et al. Treatment of Mycobacterium Avium Complex Pulmonary Infection in Adults. UpToDate. Last updated September 2022. Literature review current through August 2023.
3	Daley CL, Iaccarino JM, Lange C, et al. Treatment of Nontuberculous Mycobacterial Pulmonary Disease: An Official ATS/ERS/ESCMID/IDSA Clinical Practice Guideline. Clin Infect Dis. 2020;71(4):e1-e36.
4	Haworth CS, Banks J, Capstick T, et al. British Thoracic Society Guidelines for the Management of Non-Tuberculous Mycobacterial Pulmonary Disease (NTM-PD). Thorax. 2017;72:ii1-ii64.
5	Griffith DE, et al. Overview of Nontuberculous Mycobacterial Infections. UpToDate. Last updated October 2020. Literature review current through August 2023.
6	Olivier KN, Shaw PA, Glaser TS, et al. Inhaled Amikacin for Treatment of Refractory Pulmonary Nontuberculous Mycobacterial Disease. Ann Am Thorac Soc. 2014;11(1):30-35.
7	Griffith DE, Eagle G, Thomson R, et al. Amikacin Liposome Inhalation Suspension for Treatment-Refractory Lung Disease Caused by Mycobacterium Avium Complex (CONVERT): A Prospective, Open-Label, Randomized Study. Am J Respir Crit Care Med. 2018;198(12).

Number	Reference
8	Floto RA, Olivier KN, Saiman L, et al. US Cystic Fibrosis Foundation and European Cystic Fibrosis Society Consensus Recommendations for the Management of Non-Tuberculous Mycobacteria in Individuals with Cystic Fibrosis. Thorax. 2016;71:i1-i22.
9	Griffith DE, Thomson R, Addrizzo-Harris DJ, et al. Durability of Culture Conversion in Patients Receiving Amikacin Liposome Inhalation Suspension (ALIS) for Treatment-Refractory Mycobacterium Avium Complex Lung Disease (MAC-LD) in the CONVERT Study. Eur Respir J. 2019;54(63):OA4951.
10	Griffith DE, Aksamit T, Brown-Elliott BA, et al. Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases: An Official ATS/IDSA Statement. Am J Respir Crit Care Med. 2007;175:367-416.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of *Mycobacterium avium* complex (MAC) lung disease as confirmed by BOTH of the following: A. Information has been provided that indicates the patient has at least ONE of the following clinical findings: pulmonary or systemic symptoms; nodular or cavitary opacities on chest radiograph; a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules **AND** B. Information has been provided that indicates the patient has at least ONE of the following microbiological findings: positive culture results from at least two separate expectorated sputum samples; positive culture result from at least one bronchial wash or lavage; transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or acid-fast bacilli [AFB]) AND positive culture for nontuberculous mycobacteria (NTM); biopsy showing mycobacterial histopathologic features (granulomatous inflammation or AFB) AND one or more sputum or bronchial washings that are culture positive for NTM **AND** 2. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**

Module	Clinical Criteria for Approval
	B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 3. The patient has positive sputum cultures despite at least 6 consecutive months of treatment with guideline-based combination antibiotic therapy for MAC lung disease (e.g., standard combination may include a macrolide [clarithromycin, azithromycin], a rifamycin [rifampin, rifabutin], and ethambutol) **AND** 4. The patient will continue treatment with guideline-based combination antibiotic therapy for MAC lung disease with the requested agent (e.g., combination may include a macrolide [clarithromycin, azithromycin], a rifamycin [rifampin, rifabutin], and ethambutol) **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., infectious disease, immunologist, pulmonologist, thoracic specialist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. ONE of the following: A. The patient is NOT currently being treated with another inhaled antibiotic (e.g., aztreonam for inhalation, tobramycin for inhalation) **OR** B. The patient is currently being treated with another inhaled antibiotic AND ONE of the following: 1. The patient will discontinue the other inhaled antibiotic prior to starting the requested agent **OR** 2. The prescriber has provided information in support of another inhaled antibiotic used concurrently with the requested agent **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The patient will continue treatment with guideline-based combination antibiotic therapy for *Mycobacterium avium* complex (MAC) lung disease with the requested agent (e.g., combination may include a macrolide [clarithromycin, azithromycin], a rifamycin [rifampin, rifabutin], and ethambutol) **AND**

Module	Clinical Criteria for Approval
	4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., infectious disease, immunologist, pulmonologist, thoracic specialist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. ONE of the following: A. The patient is NOT currently being treated with another inhaled antibiotic (e.g., aztreonam for inhalation, tobramycin for inhalation) **OR** B. The patient is currently being treated with another inhaled antibiotic AND ONE of the following: 1. The patient will discontinue the other inhaled antibiotic prior to starting the requested agent **OR** 2. The prescriber has provided information in support of another inhaled antibiotic used concurrently with the requested agent **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** 12 months

ATTR Amyloidosis

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Tegsedi® (inotersen) Subcutaneous injection	Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults		1
Vyndamax® (tafamidis) Capsule	Treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization		2
Vyndaqel® (tafamidis meglumine) Capsule	Treatment of the cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis (ATTR-CM) in adults to reduce cardiovascular mortality and cardiovascular-related hospitalization		2
WAINUA™ (eplontersen) Subcutaneous injection	Treatment of the polyneuropathy of hereditary transthyretin-mediated amyloidosis in adults		9

CLINICAL RATIONALE

Amyloidosis	Amyloidosis is a protein disorder in which proteins misfold, then bind together to form amyloid fibrils which deposit into organs.(3) Transthyretin (TTR) is a protein primarily synthesized in the liver and carries thyroxine and retinol-binding protein. Dissociation of TTR followed by aggregation and misfolding of the TTR protein causes formation of insoluble amyloid fibrils. These fibrils deposit systemically, causing multisystem disease with rapidly progressing polyneuropathy and other

	systemic manifestations, particularly cardiomyopathy.(4,5) There are two types of ATTR (transthyretin amyloid) amyloidosis: hereditary ATTR (hATTR or ATTRm) and wild-type ATTR (ATTRwt). Hereditary ATTR results from an inherited mutation in the DNA that encodes for an unstable TTR protein, making TTR more likely to form amyloid fibrils. Wild-type ATTR is a result of aging and sex; as one gets older, normal TTR protein becomes unstable, misfolding and forming amyloid fibrils.(3)
Neuropathy	A range of sensory and motor impairments are reported by patients with hATTR amyloidosis with polyneuropathy. The most common of these include neuropathic pain, altered sensation (i.e., decreased pain sensation), numbness, and tingling, along with muscle weakness and impaired balance which lead to difficulty walking. The pathologic process typically involves small-fiber damage early in the disease course, often with subsequent damage to peripheral motor and sensory nerves that results in sensorimotor polyneuropathy. Autonomic impairment is also frequently observed, and includes nausea and vomiting, changes in gastrointestinal motility, orthostatic hypotension, bladder dysfunction, and erectile dysfunction. Historically, measuring the disease has utilized the Familial Amyloidotic Polyneuropathy (FAP) staging system and/or the polyneuropathy disability (PND) scoring system. However, these scales provide only a generic indicator of overall disease status and are not sensitive to track disease progression in the short-term period. Recently developed and used in hATTR amyloidosis studies is the modified Neuropathy Impairment Score +7 (NIS+7). This system is highly standardized, quantitative, and referenced assessments to quantify decreased muscle weakness, muscle stretch reflexes, sensory loss, and autonomic impairment. NIS+7 is more sensitive to disease progression over shorter time periods and better at capturing the different features of polyneuropathy. This scale has been further modified (mNIS+7 Alnylam and mNIS+7 Ionis) to afford more sensitive detection of disease progression.(5,7) Diagnosis of hATTR neuropathy can be challenging without positive family history as clinical presentation may mimic various peripheral neuropathies. In patients with peripheral neuropathy of otherwise undetermined etiology, early search for associated clinical features, especially cardiac involvement can help reveal amyloidosis. Diagnosis can be confirmed by demonstration of amyloid in a biopsy sample and/or detection of any amyloidogic mutation by TTR genetic testing.(7)
Cardiomyopathy	Cardiomyopathy is a manifestation of ATTR amyloidosis in which transthyretin protein misfolds to form fibrils that deposit in the myocardium, leading to cardiomyopathy and symptoms of heart failure. Transthyretin amyloid

	cardiomyopathy (ATTR-CM) is a late-onset disease; symptoms are predominately manifested in male patients 60 years of age or older. The condition can be inherited as an autosomal dominant trait caused by pathogenic mutations in the transthyretin gene TTR (ATTRm) or by the deposition of wild-type transthyretin protein (ATTRwt). There are more than 120 pathogenic mutations in TTR that result in a variable phenotypic presentation. The prevalence of ATTRwt is uncertain, some studies have reported a prevalence of 13% among patients with heart failure with a preserved ejection fraction, 16% among patients undergoing transcatheter aortic-valve replacement for severe aortic stenosis, and 5% among patients with presumed hypertrophic cardiomyopathy. Treatments have previously been limited to supportive care. Median survival in untreated patients is reported to be 2.5 years after diagnosis for ATTRm caused by the TTR Val122Ile mutation and 3.6 years for ATTRwt.(6) Patients with ATTR-CM often show common signs and symptoms of heart failure, such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, fatigue, exercise intolerance, dizziness/syncope, palpitations, electrical conduction abnormalities, and arrhythmias. Therefore, ATTR-CM is sometimes mistakenly diagnosed as hypertrophic cardiomyopathy or as generic, undifferentiated heart failure with preserved ejection fraction rather than as amyloidosis.(6,8) Patients with suspected ATTR-CM should include testing for monoclonal protein followed by scintigraphy or biopsy. Nuclear imaging can also be performed for additive information. In some cases, endomyocardial biopsy is necessary for a definitive diagnosis but if no monoclonal protein is detected and a diagnosis of light chain amyloidosis (AL) has been ruled out, scintigraphy alone can definitively diagnose ATTR-CM. If ATTR-CM is identified, TTR genotyping should be performed.(8)
Efficacy	Inotersen is an antisense oligonucleotide (ASO) that causes degradation of mutant and wild-type transthyretin (TTR) mRNA through binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. The efficacy of Tegsedi was demonstrated in the NEURO-TTR trial, a randomized, double-blind, placebo-controlled, multicenter clinical trial in adult patients with polyneuropathy cause by hATTR amyloidsis (Study 1; NCT 01737398) Patients were randomized in a 2:1 ratio to receive either Tegsedi (113 patients) or placebo (60 patients), as a subcutaneous injection once per week for 65 weeks. Seventy seven percent of Tegsedi-treated patients and 87% of patients on placebo completed 66 weeks. Patients were FAP stage 1 or 2 (ambulatory or ambulatory with assistance, respectively) and had no prior liver transplant or anticipated liver transplant within 1 year of screening. Primary endpoints were the change in the mNIS+7 score and the change in the Norfolk QoL-DN score. At 66 weeks, both primary efficacy assessments favored

	inotersen. The least squares mean change from baseline was -19.7 points (95% CI, -26.4 to -13.0; p<0.001) for the mNIS+7 and -11.7 points (95% CI, -18.3 to -5.1; P<0.001) for the Norfolk QoL-DN score.(1) Tafamidis is a selective stabilizer of TTR. Tafamidis binds to TTR at the thyroxine binding sites, stabilizing the tetramer and slowing dissociation into monomers, the rate-limiting step in the amyloidogenic process. Efficacy was demonstrated in a multicenter, international, randomized, double-blind, placebo-controlled study in 441 patients with wild type or hereditary ATTR-cardiomyopathy (ATTR-CM), with no prior liver or heart transplantation. Patients were randomized in a 1:2:2 ratio to receive Vyndaqel 20 mg (88 patients), Vyndaqel 80 mg (176 patients), or placebo (177 patients) once daily for 30 months, in addition to standard of care (e.g., diuretics). Treatment assignment was stratified by the presence or absence of a variant TTR genotype as well as baseline disease severity (NYHA Class). The primary analysis points were all-cause mortality and frequency of cardiovascular-related hospitalizations. The analysis demonstrated a significant reduction in all-cause mortality and frequency of cardiovascular-related hospitalizations in the pooled Vyndaqel group.(2) Eplontersen is a transthyretin-directed ASO that causes degradation of mutant and wild-type TTR mRNA through binding to the TTR mRNA, which results in a reduction of serum TTR protein and TTR protein deposits in tissues. The efficacy of WAINUA was demonstrated in a randomized, open-label, multicenter trial and adult patients with polyneuropathy caused by hATTR amyloidosis (Study 1; NCT04136184). Patients were randomized in a 6:1 ration to receive subcutaneous injections of either 45mg of WAINUA once every 4 weeks (144 patients), or 284mg of inotersen once weekly (24 patients), respectively. Efficacy assessments were based on a comparison of the WAINUA arm of Study 1 with an external placebo group (60 patients) from another study (NCT01737398) of a comparable population of adult patients with the same indication. Endpoint was change from baseline to week 35 in the mNIS+7 composite score and change from baseline to week 35 in the QoL-DN total score. Treatment with WAINUA resulted in statistically significant improvements in the mNIS+7 and Norfolk QoL-DH total scores compared to placebo control (p<0.001) at week 35. The least squares mean change from baseline was -9.0 points (95% CI, -13.5 to -4.5; p<0.001) for the mNIS+7 and -11.8 points (95% CI, -16.5 to -6.8; P<0.001) for the Norfolk QoL-DN score.(9)
Safety	Tegsedi has a the following boxed warnings:(1) • Thrombocytopenia: Tegsedi causes reductions in platelet count that may result in sudden and unpredictable thrombocytopenia, which can be life-

	threatening. Tegsedi is contraindicated in patients with a platelet count below 100 x 10^9/L. Prior to starting Tegsedi, obtain a platelet count. During treatment, monitor platelet counts weekly if values are 75 x 10^9/L or greater, and more frequently if values are less than 75 x10^9/L. • Glomerulonephritis: Tegsedi can cause glomerulonephritis that may require immunosuppressive treatment and may result in dialysis-dependent renal failure. Tegsedi should generally not be initiated in patients with urinary protein to creatinine ratio (UPCR) of 1000 mg/g or higher. Prior to starting Tegsedi, measure serum creatinine, estimated glomerular filtration rate (eGFR), UPCR, and perform a urinalysis. During treatment, monitor serum creatinine, eGFR urinalysis, and UPCR every two weeks. Tegsedi should not be given to patients who develop a UPCR of 1000 mg/g or higher, or eGFR below 45 mL/minute/1.73 m^2, pending further evaluation of the cause. If a dose is held, once eGFR increases to greater than or equal to 45 mL/minute/1.73 m^2, UPCR decreases to below 1000 mg/g, or the underlying cause of the decline in renal function is corrected, weekly dosing may be reinitiated. In patients with UPCR of 2000 mg/g or higher, perform further evaluation for acute glomerulonephritis, as clinically indicated. If acute glomerulonephritis is confirmed, Tegsedi should be permanently discontinued. • Tegsedi REMS Program: Because of the risks of serious bleeding caused by severe thrombocytopenia and because of glomerulonephritis, both of which require frequent monitoring, Tegsedi is available only through a restricted distribution program under a Risk Evaluation and Mitigation Strategy (REMS). Tegsedi has the following contraindications:(1) • Platelet count below 100 x10^9/L • History of acute glomerulonephritis caused by inotersen • History of a hypersensitivity reaction to inotersen Vyndaqel and Vyndamax have no FDA labeled contraindications for use.(2) WAINUA has no FDA labeled contraindications for use.(9)

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Number	Reference
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4	Kapoor M, Rossor AM, Laura M, et al. Clinical Presentation, Diagnosis and Treatment of TTR Amyloidosis. *Journal of Neuromuscular Diseases.* 6 (2019) 189-199. https://content.iospress.com/download/journal-of-neuromuscular-diseases/jnd180371?id=journal-of-neuromuscular-diseases%2Fjnd180371
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6	Maurer MS, Schwartz JH, Gundapeneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. *N Engl J Med* 2018; 379:1007-16. https://www.nejm.org/doi/full/10.1056/NEJMoa1805689
7	Luigetti M, Romano A, Di Paolantonio A, Bisogni G, Sabatelli M. Diagnosis and Treatment of Hereditary Transthyretin Amyloidosis (hATTR) Polyneuropathy: Current Perspectives on Improving Patient Care. *Ther Clin Risk Manag*. 2020;16:109-123. doi:10.2147/TCRM.S219979.
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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has ONE of the following: A. ALL of the following: 1. A diagnosis of polyneuropathy of hereditary transthyretin-mediated amyloidosis confirmed by testing (e.g., genetic testing, biopsy) **AND** 2. The requested agent is FDA approved for use in polyneuropathy of hereditary transthyretin-mediated amyloidosis **AND** 3. The patient has clinical manifestations of polyneuropathy (e.g., neuropathic pain, altered sensation, numbness, tingling, impaired balance, motor disability) **OR** B. ALL of the following: 1. A diagnosis of cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis confirmed by testing [e.g., stannous pyrophosphate (PYP) scanning, monoclonal antibody studies, biopsy, scintigraphy, genetic testing (TTR genotyping)] **AND** 2. The requested agent is FDA approved for use in cardiomyopathy of wild type or hereditary transthyretin-mediated amyloidosis **AND** 3. The patient has clinical manifestations of cardiomyopathy (e.g., dyspnea, fatigue, orthostatic hypotension, syncope, peripheral edema) **OR** C. The patient has another FDA approved indication for the requested agent and route of administration **AND** 2. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 3. The patient has NOT received a liver transplant **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, geneticist, neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient will NOT be using the requested agent in combination with another agent targeted in this program, Onpattro (patisiran), OR Amvuttra (vutrisiran) for the requested indication **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent

Module	Clinical Criteria for Approval
	Length of Approval: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, geneticist, neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient has NOT received a liver transplant **AND** 5. The patient will NOT be using the requested agent in combination with another agent targeted in this program, Onpattro (patisiran), OR Amvuttra (vutrisiran) for the requested indication **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** 12 months

Atypical Antipsychotics

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Abilify Mycite® (aripiprazole) Tablet with sensor, strips, and pod (Starter kit) Tablet with sensor and strips (Maintenance kit)	Treatment of: • Schizophrenia • Acute Treatment of Manic and Mixed Episodes associated with Bipolar I Disorder • Adjunctive Treatment of Major Depressive Disorder • Irritability Associated with Autistic Disorder • Tourette's Disorder		34
Abilify® (aripiprazole)* Tablet Oral solution Orally disintegrating tablet	Treatment of: • Schizophrenia • Acute Treatment of Manic and Mixed Episodes associated with Bipolar I Disorder • Adjunctive Treatment of Major Depressive Disorder • Irritability Associated with Autistic Disorder • Tourette's Disorder	*generic available	6
Caplyta® (lumateperone) Capsule	-Schizophrenia in adults -Depressive episodes associated with bipolar I or II disorder (bipolar depression) in adults, as monotherapy and as adjunctive therapy with lithium or valproate.		36
Clozapine ODT, Clozaril®	- Treatment-resistant schizophrenia	*generic available	1; 15

Agent(s)	FDA Indication(s)	Notes	Ref#
(clozapine) Tablet* Orally disintegrating tablet*^	- Reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder	^12.5mg ODT brand name only	
COBENFY™ (xanomeline tartrate-trospium) Capsule	Treatment of schizophrenia in adults		34
Fanapt® (iloperidone) Tablet	Treatment of schizophrenia		10
Geodon® (ziprasidone) Capsule*	- Treatment of schizophrenia - Acute treatment as monotherapy of manic or mixed episodes associated with bipolar I disorder - Maintenance treatment of bipolar I disorder as an adjunct to lithium or valproate	*generic available	5
Invega ER® (paliperidone ER) Tablet*	- Treatment of schizophrenia - Treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers and/or antidepressants	*generic available	7
Latuda® (lurasidone) Tablet*	Treatment of: • Schizophrenia • Depressive Episodes associated with Bipolar I Disorder (bipolar depression), as monotherapy and as adjunctive therapy with lithium or valproate		11
Lybalvi®	- Schizophrenia in adults		37

Agent(s)	FDA Indication(s)	Notes	Ref#
(olanzapine-samidorphan) Tablet	- Bipolar I disorder in adults • Acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate • Maintenance monotherapy treatment		
Rexulti® (brexpiprazole) Tablet	- Treatment of schizophrenia in adults and pediatric patients ages 13 years and older - Use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) - Treatment of agitation associated with dementia due to Alzheimer's disease Limitation of Use: Rexulti is not indicated as an as needed ("prn") treatment for agitation associated with dementia due to Alzheimer's disease		14
Risperdal®, Risperidone ODT (risperidone) Tablet* Orally disintegrating tablet*^ Oral solution*	- Treatment of schizophrenia - As monotherapy or adjunctive therapy with lithium or valproate, for the treatment of acute manic or mixed episodes associated with Bipolar I Disorder - Treatment of irritability associated with autistic disorder	*generic available ^0.25mg tablet brand name only	2
Saphris® (asenapine) Sublingual tablet*	- Treatment of schizophrenia - Bipolar I disorder - Acute monotherapy treatment of manic or mixed episodes, in adults and pediatric patients 10 to 17 years of age	*generic available	9

Agent(s)	FDA Indication(s)	Notes	Ref#
	- Adjunctive treatment to lithium or valproate in adults - Maintenance monotherapy treatment in adults		
Secuado® (asenapine) Transdermal system	- Treatment of schizophrenia		35
Seroquel® (quetiapine) Tablet*	- Treatment of schizophrenia - Bipolar I disorder manic episodes - Bipolar disorder, depressive episodes	*generic available	4
Seroquel XR® (quetiapine) Tablet*	- Treatment of schizophrenia - Bipolar I disorder, manic, or mixed episodes - Bipolar disorder, depressive episodes - Major depressive disorder, adjunctive therapy with antidepressants	*generic available	8
Versacloz® (clozapine) Oral suspension	- Treatment-resistant schizophrenia. - Reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder		13
Vraylar® (cariprazine) Capsule	- Treatment of schizophrenia in adults - Acute treatment of manic or mixed episodes associated with bipolar I disorder in adults - Treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults		15

Agent(s)	FDA Indication(s)	Notes	Ref#
	- Adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults		
Zyprexa®, Zyprexa® Zydis® (olanzapine)* Tablet Orally disintegrating tablet	- Treatment of schizophrenia - Acute treatment of manic or mixed episodes associated with bipolar I disorder and maintenance treatment of bipolar I disorder - Adjunct to valproate or lithium in the treatment of manic or mixed episodes associated with bipolar I disorder. As ZYPREXA and fluoxetine in combination for the: • Treatment of depressive episodes associated with bipolar I disorder. • Treatment of treatment resistant depression (major depressive disorder in patients who do not respond to 2 separate trials of different antidepressants of adequate dose and duration in the current episode	*generic available	3

CLINICAL RATIONALE

Schizophrenia	Schizophrenia is a psychiatric disorder that involves chronic or recurrent psychosis. Antipsychotic medications are first-line treatment for schizophrenia. Antipsychotics have been shown to reduce positive symptoms of schizophrenia, such as hallucinations, delusions, and suspiciousness. Negative symptoms of schizophrenia, such as diminished emotional expression and lack of motivation, have proven particularly difficult to treat. Clozapine is generally considered the most effective antipsychotic drug for the treatment of schizophrenia. Due to adverse effects such as agranulocytosis and seizures, it's use is reserved for patients with treatment-resistant disease, suicide risk, or risk of aggressive

	behavior despite other treatments. Antipsychotic medications are commonly grouped into two categories, with “second-generation” or “atypical” applied to clozapine and all antipsychotics first marketed after clozapine was approved in 1989, and “first-generation” applied to all antipsychotics marketed previously. Atypical antipsychotics tend to cause fewer extrapyramidal side effects than first generation antipsychotics. Elderly patients, in particular, are at increased risk of chronic confusion and disorientation during treatment with first generation antipsychotic drugs.(16,17)
Bipolar Disorder	Bipolar disorder is a mood disorder that is characterized by episodes of mania, hypomania, and major depression. Initiation of maintenance therapy is recommended to prevent relapse, minimize suicide attempts, and maybe associated with reduced rates of violent behavior. First line maintenance therapy is recommended, if possible, to consist of the same regimen that successfully treated the acute bipolar mood episode. Lithium, quetiapine, divalproex, and lamotrigine monotherapy are considered first-line treatments. Second line therapy is reserved for those who do not tolerate first-line maintenance pharmacotherapy. Olanzapine, risperidone, carbamazepine, paliperidone, ziprasidone, and lurasidone are all considered second-line therapies.(18,19)
Major Depressive Disorder	Major depressive disorder (MDD), also known as unipolar major depression, is diagnosed when a patient has suffered at least one major depressive episode and have no history of mania or hypomania. Goal of initial treatment for depression is symptom remission and restoring baseline functioning. Selective serotonin reuptake inhibitors (SSRIs) along with serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, and mirtazapine are considered first line treatment options for adults with major depressive disorder (MDD). Guidelines do not consider antipsychotics as a first line treatment of major depressive disorder without psychosis. However, they suggest that psychotic depression typically responds better to the combination of an antipsychotic and an antidepressant medication rather than either component alone, although some research has shown comparable responses for anti-depressive treatment or antipsychotic treatment alone.(20,21)
Autism	Practice Parameters-American Academy of Child and Adolescent Psychiatry (AACAP, 2014) suggest pharmacotherapy may be offered when there is a specific target symptom or comorbid condition, potentially increasing patient ability to profit from educational and other interventions, and allow less restrictive environments through management of severe and challenging behaviors. Frequent targets for pharmacologic intervention include associated comorbid conditions (e.g., anxiety, depression) and other features (e.g., aggression, self-injurious behavior, hyperactivity, inattention, compulsive-like behaviors, repetitive or stereotypic behaviors, and sleep disturbances). Various

	considerations (e.g., adverse effects) should inform pharmacologic treatment. Risperidone and aripiprazole have been FDA approved for the treatment of irritability (e.g., physical aggression, severe tantrum behavior) associated with autism. There is a growing body of controlled evidence for pharmacologic intervention. The guideline provides a summary chart of medications supported by RCTs for use in children with autism spectrum disorder (ASD), including target symptoms, ages, dosing, potential adverse effects, and outcomes. ▪ Antipsychotics supported by RCTs showing positive effects on various target symptoms in ASD include aripiprazole, haloperidol, olanzapine, and risperidone. ▪ Combining medication with parent training is moderately more efficacious than medication alone for decreasing serious behavioral disturbance and modestly more efficacious for adaptive functioning. Individuals with ASD may be nonverbal, so treatment response is often judged by caregiver report and observation of specific behaviors. Although this may help document the effectiveness of the selected medication, an overall goal of treatment is to facilitate the child's adjustment and engagement with educational intervention. Despite many randomized trials, confidence in reported improvements remains low for most interventions. Risperidone and aripiprazole improved challenging behavior in the short term (less than 6 months) but also significant harms including weight gain, appetite changes, and EPS.(22,23)
Dementia-Related Psychosis (off-label use)	The American Psychiatric Association (APA) recommends that nonpharmacologic interventions be attempted before a trial of antipsychotic drug therapy and that the interventions attempted be guided by the patient's level of distress and the risk to the patients and caregiver. In addition, the FDA states that physicians who prescribe antipsychotics to elderly patients with dementia-related psychosis should discuss the risk of increased mortality with their patients, patients' families, and caregivers. Evidence indicates that antipsychotics provide weak benefits for the treatment of psychosis and agitation in patients with dementia. Adverse effects of antipsychotics include sedation, metabolic effects, and cognitive impairment. For many patients with Alzheimer's disease, antipsychotics can be tapered and discontinued without significant signs of withdrawal or return of behavioral symptoms. Antipsychotic drug therapy generally is reserved for patients who have severe symptoms or when associated agitation, combativeness, or violent behavior puts the patient or others in danger. Current evidence indicates that the atypical antipsychotics can provide modest improvement in behavioral manifestations;

	some evidence suggests that efficacy may be better for psychosis than for other manifestations. Antipsychotic efficacy appears to be similar among available agents and therefore the choice of agent should be based on adverse effect profile and other patient considerations; to minimize adverse effects, the lowest possible effective dose should be used.(24,25)
Tourette's Disorder	Tourette's disorder is a neuropsychiatric disorder characterized by involuntary motor and vocal tics. Although the etiology of Tourette's disorder is unknown, evidence suggests that pathophysiology of this disorder involves an abnormality in the central dopaminergic system. Currently, the medications that are FDA approved for the treatment of Tourette's disorder are aripiprazole, haloperidol, and pimozide although most clinicians use atypical antipsychotics prior to the two approved agents. Clonidine and guanfacine are considered first line agents due to their low side effect profile. However, the level of evidence for their effectiveness is less than antipsychotics and they lack an FDA approval. Atypical neuroleptics (aripiprazole or risperidone) are typically used if the alpha-2 agonists are ineffective or intolerable. According to the American Academy of Neurology guidelines, there was moderate confidence that haloperidol, risperidone, aripiprazole, tiapride, clonidine, onabotulinumtoxin A injections were probably more likely than placebo to reduce tics. There was low confidence that pimozide, ziprasidone, metoclopramide, guanfacine, topiramate, and tetrahydrocannabinol were possibly more likely than placebo to reduce tics. There is high confidence that the patients need to be counseled and monitored for adverse events such as weight gain, drug-induced movement disorders, elevated prolactin levels, sedation, and effects on the heart rate, blood pressure, and ECGs. The class of medicine is selected based on the severity of the tics and the side effect profile of the medicine based on other comorbidities such as depression, anxiety, and sleep disturbance. The American Academy of Child & Adolescent Psychiatry states that atypical antipsychotics are effective in Tourette's Disorder (TD). At the time the guidelines were published, no atypical antipsychotics were FDA approved, and only haloperidol and pimozide had been approved for TD. The guidelines found that risperidone is the most well studied non-FDA labeled atypical antipsychotic for the treatment of TD. Risperidone was found to be at least as effective as clonidine, haloperidol, and pimozide; with less frequent and severe side effects. The most common adverse reaction with risperidone therapy was mild to moderate sedation. No clinically significant extrapyramidal symptoms were observed.(26-29)
Safety	The atypical antipsychotic agents carry a boxed warning for increased mortality in elderly patients with dementia-related psychosis. The warning states that elderly patients with dementia-related psychosis treated with antipsychotic drugs

	are at an increased risk of death. These agents are not approved for the treatment of patients with dementia-related psychosis.(1-15,30-33) Abilify, Caplyta, Latuda, Rexulti, Risperdal, and Seroquel/Seroquel XR have an additional boxed warning for an increased risk of suicidal thoughts and behaviors in pediatric and young adult patients. Closely monitor all antidepressant-treated patients for worsening and emergence of suicidal thoughts and behaviors.(2,4,6,8,11,14,30,32) All clozapine agents including Versacloz, have the following boxed warnings:(1,12,13) • Severe Neutropenia: Clozaril can cause severe neutropenia, which can lead to serious and fatal infections. Patients initiating and continuing treatment with Clozaril must have a baseline blood absolute neutrophil count (ANC) measured before treatment initiation and regular ANC monitoring during treatment. • Clozaril is available only through a restricted program called the Clozapine Risk Evaluation and Mitigation Strategy (REMS). • Orthostatic Hypotension, Bradycardia, and Syncope: Risk is dose related. Starting dose is 12.5 mg. Titrate gradually and use divided dosages. • Seizure: Risk is dose related. Titrate gradually and use divided doses. Use with caution in patients with history of seizure or risk factors for seizure. • Myocarditis, Cardiomyopathy and Mitral Valve Incompetence: Can be fatal. Discontinue and obtain cardiac evaluation if findings suggest these cardiac reactions. • Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Clozaril is not approved for this condition. COBENFY has the following contraindications:(34) • Urinary retention • Moderate or severe hepatic impairment • Gastric retention • History of hypersensitivity to COBENFY or trospium chloride • Untreated narrow-angle glaucoma

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QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	2. There is support why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Baclofen

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Fleqsuvy® (baclofen) Oral suspension*	Treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscle rigidity May also be of some value in patients with spinal cord injuries and other spinal cord diseases Limitations of Use: Fleqsuvy is not indicated in the treatment of skeletal muscle spasm resulting from rheumatic disorders.	*generic available	6
LYVISPAH® (baclofen) Oral granules	Treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscular rigidity May also be of some value in patients with spinal cord injuries and other spinal cord diseases Limitations of Use: LYVISPAH is not indicated in the treatment of skeletal muscle spasm resulting from rheumatic disorders.		7
OZOBAX® OZOBAX® DS (baclofen) Oral solution	Treatment of spasticity resulting from multiple sclerosis, particularly for the relief of flexor spasms and concomitant pain, clonus, and muscle rigidity May also be of some value in patients with spinal cord injuries and other spinal cord diseases Limitations of Use: OZOBAX/OZOBAX DS is not indicated in the treatment of skeletal muscle spasm resulting from rheumatic disorders.		1,8

CLINICAL RATIONALE

Multiple Sclerosis	Multiple sclerosis (MS) is a disorder of the central nervous system (CNS) characterized by demyelization, inflammation, and degenerative changes. Most people with MS experience relapses and remissions of neurological symptoms, particularly early in the disease, and clinical events are usually associated with areas of CNS inflammation. Gradual worsening or progression, with or without subsequent acute attacks of inflammation or radiological activity, may take place early, but usually becomes more prominent over time. While traditionally viewed as a disease solely of CNS white matter, more advanced imaging techniques have demonstrated significant early and ongoing CNS gray matter damage as well.(2) Those diagnosed with MS may have many fluctuating and disabling symptoms (including, but not limited to, fatigue, impaired mobility, mood and cognitive changes, pain and other sensory problems, visual disturbances, and elimination dysfunction), resulting in a significant impact on quality of life for patients and their families. There are currently four major types of MS: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS).(2) Spasticity from the upper motor neuron syndrome (a complex of signs and symptoms that can be associated with exaggerated reflexes, autonomic hyperreflexia, dystonia, contractures, paresis, lack of dexterity, and fatigability, in addition to spasticity) can result from a variety of conditions affecting the cortex or spinal cord. Some of the more common conditions associated with spasticity include multiple sclerosis, spinal cord injury, traumatic brain injury, cerebral palsy, and post-stroke syndrome. In many patients with these conditions, spasticity can be disabling and painful, with a marked effect on functional ability and quality of life. Baclofen, dantrolene, and tizanidine are approved for the treatment of spasticity related to multiple sclerosis. Other medications used to treat spasticity with multiple sclerosis include benzodiazepines, clonidine, and gabapentin.(3) There is evidence that baclofen, tizanidine, and dantrolene are effective compared to placebo in patients with spasticity related to multiple sclerosis. Baclofen and tizanidine are roughly equivalent for efficacy in patients with spasticity. The overall rate of adverse effects between baclofen and tizanidine is similar, tizanidine causes more dry mouth and baclofen more weakness.(3)
Spinal Cord Injury	A spinal cord injury (SCI) is a traumatic event that results in a disturbance to normal sensory, motor, or autonomic function and can significantly impair a

	patient's quality of life, functional status, and social independence. Motor vehicle accidents are the primary cause of SCI, followed by falls in the elderly population.(9) Immobility and spasticity contribute to muscle contractures after SCI. Preventive management is extremely important and should begin immediately after an SCI and continue for long-term. Preventative management includes positioning, range-of-motion exercises, and splinting.(5) Baclofen, dantrolene, pregabalin and tizanidine are approved for spasticity with spinal cord injuries. Methylprednisolone can be used for SCI but the Congress of Neurological Surgeons states there is insufficient evidence to make a recommendation.(4)
Efficacy	The efficacy of Fleqsuvy (baclofen), LYVISPAH (baclofen), and OZOBAX/OZOBAX DS (baclofen) is based on bioavailability studies in healthy adults comparing baclofen oral tablets to Fleqsuvy, LYVISPAH, or OZOBAX/OZOBAX DS.(1,6,7,8)
Safety	Abrupt discontinuation of baclofen, regardless of the cause, has resulted in adverse reactions that include hallucinations, seizures, high fever, altered mental status, exaggerated rebound spasticity, and muscle rigidity, that in rare cases has advanced to rhabdomyolysis, multiple organ-system failure, and death. Therefore, reduce the dosage slowly when discontinuing, unless the clinical situation justifies a rapid withdrawal.(1,6,7,8) Fleqsuvy, LYVISPAH, and OZOBAX/OZOBAX DS are contraindicated in patients with hypersensitivity to baclofen.(1,6,7,8)

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when BOTH of the following are met: 1. ONE of the following: A. The patient has a diagnosis of spasticity resulting from multiple sclerosis (MS) AND BOTH of the following: 1. The requested agent will be used for at least ONE of the following: A. Flexor spasms and concomitant pain **OR** B. Clonus **OR** C. Muscular rigidity **AND** 2. ONE of the following: A. BOTH of the following: 1. ONE of the following: A. The patient has an intolerance or hypersensitivity to generic baclofen tablets that is not expected to occur with the requested agent **OR**

Module	Clinical Criteria for Approval
	B. The patient has an FDA labeled contraindication to generic baclofen tablets that is not expected to occur with the requested agent **OR** C. The prescriber has provided information to support use of the requested agent over generic baclofen tablets **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to another muscle relaxant (e.g., dantrolene, tizanidine) used for spasticity related to multiple sclerosis **OR** B. The patient has an intolerance or hypersensitivity to ALL muscle relaxants used for spasticity related to multiple sclerosis **OR** C. The patient has an FDA labeled contraindication to ALL muscle relaxants used for spasticity related to multiple sclerosis **OR** B. The prescriber has provided information on why the patient is unable to use a solid dosage form (e.g., difficulty swallowing tablets or capsules, feeding tube) **OR** B. The patient has a diagnosis of spasticity related to spinal cord injury or other spinal cord disease AND ONE of the following: 1. BOTH of the following: A. ONE of the following: 1. The patient has an intolerance or hypersensitivity to generic baclofen tablets that is not expected to occur with the requested agent **OR** 2. The patient has an FDA labeled contraindication to generic baclofen tablets that is not expected to occur with the requested agent **OR** 3. The prescriber has provided information to support use of the requested agent over generic baclofen tablets **AND** B. ONE of the following: 1. The patient has tried and had an inadequate response another muscle relaxant (e.g., dantrolene, pregabalin, tizanidine) used for spasticity related to spinal cord injuries or other spinal diseases **OR** 2. The patient has an intolerance, or hypersensitivity to ALL muscle relaxants used for spasticity related to spinal cord injuries or other spinal cord diseases **OR**

Module	Clinical Criteria for Approval
	3. The patient has an FDA labeled contraindication to ALL muscle relaxants used for spasticity related to spinal cord injuries or other spinal cord diseases **OR** 2. The prescriber has provided information on why the patient is unable to use a solid dosage form (e.g., difficulty swallowing tablets or capsules, feeding tube) **AND** 2. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient has had clinical benefit with the requested agent (e.g., decreased spasms) **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** Initial: 6 months, Renewal:12 months

Bempedoic Acid

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Nexletol® (bempedoic acid) Tablet	Reduce the risk of myocardial infarction and coronary revascularization in adults who are unable to take recommended statin therapy (including those not taking a statin) with: • established cardiovascular disease (CVD), or • a high risk for a CVD event but without established CVD Adjunct to diet, in combination with other low-density lipoprotein cholesterol (LDL-C) lowering therapies, or alone when concomitant LDL-C lowering therapy is not possible, to reduce LDL-C in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH)		1
Nexlizet® (bempedoic acid/ezetimibe) Tablet	Reduce the risk of myocardial infarction and coronary revascularization in adults who are unable to take recommended statin therapy (including those not taking a statin) with: • established cardiovascular disease (CVD), or • a high risk for a CVD event but without established CVD Adjunct to diet, alone or in combination with other LDL-C lowering therapies, to reduce LDL-C in adults with primary hyperlipidemia, including HeFH		2

CLINICAL RATIONALE

Familial hypercholesterolemia	Familial hypercholesterolemia (FH) is a common yet underdiagnosed autosomal dominant disorder that affects 1 in 220 individuals globally. An individual who is heterozygous for FH (HeFH) has a 50% chance of passing the gene to his or her children. FH is characterized by lifelong elevation of low-density lipoprotein cholesterol (LDL-C) and, if untreated, leads to early-onset atherosclerosis and increased risk of cardiovascular events. Affected men and women who are untreated have a 30% to 50% risk of a fatal or nonfatal cardiac event by ages 50 and 60 years, respectively. FH is generally a silent disease. Given the broad range of causes of hypercholesterolemia and early-onset coronary artery disease (CAD), it is not surprising that FH is not always in the differential diagnosis for healthcare professionals when confronted with a patient presenting with early CAD. Although diagnosis can be made on the basis of clinical features, genetic testing may offer additional insight regarding cardiac risk and diagnosis. There are no internationally agreed-upon criteria for the diagnosis of FH, so useful diagnostic criteria have been developed. Two of the criteria, the UK Simon Broome system and the Dutch Lipid Clinic Network criteria incorporate genetic tests into their algorithm.(3)
Management	Since publication of the 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol, three additional non-statin therapies have received FDA approval for management of hypercholesterolemia (bempedoic acid, evinacumab, inclisiran). The American College of Cardiology (ACC) recognized that clinicians, patients, and payers may seek more specific recommendations on when to use newer non-statin therapies if the response to statin therapy, ezetimibe, and/or PCSK9 inhibitors is deemed inadequate. The 2022 ACC Consensus Decision Pathway was designed to address current gaps in care for LDL-C lowering to reduce ASCVD risk and provides further recommendations regarding the use of newer non-statin therapies.(8,9) The key updates that the 2022 ACC Consensus Pathway recommend are for adults with ASCVD at very high risk on a maximally tolerated statin therapy that require additional lowering of LDL-C (patient has achieved<50% reduction in LDL-C or LDL-C greater than or equal to 55 mg/dL or non–HDL-C greater than or equal to 85 mg/dL) despite maximally tolerated statin therapy, a PCSK9 inhibitor and/or ezetimibe are preferred as the initial non-statin therapy followed by bempedoic acid or inclisiran for further LDL-C lowering. For adults with ASCVD NOT at very high risk on a maximally tolerated statin therapy that require additional lowering of LDL-C C (patient has achieved<50% reduction in LDL-C or LDL-C greater than or equal to 70 mg/dL or non–HDL-C greater than or equal to

	100 mg/dL) despite maximally tolerated statin therapy, when considering the addition of a non-statin therapy, ezetimibe is the preferred initial non-statin followed by adding or replacing with a PCSK9 inhibitor, then trying bempedoic acid or inclisiran.(8) The CLEAR Outcomes trial was a double-blind trial conducted in 32 countries and included 13,970 patients who were unable or unwilling to take guideline-recommended doses of statins that were randomized to oral bempedoic acid 180 mg daily or placebo and followed for a median of 3.4 years that was completed November 7th, 2022. The primary end point was a four-component composite of major adverse cardiovascular events, defined as cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization. The results of this trial indicate among statin-intolerant patients, treatment with bempedoic acid was associated with a lower risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization).(7)
Safety	Nexletol is contraindicated in patients with known hypersensitivity to any excipients in the product.(1) Nexlizet is contraindicated in patients with known hypersensitivity to ezetimibe tablets or any excipients in the product.(2)

REFERENCES

Number	Reference
1	Nexletol prescribing information. Esperion Therapeutics, Inc. March 2024.
2	Nexlizet prescribing information. Esperion Therapeutics, Inc. March 2024.
3	McGowan MP, Dehkordi SHH, Moriarty PM, Duell PB. Diagnosis and treatment of heterozygous familial hypercholesterolemia. *Journal of the American Heart Association*. 2019;8(24). doi:10.1161/jaha.119.013225
4	Reference no longer used
5	Reference no longer used

Number	Reference
6	Reference no longer used
7	Nissen SE, Lincoff AM, Brennan DM, et al. Bempedoic acid and cardiovascular outcomes in Statin-Intolerant patients. *The New England Journal of Medicine*. 2023;388(15):1353-1364. doi:10.1056/nejmoa2215024
8	Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2022 ACC Expert Consensus Decision Pathway on the role of nonstatin therapies for LDL-Cholesterol Lowering in the management of atherosclerotic cardiovascular Disease risk. *Journal of the American College of Cardiology*. 2022;80(14):1366-1418. doi:10.1016/j.jacc.2022.07.006
9	Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;139(25). doi:10.1161/cir.0000000000000625
10	Reference no longer used
11	Reference no longer used

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. BOTH of the following: 1. ONE of the following: A. The patient has a diagnosis of primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) **OR**

Module	Clinical Criteria for Approval
	B. The patient is using the requested agent to reduce the risk of myocardial infarction and coronary revascularization AND ONE of the following: 1. The patient has established cardiovascular disease (CVD) **OR** 2. The patient has a high risk for a CVD event **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to at least ONE statin **OR** B. The patient has an intolerance or hypersensitivity to statin therapy **OR** C. The patient has an FDA labeled contraindication to ALL statins **OR** B. The patient has another FDA labeled indication for the requested agent and route of administration **OR** C. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following criteria are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence

Module	Clinical Criteria for Approval
	Length of approval: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Biologic Immunomodulators

Prior Authorization with Quantity Limit

Your health benefit plan may not cover certain prescription drug products or drug categories included in this document. Please consult your benefit plan materials for details about your particular benefit. This document may include drugs that are not included on your plan's formulary. For drug coverage status, please consult your plan's formulary.

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Abrilada™ (adalimumab-afzb) Subcutaneous injection	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA) Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients 2 years of age and older Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with psoriatic arthritis (PsA) Reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) Treatment of moderately to severely active Crohn's disease (CD) in adults and pediatric patients 6 years of age and older Treatment of moderately to severely active ulcerative colitis (UC) in adult patients • Limitations of Use: ○ Effectiveness has not been established in patients who have lost response to or were	Tumor Necrosis Factor (TNF) - Alpha Inhibitor	83

Agent(s)	FDA Indication(s)	Notes	Ref#
	intolerant to tumor necrosis factor (TNF) blockers Treatment of adult patients with moderate to severe chronic plaque psoriasis (PS) who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate Treatment of moderate to severe hidradenitis suppurativa (HS) in adult patients Treatment of non-infectious intermediate, posterior, and panuveitis (UV) in adult patients		

Actemra®
 	
(tocilizumab)
 	
Subcutaneous injection
	Treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs)
	
	Treatment of giant cell arteritis (GCA) in adult patients
	
	Slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis associated interstitial lung disease (SSc-ILD)
	
	• Note:
	  ○ Subcutaneous administration with the prefilled ACTPen autoinjector has not been studied in SSc-ILD
	  ○ Intravenous administration is not approved for SSc-ILD
	
	Treatment of active polyarticular juvenile idiopathic arthritis (PJIA) in patients 2 years of age and older
	
	Treatment of active systemic juvenile idiopathic arthritis (SJIA) in patients 2 years of age and older
	
	Treatment of chimeric antigen receptor (CAR) T-cell induced severe or life-threatening cytokine release
		Interleukin-6 Inhibitor	1

Agent(s)	FDA Indication(s)	Notes	Ref#
	syndrome (CRS) in adults and pediatric patients 2 years of age and older • Note: Subcutaneous administration is not approved for CRS, use only the intravenous route for treatment of CRS Treatment of Coronavirus disease 2019 (COVID-19) in hospitalized adult patients who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) • Note: Subcutaneous administration is not approved for COVID-19, administer by intravenous infusion only for COVID-19		
Amjevita® (adalimumab-atto) Subcutaneous injection	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA) Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA) in patients 2 years of age and older Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis (PSA) Reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) Treatment of moderately to severely active Crohn's disease (CD) in adults and pediatric patients 6 years of age and older	Tumor Necrosis Factor (TNF) - Alpha Inhibitor	71

Agent(s)	FDA Indication(s)	Notes	Ref#
	Treatment of moderately to severely active ulcerative colitis (UC) in adult patients • Limitation of use: ○ The effectiveness of adalimumab products has not been established in patients who have lost response to or were intolerant to TNF blockers Treatment of adult patients with moderate to severe chronic plaque psoriasis (PS) who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate Treatment of moderate to severe hidradenitis suppurativa (HS) in adult patients Treatment of non-infectious intermediate, posterior, and panuveitis (UV) in adult patients		
Bimzelx® (bimekizumab-bkzx) Subcutaneous injection	Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy Treatment of adult patients with active psoriatic arthritis (PSA) Treatment of adult patients with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation Treatment of adult patients with active ankylosing spondylitis (AS)	Interleukin F17A and F antagonist	84
Cimzia® (certolizumab pegol) Subcutaneous injection	Reducing signs and symptoms of Crohn's disease (CD) and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy	Tumor Necrosis Factor (TNF) - Alpha Inhibitor	2

Agent(s)	FDA Indication(s)	Notes	Ref#
	Treatment of adults with moderately to severely active rheumatoid arthritis (RA) Treatment of adult patients with active psoriatic arthritis (PSA) Treatment of adults with active ankylosing spondylitis (AS) Treatment of adults with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation Treatment of adults with moderate-to-severe plaque psoriasis (PS) who are candidates for systemic therapy or phototherapy Treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older		
Cosentyx® (secukinumab) Subcutaneous injection	Treatment of moderate to severe plaque psoriasis (PS) in patients 6 years and older who are candidates for systemic therapy or phototherapy Treatment of active psoriatic arthritis (PSA) in patients 2 years of age and older Treatment of adult patients with active ankylosing spondylitis (AS) Treatment of adult patients with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation Treatment of active enthesitis-related arthritis (ERA) in patients 4 years of age and older Treatment of adults with moderate to severe hidradenitis suppurativa (HS)	Interleukin-17 Inhibitor	3

Agent(s)	FDA Indication(s)	Notes	Ref#
Cyltezo® Adalimumab-adbm Subcutaneous injection	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA) Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA) in patients 2 years of age and older Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis (PSA) Reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) Treatment of moderately to severely active Crohn's disease (CD) in adults and pediatric patients 6 years of age and older Treatment of moderately to severely active ulcerative colitis (UC) in adult patients • Limitation of use: ○ The effectiveness has not been established in patients with UC who have lost response to or were intolerant to TNF blockers Treatment of adult patients with moderate to severe chronic plaque psoriasis (PS) who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate Treatment of moderate to severe hidradenitis suppurativa (HS) in adult patients Treatment of non-infectious intermediate, posterior, and panuveitis (UV) in adult patients	Tumor Necrosis Factor (TNF) - Alpha Inhibitor	76

Agent(s)	FDA Indication(s)	Notes	Ref#
Enbrel® (etanercept) Subcutaneous injection	Reduce the signs and symptoms, including major clinical response, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis (RA) Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA) in patients ages 2 and older Reducing signs and symptoms, inhibiting the progression of structural damage of active arthritis, and improving physical function in patients with psoriatic arthritis (PSA) Reducing signs and symptoms in patients with active ankylosing spondylitis (AS) Treatment of patients 4 years or older with chronic moderate to severe plaque psoriasis (PS) who are candidates for systemic therapy or phototherapy Treatment of active juvenile psoriatic arthritis (JPsA) in pediatric patients 2 years of age and older	Tumor Necrosis Factor (TNF) - Alpha Inhibitor	4
Entyvio® (vedolizumab) Subcutaneous injection	Treatment in adults for moderately to severely active ulcerative colitis (UC) Treatment in adults for moderately to severely active Crohn's disease (CD)	Integrin receptor antagonist	5
Hadlima™ (adalimumab-bwwd) Subcutaneous Injection	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA) Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA) in patients 2 years of age and older	Tumor Necrosis Factor (TNF) - Alpha Inhibitor	77

Agent(s)	FDA Indication(s)	Notes	Ref#
	Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis (PSA) Reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) Treatment of moderately to severely active Crohn's disease (CD) in adults and pediatric patients 6 years of age and older Treatment of moderately to severely active ulcerative colitis (UC) in adult patients • Limitation of use: ○ Effectiveness has not been established in patients with UC who have lost response to or were intolerant to TNF blockers Treatment of adult patients with moderate to severe chronic plaque psoriasis (PS) who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate Treatment of moderate to severe hidradenitis suppurativa (HS) in adult patients Treatment of non-infectious intermediate, posterior, and panuveitis (UV) in adult patients		
Hulio® Adalimumab-fkjp Subcutaneous injection	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA) Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA) in patients 2 years of age and older	Tumor Necrosis Factor (TNF) - Alpha Inhibitor	74

Agent(s)	FDA Indication(s)	Notes	Ref#
	Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis (PSA) Reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) Treatment of moderately to severely active Crohn's disease (CD) in adults and pediatric patients 6 years of age and older Treatment of moderately to severely active ulcerative colitis (UC) in adult patients • Limitation of use: ○ Effectiveness has not been established in patients with UC who have lost response to or were intolerant to TNF blockers Treatment of adult patients with moderate to severe chronic plaque psoriasis (PS) who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate Treatment of moderate to severe hidradenitis suppurativa (HS) in adult patients Treatment of non-infectious intermediate, posterior, and panuveitis (UV) in adult patients		
Humira® (adalimumab) Subcutaneous injection	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA) Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA) in patients 2 years of age and older	Tumor Necrosis Factor (TNF) - Alpha Inhibitor	6

Agent(s)	FDA Indication(s)	Notes	Ref#
	Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis (PSA) Reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) Treatment of moderately to severely active Crohn's disease (CD) in adults and pediatric patients 6 years of age and older Treatment of moderately to severely active ulcerative colitis (UC) in adults and pediatric patients 5 years of age and older • Limitation of use: ○ The effectiveness of Humira has not been established in patients with UC who have lost response to or were intolerant to TNF blockers Treatment of adult patients with moderate to severe chronic plaque psoriasis (PS) who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate Treatment of moderate to severe hidradenitis suppurativa (HS) in patients 12 years of age and older Treatment of non-infectious intermediate, posterior, and panuveitis (UV) in adults and pediatric patients 2 years of age and older		
Hyrimoz® Adalimumab-adaz Subcutaneous injection	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA)	Tumor Necrosis Factor (TNF) - Alpha Inhibitor	80

Agent(s)	FDA Indication(s)	Notes	Ref#
	Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA) in patients 2 years of age and older Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis (PSA) Reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) Treatment of moderately to severely active Crohn's disease (CD) in adults and pediatric patients 6 years of age and older Treatment of moderately to severely active ulcerative colitis (UC) in adult patients • Limitation of use: ○ Effectiveness has not been established in patients with UC who have lost response to or were intolerant to TNF blockers Treatment of adult patients with moderate to severe chronic plaque psoriasis (PS) who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate Treatment of moderate to severe hidradenitis suppurativa (HS) in adult patients Treatment of non-infectious intermediate, posterior, and panuveitis (UV) in adult patients		
Idacio® Adalimumab-aacf Subcutaneous injection	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA)	Tumor Necrosis Factor (TNF) - Alpha Inhibitor	75

Agent(s)	FDA Indication(s)	Notes	Ref#
	Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA) in patients 2 years of age and older Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis (PSA) Reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) Treatment of moderately to severely active Crohn's disease (CD) in adults and pediatric patients 6 years of age and older Treatment of moderately to severely active ulcerative colitis (UC) in adult patients • Limitation of use: ○ Effectiveness has not been established in patients with UC who have lost response to or were intolerant to TNF blockers Treatment of adult patients with moderate to severe chronic plaque psoriasis (PS) who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate Treatment of moderate to severe hidradenitis suppurativa (HS) in adult patients Treatment of non-infectious intermediate, posterior, and panuveitis (UV) in adults		
Kevzara® (sarilumab) Subcutaneous injection	Treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs)	Interleukin-6 Inhibitor	7

Agent(s)	FDA Indication(s)	Notes	Ref#
	Treatment of adult patients with polymyalgia rheumatica who have had an inadequate response to corticosteroids or who cannot tolerate corticosteroid taper Treatment of active polyarticular juvenile idiopathic arthritis (pJIA) in patients who weigh 63 kg or greater		
Kineret® (anakinra) Subcutaneous injection	Reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active rheumatoid arthritis (RA), in patients 18 years of age or older who have failed 1 or more disease modifying antirheumatic drugs (DMARDs) Treatment of Neonatal-Onset Multisystem Inflammatory Disease (NOMID)* Treatment of Deficiency of Interleukin-1 Receptor Antagonist (DIRA)*	Interleukin-1 Inhibitor *- approved for use in pediatric patients as young as 1 month of age	8
Litfulo™ (ritlecitinib) Capsule	Treatment of severe alopecia areata in adults and adolescents 12 years and older • Limitations of Use: ○ Not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, cyclosporine, or other potent immunosuppressants	Janus Kinase (JAK) inhibitor	81
Olumiant® (baricitinib) Oral tablet	Treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more tumor necrosis factor (TNF) blockers • Limitation of Use: ○ Not recommended for use in combination with other JAK inhibitors, biologic disease modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine	Janus Kinase (JAK) Inhibitor	9

Agent(s)	FDA Indication(s)	Notes	Ref#
	Treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) Treatment of adult patients with severe alopecia areata • Limitation of Use: ○ Not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, cyclosporine or other potent immunosuppressants		
Omvoh™ (mirikizumab-mrkz) Subcutaneous injection	Treatment of moderately to severely active ulcerative colitis in adults	Interleukin-23 Inhibitor	86
Orencia® (abatacept) Subcutaneous injection	Treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) Treatment of patients 2 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA) Treatment of patients 2 years of age and older with active psoriatic arthritis (PSA) Prophylaxis of acute graft versus host disease (aGVHD), in combination with calcineurin inhibitor and methotrexate, in adults and pediatric patients 2 years of age and older undergoing hematopoietic stem cell transplantation (HSCT) from a matched or 1 allele-mismatched unrelated-donor • Note: Subcutaneous administration is not approved for prophylaxis of aGVHD	T-cell Costimulation Blocker	10

Agent(s)	FDA Indication(s)	Notes	Ref#
	Limitation of Use: • Concomitant use with other potent immunosuppressants (e.g., biologic disease modifying antirheumatic drugs [bDMARDS], Janus kinase [JAK] inhibitors) is not recommended		
Rinvoq® LQ (upadacitinib) Oral solution	Treatment of adults and pediatric patients 2 years of age and older with active psoriatic arthritis (PSA) who have had an inadequate response or intolerance to one or more TNF blockers • Limitations of Use: Rinvoq LQ is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine Treatment of patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (PJIA) who have had an inadequate response or intolerance to one or more TNF blockers • Limitations of Use: Rinvoq LQ is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine	Janus Kinase (JAK) Inhibitor	44
Rinvoq® (upadacitinib extended release) Oral tablet	Treatment of adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more TNF blockers • Limitations of Use: ○ Rinvoq is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent	Janus Kinase (JAK) Inhibitor	44

Agent(s)	FDA Indication(s)	Notes	Ref#
	immunosuppressants such as azathioprine and cyclosporine Treatment of adults and pediatric patients 2 years of age and older with active psoriatic arthritis (PSA) who have had an inadequate response or intolerance to one or more TNF blockers • Limitations of Use: ○ Rinvoq is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine Treatment of adult and pediatric patients 12 years of age and older with refractory, moderate to severe atopic dermatitis (AD) whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies are inadvisable • Limitations of Use: ○ Rinvoq is not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants Treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response or intolerance to one or more TNF blockers • Limitations of Use: ○ Rinvoq is not recommended for use in combination with other JAK inhibitors, biological therapies for ulcerative colitis, or with potent immunosuppressants such as azathioprine and cyclosporine		

Agent(s)	FDA Indication(s)	Notes	Ref#

	Treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response or intolerance to one or more TNF blockers
	
	• Limitations of Use:
	  ○ Rinvoq is not recommended for use in combination with other JAK inhibitors, biological therapies for Crohn's disease, or with potent immunosuppressants such as azathioprine and cyclosporine
	
	Treatment of adults with active ankylosing spondylitis (AS) who have had an inadequate response or intolerance to one or more TNF blockers
	
	• Limitations of Use:
	  ○ Rinvoq is not recommended foe use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine
	
	Treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation who have had an inadequate response or intolerance to TNF blocker therapy
	
	• Limitations of Use:
	  ○ Rinvoq is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine
	
	Treatment of patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (PJIA) who have had an inadequate response or intolerance to one or more TNF blockers
	
	• Limitations of Use:		

Agent(s)	FDA Indication(s)	Notes	Ref#
	○ Rinvoq is not recommended for use in combination with other JAK inhibitors, biologic DMARDs, or with potent immunosuppressants such as azathioprine and cyclosporine		
Siliq® (brodalumab) Subcutaneous injection	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies	Interleukin-17 Receptor Antagonist	11
Simlandi® Adalimumab-ryvk Subcutaneous injection	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA) Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (JIA) in patients 2 years of age and older Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with psoriatic arthritis (PsA) Reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) Treatment of moderately to severely active Crohn's disease (CD) in adults and pediatric patients 6 years of age and older Treatment of moderately to severely active ulcerative colitis (UC) in adult patients • Limitations of Use: ○ Effectiveness has not been established in patients who have lost response to or were	Tumor Necrosis Factor (TNF) - Alpha Inhibitor	90

Agent(s)	FDA Indication(s)	Notes	Ref#
	intolerant to tumor necrosis factor (TNF) blockers Treatment of adult patients with moderate to severe chronic plaque psoriasis (PS) who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate Treatment of moderate to severe hidradenitis suppurativa (HS) in adult patients Treatment of non-infectious intermediate, posterior, and panuveitis (UV) in adult patients		
Simponi® (golimumab) Subcutaneous injection	Treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) in combination with methotrexate Treatment of adult patients with active psoriatic arthritis (PSA) Treatment of adult patients with active ankylosing spondylitis (AS) Adult patients with moderately to severely active ulcerative colitis with inadequate response or intolerant to prior treatment or requiring continuous steroid therapy • Inducing and maintaining clinical response • Improving endoscopic appearance of the mucosa during induction • Inducing clinical remission • Achieving and sustaining clinical remission in induction responders	Tumor Necrosis Factor (TNF) - Alpha Inhibitor	12
Skyrizi® (risankizumab-rzaa) Subcutaneous injection	Treatment of moderate-to-severe plaque psoriasis (PS) in adults who are candidates for systemic therapy or phototherapy Treatment of active psoriatic arthritis (PSA) in adults	Interleukin-23 Inhibitor	43

Agent(s)	FDA Indication(s)	Notes	Ref#
	Treatment of moderately to severely active Crohn's disease in adults Treatment of moderately to severely active ulcerative colitis in adults		
Sotyktu® (deucravacitinib) Tablet	Treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy • Limitation of Use: ○ Not recommended for use in combination with other potent immunosuppressants	Tyrosine Kinase Inhibitor	67
Stelara® (ustekinumab) Subcutaneous injection	Treatment of patients 6 years and older with moderate to severe plaque psoriasis (PS) who are candidates for phototherapy for systemic therapy Treatment of patients 6 years and older with active psoriatic arthritis (PSA) Treatment of adult patients with moderately to severely active Crohn’s disease (CD) Treatment of adult patients with moderately to severely active ulcerative colitis (UC)	Interleukin-23 Inhibitor	13
Taltz® (ixekizumab) Subcutaneous injection	Treatment of patients 6 years of age and older with moderate-to severe plaque psoriasis (PS) who are candidates for systemic therapy or phototherapy Treatment of adult patients with active psoriatic arthritis (PSA) Treatment of adult patients with active ankylosing spondylitis (AS) Treatment of adult patents with active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation	Interleukin-17 Inhibitor	14

Agent(s)	FDA Indication(s)	Notes	Ref#
Tremfya® (guselkumab) Subcutaneous injection	Treatment of adults with moderate-to-severe plaque psoriasis (PS) who are candidates for systemic therapy or phototherapy Treatment of adult patients with active psoriatic arthritis (PSA) Treatment of adult patients with moderately to severely active ulcerative colitis	Interleukin-23 Inhibitor	15
Tyenne® (tocilizumab-aazg) Subcutaneous injection	Treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs) Treatment of giant cell arteritis (GCA) in adult patients Treatment of active polyarticular juvenile idiopathic arthritis (PJIA) in patients 2 years of age and older Treatment of active systemic juvenile idiopathic arthritis (SJIA) in patients 2 years of age and older	Interleukin-6 Inhibitor	50
Velsipity™ (etrasimod) Tablets	Treatment of moderately to severely active ulcerative colitis in adults	Sphingosine 1-phosphate (SIP-1) receptor modulator	85
Xeljanz® (tofacitinib) Oral Solution	Treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older who have had an inadequate response or intolerance to one or more TNF blockers • Limitations of use: ○ Use of Xeljanz in combination with biologics DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended	Janus Kinase (JAK) Inhibitor	16

Agent(s)	FDA Indication(s)	Notes	Ref#

Xeljanz®
 	
(tofacitinib)
 	
Oral tablet
	Treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more TNF blockers
	
	• Limitations of use:
	  ○ Use of Xeljanz in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended
	
	Treatment of adult patients with active psoriatic arthritis (PSA) who have had an inadequate response or intolerance to one or more TNF blockers
	
	• Limitations of use:
	  ○ Use of Xeljanz in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended
	
	Treatment of adult patients with active ankylosing spondylitis (AS) who have had an inadequate response or intolerance to one or more TNF blockers
	
	• Limitations of use:
	  ○ Use of Xeljanz in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended
	
	Treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response or intolerance to one or more TNF blockers
	
	• Limitations of use:
	  ○ Use of Xeljanz in combination with biological therapies for UC or with potent
		Janus Kinase (JAK) Inhibitor	16

Agent(s)	FDA Indication(s)	Notes	Ref#
	immunosuppressants such as azathioprine and cyclosporine is not recommended Treatment of active polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older who have had an inadequate response or intolerance to one or more TNF blockers • Limitations of use: ○ Use of Xeljanz in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended		
Xeljanz® XR (tofacitinib extended release) Oral tablet	Treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to one or more TNF blockers • Limitations of use: ○ Use of Xeljanz XR in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended Treatment of adult patients with active psoriatic arthritis (PSA) who have had an inadequate response or intolerance to one or more TNF blockers • Limitations of use: ○ Use of Xeljanz XR in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended Treatment of adult patients with active ankylosing spondylitis (AS) who have had an inadequate response or intolerance to one or more TNF blockers • Limitations of use:	Janus Kinase (JAK) Inhibitor	16

Agent(s)	FDA Indication(s)	Notes	Ref#
	○ Use of Xeljanz XR in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended Treatment of adult patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response or intolerance to one or more TNF blockers • Limitation of use: ○ Use of Xeljanz XR in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended		
Yuflyma® Adalimumab-aaty Subcutaneous injection	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA) Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA) in patients 2 years of age and older Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis (PSA) Reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) Treatment of moderately to severely active Crohn's disease (CD) in adults and pediatric patients 6 years of age and older Treatment of moderately to severely active ulcerative colitis (UC) in adult patients • Limitation of use:	Tumor Necrosis Factor (TNF) - Alpha Inhibitor	78

Agent(s)	FDA Indication(s)	Notes	Ref#
	○ Effectiveness has not been established in patients with UC who have lost response to or were intolerant to TNF blockers Treatment of adult patients with moderate to severe chronic plaque psoriasis (PS) who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate Treatment of moderate to severe hidradenitis suppurativa (HS) in adult patients Treatment of non-infectious intermediate, posterior, and panuveitis (UV) in adult patients		
Yusimry™ (adalimumab-aqvh) Subcutaneous injection	Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis (RA) Reducing signs and symptoms of moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA) in patients 2 years of age and older Reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active psoriatic arthritis (PSA) Reducing signs and symptoms in adult patients with active ankylosing spondylitis (AS) Treatment of moderately to severely active Crohn's disease (CD) in adults and pediatric patients 6 years of age and older Treatment of moderately to severely active ulcerative colitis (UC) in adult patients • Limitation of use:	Tumor Necrosis Factor (TNF) - Alpha Inhibitor	79

Agent(s)	FDA Indication(s)	Notes	Ref#
	○ Effectiveness has not been established in patients with UC who have lost response to or were intolerant to TNF blockers Treatment of adult patients with moderate to severe chronic plaque psoriasis (PS) who are candidates for systemic therapy or phototherapy, and when other systemic therapies are medically less appropriate Treatment of moderate to severe hidradenitis suppurativa (HS) in adult patients Treatment of non-infectious intermediate, posterior, and panuveitis (UV) in adult patients		
Zymfentra™ (infliximab-dyyb) Subcutaneous injection	Maintenance treatment of moderately to severely active ulcerative colitis in adults following treatment with an infliximab product administered intravenously Maintenance treatment of moderately to severely active Crohn's disease in adults following treatment with an infliximab product administered intravenously	Tumor Necrosis Factor (TNF) - Alpha Inhibitor	89

CLINICAL RATIONALE

RHEUMATOID DISORDERS - Ankylosing spondylitis (AS)	Ankylosing spondylitis (AS) is a form of chronic inflammatory arthritis characterized by sacroiliitis, enthesitis, and a marked propensity for sacroiliac joint and spinal fusion. AS is distinguished by universal involvement with sacroiliac joint inflammation or fusion and more prevalent spinal ankylosis. Goals of treatment for AS are to reduce symptoms, maintain spinal flexibility and normal posture, reduce functional limitations, maintain work ability, and decrease disease complications. The mainstays of treatment have been nonsteroidal anti-inflammatory drugs (NSAIDs) and exercise, with the additional use of disease-modifying antirheumatic drugs (DMARDs) in patients with peripheral arthritis. The American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN) recommend the following pharmacological treatment for AS:(17,47)

	• Stable AS: First line therapy with on demand NSAIDs; there is also a conditional recommendation for continuation of TNF inhibitor as monotherapy
	• Active AS:
	  ○ First line therapy with continuous NSAIDs with physical therapy
	  ○ TNF inhibitor recommended for patients with active AS despite an adequate trial with NSAIDs
	  ▪ Lack of response (or intolerance) to at least 2 different NSAIDs over 1 month or incomplete response to at least 2 different NSAIDs over 2 months would be an adequate NSAID trial to judge response
	  ○ Recommendations for nonresponse to TNF therapy (all conditional):
	  ▪ Primary nonresponse: switch to secukinumab or ixekizumab over another TNF
	  ▪ Secondary nonresponse: switch to another TNF over a non-TNF biologic
	  ▪ Recommend against addition of sulfasalazine or MTX
	  ▪ Recommend against switching to a biosimilar of the failed TNF
	  ○ TNF-inhibitors are conditionally recommended over secukinumab or ixekizumab
	  ○ Secukinumab or ixekizumab are conditionally recommended over DMARDs in patients that have failed NSAIDs and have contraindications to TNF-inhibitors
	  ○ DMARDs (i.e., methotrexate [MTX], sulfasalazine) are only conditionally recommended in patients that have failed NSAIDs and have contraindications to TNF-inhibitors
	  ○ Methotrexate is not recommended as add on therapy to TNF inhibitors in stable and active AS
	  ○ If patient has concomitant inflammatory bowel disease (IBD) or recurrent uveitis, TNF-inhibitors are recommended over other biologics
	  ○ Glucocorticoids are not recommended

RHEUMATOID DISORDERS - Nonradiographic Axial Spondyloarthritis (nr-axSpA)	Nonradiographic axial spondyloarthritis (nr-axSpA) falls under the same spondyloarthritis family as ankylosing spondylitis (AS). Nr-axSpA includes patients with chronic back pain and features suggestive of spondyloarthritis (SpA), but do not meet the classification of AS. The goals of treatment are to reduce symptoms, maintain spinal flexibility and normal posture, reduce functional limitations, maintain work ability, and decrease disease complications.

	The mainstays of treatment have been NSAIDs and exercise, with the additional use of DMARDs in patients with peripheral arthritis. The American College of Rheumatology (ACR), Spondylitis Association of America (SAA), and Spondyloarthritis Research and Treatment Network (SPARTAN) recommendation for nr-axSpA are the same as AS:(17,47)
	
	• Stable SpA: conditional recommendation for on-demand treatment with NSAIDs
	• Active SpA:
	  ○ First line therapy with continuous NSAIDs with physical therapy
	  ○ TNF inhibitor conditionally recommended for patients with active SpA despite an adequate trial with NSAIDs
	  ▪ Lack of response (or intolerance) to at least 2 different NSAIDs over 1 month or incomplete response to at least 2 different NSAIDs over 2 months would be an adequate NSAID trial to judge response
	  ○ TNF-inhibitors are conditionally recommended over secukinumab or ixekizumab
	  ○ Secukinumab or ixekizumab are conditionally recommended over DMARDs in patients that have failed NSAIDs and have contraindications to TNF-inhibitors
	  ○ Recommendations for nonresponse to TNF therapy (all conditional):
	  ▪ Primary nonresponse: switch to secukinumab or ixekizumab over another TNF
	  ▪ Secondary nonresponse: switch to another TNF over a non-TNF biologic
	  ▪ Recommend against addition of sulfasalazine or MTX
	  ▪ Recommend against switching to a biosimilar of the failed TNF
	  ○ DMARDs (i.e., methotrexate, sulfasalazine) are only conditionally recommended in patients that have failed NSAIDs and have contraindications to TNF-inhibitors
	  ○ Methotrexate is not recommended as add on therapy to TNF inhibitors in stable and active AS
	  ○ If patient has concomitant inflammatory bowel disease or recurrent uveitis, TNF-inhibitors are recommended over other biologics
	  ○ Glucocorticoids are not recommended

RHEUMATOID DISORDERS - Rheumatoid arthritis (RA)	Rheumatoid arthritis (RA) is the most common inflammatory autoimmune arthritis in adults. The main goal of therapy is to achieve remission, but additional goals include decrease inflammation, relieve symptoms, prevent joint and organ damage, improve physical function/overall well-being, and reduce long term complications.(18,25) The choice of therapy depends on several factors, including the severity of disease activity when therapy is initiated and the response of the patient to prior therapeutic interventions.(18)
	
	American College of Rheumatology (ACR) guidelines list the following guiding principles in the treatment of RA:(18)
	
	• RA requires early evaluation, diagnosis, and management
	• Treatment decisions should follow a shared decision-making process
	• Treatment decisions should be reevaluated within a minimum of 3 months based on efficacy and tolerability of the DMARD(s) chosen
	• Recommendations are limited to DMARDs approved by the US FDA for treatment of RA:
	  ○ csDMARDs: hydroxychloroquine, sulfasalazine, methotrexate (MTX), leflunomide
	  ○ bDMARDs: TNF inhibitors (etanercept, adalimumab, infliximab, golimumab, certolizumab pegol), T cell costimulatory inhibitor (abatacept), IL-6 receptor inhibitors (tocilizumab, sarilumab), anti-CD20 antibody (rituximab)
	  ○ tsDMARDs: JAK inhibitors (tofacitinib, baricitinib, upadacitinib)
	• Triple therapy refers to hydroxychloroquine, sulfasalazine, and either methotrexate or leflunomide
	• Biosimilars are considered equivalent to FDA-approved originator bDMARDs
	• Recommendations referring to bDMARDs exclude rituximab unless patients have had an inadequate response to TNF inhibitors (in order to be consistent with FDA approval) or have a history of lymphoproliferative disorder for which rituximab is an approved therapy
	• Treat-to-target refers to a systematic approach involving frequent monitoring of disease activity using validated instruments and modifications of treatment to minimize disease activity with the goal of reaching a predefined target (low disease activity or remission)
	
	ACR guidelines are broken down by previous treatment and disease activity:(18)
	
	• DMARD-naïve patients with moderate-to-high disease activity initial treatment:

	○ MTX monotherapy is strongly recommended over hydroxychloroquine, sulfasalazine, bDMARDs monotherapy, tsDMARD monotherapy, or combination of MTX plus a non-TNF bDMARD or tsDMARD ○ MTX monotherapy is conditionally recommended over leflunomide, dual or triple csDMARD therapy, or combination MTX plus a TNF inhibitor • DMARD-naïve patients with low disease activity initial treatment: ○ Hydroxychloroquine is conditionally recommended over other csDMARDs ○ Sulfasalazine is conditionally recommended over MTX ○ MTX is conditionally recommended over leflunomide • Initial therapy in csDMARD-treated patients, but MTX naïve, with moderate-to high disease activity: ○ MTX monotherapy is conditionally recommended over combination MTX and a bDMARD or tsDMARD • Treatment Modifications in patients treated with DMARDs who are not at target: ○ Addition of a bDMARD or tsDMARD is conditionally recommended over triple therapy for patients taking maximally tolerated doses of MTX who are not at target ○ Switching to a bDMARD or tsDMARD of a different class is conditionally recommended over switching to a bDMARD or tsDMARD belonging to the same class for patients taking a bDMARD or tsDMARD who are not at target Early use of DMARD, particularly MTX, is recommended as soon as possible following diagnosis of RA. Dosing of MTX for RA is once weekly dosing with starting doses at 7.5 mg or 15 mg once weekly.(26,27,28) MTX dose is increased as tolerated and as needed to control symptoms and signs of RA disease. The usual target dose is at least 15 mg weekly and the usual maximum dose is 25 mg weekly.(27,28) ACR defines optimal dosing for RA treatments as 1) dosing to achieve a therapeutic target derived from mutual patient-clinician consideration of patient priorities and 2) given for at least 3 months before therapy escalation or switching. For patients who are unable to take MTX, hydroxychloroquine, sulfasalazine, or leflunomide are other DMARD options. In patients resistant to initial MTX treatment, combination DMARD (e.g., MTX plus sulfasalazine or hydroxychloroquine or a TNF-inhibitor) is recommended.(18) For patients who are resistant to MTX after 3 months of treatment at optimal doses (usually 25 mg per week), it is recommended to either use DMARD triple therapy with MTX plus sulfasalazine and hydroxychloroquine or combination of

	MTX with TNF inhibitor. Triple therapy regimen has been found to be of similar clinical efficacy to MTX with biologics in several randomized trials, including in patients with high level of disease activity or with adverse prognostic features. The use of triple therapy has been shown to be highly cost-effective compared with combining a biologic with MTX, providing comparable or near comparable clinical benefit. The use of biologic with MTX combination is preferred when patients have high disease activity and clinical benefit from a more rapid response is needed and when patients who do not achieve satisfactory response within 3 months with non-biologic triple therapy following an inadequate response to MTX therapy.(18,28)

RHEUMATOID DISORDERS - Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Juvenile idiopathic arthritis (JIA) is arthritis that begins before the 16th birthday and persists for at least 6 weeks with other known conditions excluded. Polyarticular juvenile idiopathic arthritis (PJIA) is a subset of JIA. The ACR defines PJIA as arthritis in more than 4 joints during their disease course and excludes systemic JIA. Treatment goals are aimed at achieving clinically inactive disease and to prevent long-term morbidities, including growth disturbances, joint contractures and destruction, functional limitations, and blindness or visual impairment from chronic uveitis.(34,35)
	
	The ACR 2019 guidelines recommend the following treatment approach for PJIA:(34,35)
	
	• NSAIDs are conditionally recommended as adjunct therapy
	• DMARD therapy:
	  ○ Methotrexate (MTX) is conditionally recommended over leflunomide and sulfasalazine
	  ○ Subcutaneous MTX is conditionally recommended over oral MTX
	• Intraarticular glucocorticoids are conditionally recommended as adjunct therapy and conditionally recommended for bridging only in patients with moderate to high disease activity
	• Strongly recommend against chronic low-dose glucocorticoid use, irrespective of disease activity and/or risk factors
	• Strongly recommend combination use of a DMARD and infliximab
	• Initial therapy for all patients:
	  ○ DMARD is strongly recommended over NSAID monotherapy
	  ○ MTX monotherapy is conditionally recommended over triple DMARD therapy
	  ○ DMARD is conditionally recommended over a biologic
	  ○ Initial biologic therapy may be considered for patients with risk factors and involvement of high-risk joints (e.g., cervical spine,

	wrist, hip), high disease activity, and/or those judged by their physician to be at high risk of disabling joint damage
	• Subsequent therapy:
	  ○ Low disease activity:
	  ▪ Escalating therapy (e.g., intraarticular glucocorticoid injections, optimization of DMARD dose, trial of MTX if not already done, and adding or changing biologic agent)
	  ○ Moderate to high disease activity:
	  ▪ Add a biologic to original DMARD over changing to a second DMARD or changing to triple DMARD therapy
	  ▪ Switch to a non-TNF biologic if currently treated with first TNF +/- DMARD over switching to another TNF (unless the patient had good initial response to first TNF)
	  ▪ TNF, abatacept, or tocilizumab (depending on prior biologics received) over rituximab after trial of second biologic

RHEUMATOID DISORDERS - Systemic Juvenile Idiopathic Arthritis (SJIA)	Systemic juvenile idiopathic arthritis (SJIA) is a subset of JIA. SJIA is distinct from all other categories of JIA due to fever, rash, and visceral involvement. Disease pathogenesis and cytokine involvement in SJIA are different than other JIA categories. Up to 40% of cases of SJIA are associated with macrophage activation syndrome (MAS), a secondary hemophagocytic syndrome that is a life-threatening complication requiring urgent recognition and treatment. MAS presents with fevers, high ferritin levels, cytopenias, elevated liver enzyme levels, low fibrinogen levels, and high triglyceride levels. As it may occur at any point during the disease course careful monitoring is necessary for children with or without MAS at presentation. Goals of therapy for SJIA includes control of active inflammation and symptoms, and the prevention of a number of disease and/or treatment related morbidities, such as growth disturbances, joint damage, and functional limitations.(19) SJIA is defined as:(19) • Patient age 6 months to 18 years • Fever of at least 2 weeks duration (daily fever is not required but at some point exhibit a quotidian (daily) fever pattern, defined as a fever that rises to greater than or equal to 39 degrees Celsius at least once a day and returns to less than or equal to 37 degrees Celsius between fever peaks • Arthritis in greater than or equal to 1 joint • Accompanied by one or more of the following: ○ Evanescent erythematous rash

	○ Generalized lymphadenopathy ○ Hepatomegaly or splenomegaly ○ Pericarditis, pleuritis and/or peritonitis **SJIA without MAS** The American College of Rheumatology conditionally recommends IL-1 or IL-6 inhibitors and/or a brief trial of scheduled non-steroidal anti-inflammatories (NSAIDs) for initial treatment for SJIA without MAS. Studies suggest that a small proportion of patients with systemic JIA will respond to NSAIDs alone. If clinical response is not rapid and complete, rapid escalation of therapy is recommended. There is no consensus on the appropriate duration of initial use of NSAIDs before escalating therapy, as many prescribers prefer that the use of NSAIDs be avoided altogether for SJIA. Oral glucocorticoids are conditionally recommended against use in this population (the recommendation is conditional, as IL-1 or IL-6 inhibitors may not always be immediately available, and glucocorticoids may help control systemic and joint manifestations until IL-1 or IL-6 inhibitors can be started. Conventional synthetic disease modifying antirheumatic drugs (DMARDs) are strongly recommended against as initial therapy in this population. For subsequent therapy IL-1 and IL-6 inhibitors are strongly recommended over a single or combination of conventional synthetic DMARDs for inadequate response to intolerance of NSAIDs and/or glucocorticoids.(19) **SJIA with MAS** The American College of Rheumatology conditionally recommends IL-1 or IL-6 inhibitors over calcineurin inhibitors alone to achieve inactive disease and resolution of MAS. Glucocorticoids are conditionally recommended as part of initial treatment in patients with SJIA with MAS. Systemic glucocorticoids may be necessary for severely ill patients because they can have rapid onset of action. Longer-term glucocorticoids therapy in children is not appropriate because of its effects on bone health and growth.(19)
RHEUMATOID DISORDERS - Enthesitis Related Arthritis	Juvenile idiopathic arthritis (JIA) is a group of heterogenous forms of arthritis characterized by onset before 16 years of age, involving one or more joints, and lasting 6 weeks or more. Enthesitis related arthritis (ERA) is one form of JIA in which patients have predominately enthesitis, enthesitis and arthritis, juvenile ankylosing spondylitis, or inflammatory bowel disease associated arthropathy. The International League Against Rheumatism as arthritis and enthesitis that lasts at least 6 weeks in a child less than 16 years OR arthritis or enthesitis with two of the following features: sacroiliac tenderness or inflammatory spinal pain, HLA-B27 positivity, onset of arthritis in a male patient older than 6 years, and

	family history of HLA-B27 associated disease. Enthesitis is a distinct feature of ERA and is defined as inflammation of an enthesis, which is a site where a tendon, ligament, or joint capsule attaches to bone. (55) The ACR 2019 guidelines recommend the following treatment approach for ERA: • NSAIDs are strongly recommended over no treatment in children and adolescents (34) • TNF inhibitors are conditionally recommended over methotrexate or sulfasalazine in children and adolescents with active enthesitis despite treatment with NSAIDs (34) • First line therapy with continuous NSAIDs and physical therapy for adult patients (47) • DMARDs (i.e., methotrexate [MTX], sulfasalazine) are only conditionally recommended in patients that have failed NSAIDs and have contraindications to TNF-inhibitors (47) ○ Lack of response (or intolerance) to at least 2 different NSAIDs over 1 month or incomplete response to at least 2 different NSAIDs over 2 months would be an adequate NSAID trial to judge response (17)
RHEUMATOID DISORDERS - Psoriatic Arthritis (PsA)	Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease associated with psoriasis, most commonly presenting with peripheral arthritis, dactylitis, enthesitis, and spondylitis. Treatment involves the use of a variety of interventions, including many agents used for the treatment of other inflammatory arthritis, particularly spondyloarthritis and RA, and other management strategies of the cutaneous manifestations of psoriasis.(29) The American Academy of Dermatology (AAD) recommends initiating MTX in most patients with moderate to severe PsA. After 12 to 16 weeks of MTX therapy with appropriate dose escalation, the AAD recommends adding or switching to a TNF inhibitor if there is minimal improvement on MTX monotherapy.(30) The American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF) guidelines for PsA recommend a treat-to-target approach in therapy, regardless of disease activity, and the following:(29) • Active PsA is defined as symptoms at an unacceptably bothersome level as reported by the patient and health care provider to be due to PsA based on the presence of one of the following: ○ Actively inflamed joints

	○ Dactylitis ○ Enthesitis ○ Axial disease ○ Active skin and/or nail involvement ○ Extraarticular manifestations such as uveitis or inflammatory bowel disease • Disease severity includes level of disease activity at a given time point and the presence/absence of poor prognostic factors and long-term damage • Severe PsA disease includes the presence of 1 or more of the following: ○ Erosive disease ○ Elevated markers of inflammation (ESR, CRP) attributable to PsA ○ Long-term damage that interferes with function (i.e., joint deformities) ○ Highly active disease that causes a major impairment in quality of life ○ Active PsA at many sites including dactylitis, enthesitis ○ Function limiting PsA at a few sites ○ Rapidly progressive disease • Symptomatic treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, local glucocorticoid injections • Treatment recommendations for active disease: ○ Treatment naïve patients first line options include oral small molecules (OSM), TNF biologics, IL-17 inhibitor, and IL-12/23 inhibitor ▪ OSM (i.e., methotrexate [MTX], sulfasalazine, cyclosporine, leflunomide, apremilast) should be considered if the patient does not have severe PsA, does not have severe psoriasis, prefers oral therapy, has concern over starting a biologic, or has contraindications to TNF inhibitor ▪ Biologics (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) are recommended as a first line option in patients with severe PsA and/or severe psoriasis ○ Previous treatment with OSM and continued active disease: ▪ Switch to a different OSM (except apremilast) in patients without severe PsA or severe PS, contraindications to TNF biologics, prefers oral therapy OR add on apremilast to current OSM therapy ▪ May add another OSM (except apremilast) to current OSM therapy for patients that have exhibited partial response to

	current OSM in patients without severe PsA or severe PS, contraindications to TNF biologics, or prefers oral therapy ▪ Biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) monotherapy ○ Previous treatment with a biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) and continued active disease: ▪ Switch to another biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor, abatacept, or tofacitinib) monotherapy or add MTX to the current TNF biologic
RHEUMATOID DISORDERS - Polymyalgia Rheumatica (PMR)	Polymyalgia rheumatica (PMR) is a rheumatic disorder associated with musculoskeletal pain and stiffness in the neck, shoulder, and hip area. The etiology is not fully understood, but there are associated environmental and genetic factors. The incidence of PMR increases with age and is rarely seen in people under the age of 50. Women are approximately 2-3 times more likely to be affected by PMR than men. A characteristic feature of PMR is a new and relatively acute onset of proximal muscle pain and stiffness in the neck, shoulders, upper arms, hips and thighs. Patients often suffer from a pronounced morning stiffness with difficulty turning in or getting out of bed in the morning with some spontaneous relief of symptoms later in the day. The nonspecific clinical presentation and the absence of specific laboratory findings or serologic features often leads to some diagnostic delay.(72) The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) guidelines recommend the following for the treatment of PMR: (73) • Strongly recommends using glucocorticoids over NSAIDs for long term care of patients with PMR and used for the minimum effective duration • Conditionally recommends using the minimum effective glucocorticoid dose within a range of 12.5–25 mg prednisone equivalent daily as the initial treatment of PMR. A higher initial prednisone dose within this range may be considered in patients with a high risk of relapse and low risk of adverse events, whereas in patients with relevant comorbidities (e.g., diabetes, osteoporosis, glaucoma, etc.) and other risk factors for glucocorticoid -related side effects, a lower dose may be preferred. The guideline discourages conditionally the use of initial doses less than or equal to 7.5 mg/day and strongly recommends against the use of initial doses greater than 30 mg/day. • Strongly recommends individualizing dose tapering schedules, predicated to regular monitoring of patient disease activity, laboratory markers and

	adverse events. The following principles of glucocorticoid dose tapering are suggested: ○ Initial tapering: Taper dose to an oral dose of 10 mg/day prednisone equivalent within 4–8 weeks. ○ Relapse therapy: Increase oral prednisone to the pre-relapse dose and decrease it gradually (within 4–8 weeks) to the dose at which the relapse occurred. ○ Tapering once remission is achieved (following initial and relapse therapies): Taper daily oral prednisone by 1 mg every 4 weeks (or by 1.25 mg decrements using schedules such as 10/7.5 mg alternate days, etc.) until discontinuation given that remission is maintained. • Conditionally recommends considering intramuscular (IM) methylprednisolone as an alternative to oral glucocorticoids. The choice between oral glucocorticoids and IM methylprednisolone remains at the discretion of the prescriber. • Conditionally recommends using a single rather than divided daily doses of oral glucocorticoids for the treatment of PMR, except for special situations such as prominent night pain while tapering glucocorticoids below the low-dose range (prednisone or equivalent less than 5 mg daily). • Conditionally recommends considering early introduction of methotrexate (MTX) in addition to glucocorticoids, particularly in patients at a high risk for relapse and/or prolonged therapy as well as in cases with risk factors, comorbidities and/or concomitant medications where glucocorticoid-related adverse events are more likely to occur. MTX may also be considered during follow-up of patients with a relapse, without significant response to glucocorticoid or experiencing glucocorticoid-related adverse events. • Strongly recommends against the use of TNFa blocking agents for treatment of PMR.
RHEUMATOID DISORDERS - Juvenile Psoriatic Arthritis (JPsA)	Juvenile psoriatic arthritis (JPsA) is a relatively rare condition in childhood and represents approximately 5% of the whole JIA populations. JPsA is defined by the association of arthritis and psoriasis or, in the absence of typical psoriatic lesions, with at least two of the following:(87) • Dactylitis • Nail Pitting • Onycholysis • Family history of psoriasis in a first-degree relative.

Recent studies however have shown that this classification system could conceal more homogeneous subgroups of patients differing by age of onset, clinical characteristics, and prognosis. Little is known about genetic factors and pathogenetic mechanisms which distinguish JPsA from other JIA subtypes or from isolated psoriasis without joint involvement, especially in the pediatric population.(87)

Psoriatic arthritis of adulthood is a well-defined, although phenotypically heterogeneous, clinical condition. In the majority of cases, it is characterized by the onset of arthritis in patients with pre-existing psoriasis. An opposite scenario is seen in children: arthritis complicates only 2% of pediatrics psoriasis, whereas in JPsA skin disease typically occurs up to 10 years after the development of arthritis, making JPsA diagnosis often challenging. JPsA can be differentiated from adult PsA by several factors as follows:(87)

Clinical feature	**Adult PsA**	**JPsA**
Timing of psoriasis and arthritis onset	Psoriasis prior to arthritis	Arthritis prior to psoriasis
Oligoarticular peripheral arthritis	20%-55%	45%-55%
Polyarticular peripheral arthritis	20%-60%	33%-55%
Oligo-Extended peripheral arthritis	NA	15%-38%
Axial arthritis	7%-40%	10%-30%
Radiological damage	47%	25%
Enthesitis	30%-50%	12%-45%
Dactylitis	40%-50%	17%-37%
Nail involvement	41%-93%	37%-57%
Uveitis	8%	8%-13%

	<table><tr><td>Human Leukocyte antigen (HLA)-B27</td><td>40%-50%</td><td>10%-25%</td></tr><tr><td>Antinuclear antibodies (ANA)</td><td>16%</td><td>40%-46%</td></tr></table> Psoriasis occurs in 40%-60% of patients with JPsA, usually the classic vulgaris form, although guttate psoriasis is also observed. Psoriasis in children tends to be subtle with thin, soft plaques that may be similar to atopic eczema. Onychopathy is reported in more than half of patients with JPsA, compared with 30% in childhood psoriasis in general. Onycholysis may also be observed but is much less common than in adults.(87) Nonsteroidal anti-inflammatory drugs and oral glucocorticoids, as well as intra-articular glucocorticoids, are indicated as initial steps for symptom relief and bridge therapies. Disease modifying antirheumatic drugs (DMARDs) represent the mainstay second line treatment of children with polyarthritis. The most used is methotrexate which is recommended over leflunomide or sulfasalazine. Biologic agents should be considered in case of DMARDs failure or intolerance, presence of risk factors, or high disease activities.(87)
DERMATOLOGICAL DISORDERS - Alopecia Areata (AA)	Alopecia areata (AA) is a chronic, inflammatory disorder that affects hair follicles and sometimes nails. Initial presentation generally involves patches of hair loss on the scalp, but any hair-bearing skin may be involved. Short broken hairs, also known as exclamation point hairs, may be seen around the margins of the patches. The hair follicles in the growth phase prematurely transition to the non-proliferative involution and resting phases. This leads to hair shedding and inhibition of hair growth. The integrity of hair follicles are preserved, allowing for the potential regrowth of hair even in longstanding disease. Roughly 34-50% of patients will spontaneously recover within a year from symptom onset. AA often remits in patients with almost all patients experiencing multiple episodes of the disease, and roughly 14-50% of patients will progress to total scalp hair loss, known as alopecia totalis (AT), or total loss of scalp and body hair, known as alopecia universalis (AU). Severity at initial presentation is a strong predictor of long-term outcomes of the disease, with more severe disease progressing to AT or AU. Diagnosis is based off of clinical presentation and patient history. Other causes of alopecia need to be ruled out, and some patients may require a biopsy for diagnosis.(65,66) The management of AA involves counseling, and potentially antidepressants, due to the psychological effects associated with hair loss. Pharmacologic treatments

	are often temporary and do not alter the long-term course of the disease. Spontaneous remission rates also make it difficult to assess treatment efficacy, especially in patients with mild disease. Very potent topical corticosteroids have been used to treat patchy AA spots, but there is limited evidence to support long-term use. Intralesional corticosteroids are also an option for patchy AA spots and have shown more sustained hair growth. Systemic corticosteroids are generally reserved for patients with more extensive hair loss, but adverse effects tend to limit duration of use. Hair loss frequently recurs when these treatments are stopped. Conventional systemic immunomodulators and JAK inhibitors are often used for patients with disease that is refractory to corticosteroids and topical immunotherapy.(65,66)

DERMATOLOGICAL DISORDERS - Psoriasis (PS)	Psoriasis (PS) is a chronic inflammatory skin condition that is often associated with systemic manifestations, especially arthritis. Diagnosis is usually clinical, based on the presence of typical erythematous scaly patches, papules, and plaques that are often pruritic and sometimes painful.
	
	Treatment goals for psoriasis include improvement of skin, nail, and joint lesions plus enhanced quality of life.(20)
	
	The American Academy of Family Physicians (AAFP) categorizes psoriasis severity into mild to moderate (less than 5% of body surface area [BSA]) and moderate to severe (5% or more of BSA). The AAFP psoriasis treatment guidelines recommend basing treatment on disease severity:(20)
	
	• Mild to moderate (less than 5% of BSA and sparing the genitals, hands, feet, and face):
	  ○ Candidate for intermittent therapy: topical corticosteroids, vitamin D analogs (calcipotriene and calcitriol), or tazarotene (Tazorac)
	  ○ Candidate for continuous therapy: calcineurin inhibitors (tacrolimus and pimecrolimus)
	• Severe (5% or more of BSA or involving the genitals, hands, feet, and face):
	  ○ Less than 20% of BSA affected: vitamin D analogs (calcipotriene and calcitriol) with or without phototherapy. These agents have a slower onset of action but a longer disease-free interval than topical corticosteroids
	  ○ 20% or more of BSA affected: systemic therapy with MTX, cyclosporine, acitretin, or biologics. Biologics are recommended for those with concomitant PsA

	• Less commonly used topical therapies include non-medicated moisturizers, salicylic acid, coal tar, and anthralin
	
	The American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) categorize psoriasis severity as limited or mild (less than 3% of BSA), moderate (3% to 10% of BSA), or severe (greater than 10% of BSA). The AAD/NPF guidelines also note that psoriasis can be considered severe irrespective of BSA when it occurs in select locations (e.g., hands, feet, scalp, face, or genital area) or when it causes intractable pruritus.(31) The AAD psoriasis treatment guidelines recommend the following*:(30,31,33,88)
	
	• Mild to moderate disease (less than 5% of BSA):
	  ○ Topical corticosteroids (strength of recommendation A)
	  ○ Off-label use of 0.1% tacrolimus for psoriasis involving the face as well as inverse psoriasis (strength of recommendation B)
	  ○ Long-term use (up to 52 weeks) of topical vitamin D analogs including calcipotriene, calcitriol, tacalcitol, and maxacalcitol (strength of recommendation A)
	  ○ Use of calcipotriene foam and calcipotriene plus betamethasone dipropionate gel for the treatment of mild to moderate scalp psoriasis (strength of recommendation A)
	  ○ Use of tacalcitol ointment or calcipotriene combined with hydrocortisone for facial psoriasis (strength of recommendation B)
	  ○ Vitamin D analogs in combination with topical corticosteroids (strength of recommendation A)
	  ○ Topical tazarotene alone or in combination with narrowband ultraviolet B (NB-UVB) (strength of recommendation B), or topical corticosteroids (strength of recommendation A)
	  ○ Topical salicylic acid alone or in combination with topical corticosteroids (strength of recommendation B)
	  ○ Coal tar preparations (strength of evidence A)
	• Moderate to severe disease without PsA (5% or more of BSA or psoriasis in vulnerable areas [e.g., face, genitals, hands, and feet] that adversely affects quality of life):
	  ○ Methotrexate (adults) (strength of evidence A)
	  ○ Methotrexate is less effective than TNF-inhibitors (strength of evidence B)
	  ○ Combination therapy with methotrexate and NB-UVB (adult patients) (strength of evidence B)

- Cyclosporine for patients with severe, recalcitrant (strength of recommendation A), erythrodermic, generalized pustular, and/or palmoplantar psoriasis (strength of recommendation B)
- Acitretin as monotherapy or in combination with psoralen plus ultraviolet light (PUVA) or broad band ultraviolet light (BB-UVA [strength of evidence B])
- If UV-therapy is unavailable, first line therapies include MTX, cyclosporine, acitretin, and biologics
- Apremilast (strength of recommendation A)
- TNF-α inhibiters monotherapy (strength of evidence A) or in combination with topical corticosteroids with or without a vitamin D analogue (strength of evidence B) or in combination with acitretin (strength of evidence C)
- TNF-α inhibitors should be considered as a preferred treatment option for patients with concomitant PsA
- Infliximab (strength of evidence A)
- IL-12/IL-23 Inhibitors monotherapy (strength of evidence A) or in combination with topical corticosteroids with or without a vitamin D analogue (strength of evidence C) or in combination with acitretin or methotrexate (strength of evidence B)
- IL-12/IL-23 inhibitors in combination with apremilast or cyclosporine (strength of evidence C)
- IL-17 inhibitors monotherapy (strength of evidence A)
- IL-23 inhibitors monotherapy for moderate to severe plaque psoriasis or as monotherapy for generalized pustular psoriasis (strength of evidence B)

* Strength of recommendation and descriptions

Strength of recommendation	Description
A	Recommendation based on consistent and good-quality patient-oriented evidence
B	Recommendation based on inconsistent or limited-quantity patient-oriented evidence

	<table><tr><td>C</td><td>Recommendation based on consensus, opinion, case studies, or disease-oriented evidence</td></tr></table> Biologics are routinely used when one or more traditional systemic agents fail to produce adequate response, but are considered first line in patients with moderate to severe psoriasis with concomitant severe PsA. Primary failure is defined as initial nonresponse to treatment. Primary failure to a TNF-α inhibitor does not preclude successful response to a different TNF-α inhibitor. Failure of another biologic therapy does not preclude successful response to ustekinumab.(88) The National Psoriasis Foundation (NPF) medical board recommend a treat-to-target approach to therapy for psoriasis that include the following:(32) • The preferred assessment instrument for determining disease severity is BSA • Target response after treatment initiation should be BSA less than or equal to 1% after 3 months • Acceptable response is either a BSA less than or equal to 3% or a BSA improvement greater than or equal to 75% from baseline at 3 months after treatment initiation
DERMATOLOGICAL DISORDERS - Hidradenitis Suppurativa (HS)	Hidradenitis suppurativa (HS) is a chronic inflammatory disease causing painful, nodules to form in the folds of the skin and often secrete puss and blood. HS can be described as mild (single or few lesions in one area of the skin, Hurley Stage I), moderate (repeated cycles of enlarged lesions that break open and occur in more than one area of the skin, Hurley Stage II), and severe (widespread lesions, scarring, and chronic pain; Hurley Stage III).(45,46) Pharmacological treatment for mild HS includes topical clindamycin, oral tetracyclines, hormonal treatment, retinoids, intralesional corticosteroid injections (i.e., triamcinolone), and deroofing. Oral tetracyclines are recommended for mild to moderate HS for at least a 12 weeks course or as long-term maintenance. Combination clindamycin and rifampin is effective second-line therapy for mild to moderate HS, or as first-line or adjunct therapy for severe HS. Combination rifampin, moxifloxacin, and metronidazole are recommended as second or third-line therapy for moderate to severe disease. Dapsone may be effective for a minority of patients with mild to moderate HS as long-term maintenance therapy. Oral retinoids, such as acitretin and

	isotretinoin, have also been used for mild HS as second or third-line therapy. Hormonal therapy may be considered in female patients for mild to moderate disease as monotherapy, or as adjunct therapy for severe disease. such as hormonal contraceptives, metformin, finasteride, and spironolactone.(45,46) Treatment recommendations for moderate to severe and refractory HS include immunosuppressants (e.g., cyclosporine and low dose systemic corticosteroids) and biologic agents. The TNF-inhibitors that are recommended are adalimumab, at doses within FDA labeling, and infliximab, but optimal doses have not been established. Anakinra and ustekinumab may be effective, but require dose ranging studies to determine optimal doses for management.(45,46)
DERMATOLOGICAL DISORDERS - Atopic Dermatitis (AD)	Atopic dermatitis (AD), also known as atopic eczema, is a chronic, pruritic inflammatory dermatosis affecting up to 25% of children and 1-5% of adults. AD follows a relapsing course and is associated with elevated serum immunoglobulin (IgE) levels and a personal or family history of type I allergies, allergic rhinitis, and/or asthma. Onset is most common between 3 and 6 months of age, with approximately 60% of patients developing the eruption in the first year of life and 90% by age 5. While the majority of affected individuals have resolution of disease by adulthood, 10 to 30% do not, and a smaller percentage first develop symptoms as adults. AD has a complex pathogenesis involving genetic, immunologic, and environmental factors, which lead to a dysfunctional skin barrier and dysregulation of the immune system. Clinical findings include erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and lichenification. These clinical findings vary by patient age and chronicity of lesions. Pruritus is a hallmark of the condition that is responsible for much of the disease burden borne by patients and their families. Typical patterns include facial, neck and extensor involvement in infants and children; flexure involvement in any age group, with sparing of groin and axillary regions.(56) Goals of treatment are to reduce symptoms (pruritus and dermatitis), prevent exacerbations, and minimize therapeutics risks.(60) Despite its relapsing and remitting nature, the majority of patients with AD can achieve clinical improvement and disease control with topical emollient/moisturizer use and conventional topical therapies (including corticosteroids and calcineurin inhibitors).(59,60) Moisturizers reduce signs, symptoms, and inflammation in AD, and can improve severity while also increasing time between flares. Moisturizers are considered generally safe and are strongly recommended to be used as part of a treatment regimen for AD, either as monotherapy or as concurrent use with pharmacologic treatments.(58)

	Topical therapies remain the mainstay of treatment due to their proven track record and generally favorable safety profile. They can be utilized individually or in combination with other topical, physical, and/or systemic treatments; as different classes of treatment have different mechanisms of action, combining therapies allows for the targeting of AD via multiple disease pathways. The American Academy of Dermatology (AAD) strongly recommends the following topical agents:(58) • Topical corticosteroids (TCS) • Calcineurin inhibitors (TCIs) (e.g., tacrolimus, pimecrolimus) • Topical PDE-4 inhibitors (e.g., crisaborole) [mild to moderate AD] • Topical JAK inhibitors (e.g., ruxolitinib) [mild to moderate AD] TCS are the most commonly utilized FDA-approved therapies in AD and are commonly used as first-line treatment for mild-to severe dermatitis in all skin regions. TCS target a variety of immune cells and suppress the release of proinflammatory cytokines. High to very high (super) potency TCS can be used to control flares and treat severe disease, while medium potency TCS are utilized for longer courses and as maintenance therapy. Lower potency TCS may be used, and it is important to consider the anatomical site (i.e., using lower potency agents on the face, neck, genitals, and body folds) and severity of the disease when choosing a steroid potency. Most studies of TCS in AD management involve twice daily application, but some studies (particularly for potent TCS) suggest once daily use may be sufficient. Traditionally, TCS were stopped once AD signs and symptoms of an AD flare were controlled. Maintenance in between AD flares with once to twice weekly use of TCS is another approach.(58) TCIs are a safe anti-inflammatory option for mild-to-severe AD, particularly when there is concern for adverse events secondary to corticosteroid use. Both tacrolimus and pimecrolimus have been shown to be effective in treating AD, but pimecrolimus may be more appropriate for patients who have milder disease or are sensitive to local reactions.(58) Prescribing information for pimecrolimus cream and tacrolimus ointment indicate evaluation after 6 weeks if symptoms of AD do not improve for adults and pediatrics.(62,63). When AD is more severe or refractory to topical treatment, advanced treatment with phototherapy or systemic medications can be considered. Phototherapy is conditionally recommended by the AAD as a treatment for AD based on low certainty evidence. The AAD strongly recommends the following systemic therapies:(59) • Monoclonal antibodies (biologics) (e.g., dupilumab, tralokinumab)

	• JAK inhibitors (e.g., upadacitinib, abrocitinib, baricitinib) In a change from the 2014 AAD AD guidelines, the use of systemic antimetabolites such as methotrexate, immunosuppressants such as systemic corticosteroids, mycophenolate mofetil, azathioprine, and cyclosporine are now conditionally recommended for AD only in a small number of select patients due to low or very low certainty of evidence and need for monitoring. The most favored first-line systemic is dupilumab.(59) There is no clear consensus on how to operationalize a definition of the FDA indication for treatment of patients with "moderate to severe" AD. The severity of AD can vary substantially over time and, from a patient's perspective, can include a complex combination of intensity of itch, location, body surface area (BSA) involvement, and degree of skin impairment. Given the variability of patient phenotype and lack of familiarity among clinicians with scoring systems used in clinical trials, it is advisable to create a broad clinically relevant definition inclusive of multiple specific measures of disease intensity for example:(82) One of the following: • Affected BSA greater than or equal to 10% • Investigator Global Assessment (IGA) greater than or equal to 3 • Eczema Area and Severity Index (EASI) greater than or equal to 16 OR One of the following: • Affected BSA greater than or equal to 10% • Involvement of body sites that are difficult to treat with prolonged topical corticosteroid therapy (e.g., hands, feet, face, neck, scalp, genitals/groin, skin folds) • Severe itch that has been unresponsive to topical therapies
INFLAMMATORY BOWEL DISEASE - Crohn's Disease (CD)	Crohn’s Disease (CD) is an inflammatory condition that can affect any portion of the gastrointestinal tract from the mouth to the perianal area. Choice of therapy is dependent on the anatomic location of disease, the severity of disease, and whether the treatment goal is to induce remission or maintain remission.(21,36) The American Gastroenterological Association (AGA) 2021 guideline recommends the following:(21) • Biologic therapy:

	○ The AGA suggest early introduction with a biologic, with or without an immunomodulator, rather than delaying their use until after failure of 5-aminosalicylates and/or corticosteroids ○ Anti-TNF (i.e., infliximab or adalimumab) and ustekinumab are recommended over no treatment for the induction and maintenance of remission ○ Vedolizumab is suggested over no treatment for the induction and maintenance of remission ○ AGA suggests against the use of natalizumab over no treatment for the induction and maintenance of remission ○ Patients naïve to biologic therapy, the AGA recommends infliximab, adalimumab, or ustekinumab over certolizumab pegol and suggests the use of vedolizumab over certolizumab pegol for the induction of remission ○ Patients with primary non-response to anti-TNF, the AGA recommends ustekinumab and suggests vedolizumab for induction of remission ○ Patients with secondary non-response to infliximab, the AGA recommends use of adalimumab or ustekinumab and suggests the use of vedolizumab for the induction of remission (if adalimumab was the first line drug, there is indirect evidence to suggest using infliximab as a second-line agent) • DMARD therapy: ○ Corticosteroids are suggested over no treatment for the induction of remission, and are recommended against for maintenance of remission ○ Patients in corticosteroid induced remission or with quiescent moderate to severe CD, the AGA suggests thiopurines for maintenance of remission ○ Subcutaneous or intramuscular methotrexate are suggested over no treatment for the induction and maintenance of remission ○ The AGA recommends against the use of 5-aminosalicylates or sulfasalazine over no treatment for the induction or maintenance of remission ○ The AGA suggests against the use of thiopurines over no treatment for achieving remission and recommends biologic drug monotherapy over thiopurine monotherapy for induction of remission ○ The AGA suggests against the use of oral methotrexate monotherapy over no treatment for the induction and maintenance of remission

	• Combination therapy:
	  ○ Patients that are naïve to biologics and immunomodulators, the AGA suggest use of infliximab in combination with thiopurines over infliximab monotherapy for the induction and maintenance of remission (combination infliximab with methotrexate may be more effective over infliximab monotherapy)
	  ○ Patients that are naïve to biologics and immunomodulators, the AGA suggest use of adalimumab in combination with thiopurines over adalimumab monotherapy for the induction and maintenance of remission (combination adalimumab with methotrexate may be more effective over adalimumab monotherapy)
	  ○ No recommendations are being made regarding the use of ustekinumab or vedolizumab in combination with thiopurines or methotrexate over biologic monotherapy for induction or maintenance or remission
	
	The 2018 American College of Gastroenterology (ACG) guideline recommends the following(36):
	
	• Mild to moderately severe disease/low risk disease:
	  ○ Sulfasalazine (in doses of 3-6 grams daily) is effective in colonic and/or ileocolonic CD, but not those with isolated small bowel disease
	  ○ 5-aminosalicylic (ASA) suppositories and enema preparations are effective for induction and maintenance of remission in rectal and sigmoid disease
	  ○ Conventional corticosteroids are primarily used for the treatment of flares, and are often used as a bridge until immunomodulators and/or biologic agents become effective
	  ○ Controlled ileal release budesonide is effective for induction of remission in ileocecal disease
	• Moderate to severe disease/moderate to high-risk disease
	  ○ Corticosteroids are effective for short-term use in alleviating signs and symptoms of moderate to severely active CD, but do not induce mucosal healing and should be used sparingly
	  ○ Azathioprine, 6-mercaptopurine, or MTX (15 mg once weekly) may be used in treatment of active disease and as adjunctive therapy for reducing immunogenicity against biologic therapy
	  ○ TNF inhibitors should be used to treat CD that is resistant to treatment with corticosteroids and that is refractory to thiopurines or MTX

	○ Vedolizumab with or without an immunomodulator should be considered for induction of symptomatic remission for patients with moderate to severely active CD and objective evidence of active disease ○ Ustekinumab should be used in patients that have failed previous treatment with corticosteroids, thiopurines, MTX, or TNF inhibitors, or in patients with no prior TNF inhibitor exposure • Severe/fulminant disease: ○ IV corticosteroids should be used ○ TNF inhibitors can be considered • Maintenance therapy: ○ Thiopurines or methotrexate should be considered once remission is induced with corticosteroids ○ TNF inhibitors, specifically infliximab, adalimumab, and certolizumab pegol, should be used in combination with azathioprine, MTX, or 6-mercaptopurine to maintain remission of TNF induced remission ○ Vedolizumab should be used for maintenance of remission of vedolizumab induced remission ○ Ustekinumab should be used for maintenance of remission of ustekinumab induced remission
INFLAMMATORY BOWEL DISEASE - Ulcerative Colitis (UC)	Ulcerative colitis (UC) is a chronic immune-mediated inflammatory condition affecting the large intestine associated with inflammation of the rectum, but that can extend to involve additional areas of the colon. The American College of Gastroenterology (ACG) recommends a treat-to-target approach and recommend therapeutic management should be guided by diagnosis (i.e., Montreal classification), assessment of disease activity (i.e., mild, moderate, and severe), and disease prognosis. The ACG treatment recommendations are further broken down into induction therapies and maintenance of remission. The 2019 ACG treatment guidelines recommend the following for therapeutic management of UC(37): <u>Induction of remission</u>: • Mildly active disease: ○ Rectal 5-ASA at a dose of 1 g/day with or without oral 5-ASA at a dose of at least 2 g/day for left-sided UC ○ Rectal 5-ASA at a dose of 1 g/day for ulcerative proctitis ○ Oral 5-ASA at a dose of at least 2 g/day for extensive UC

	○ Add oral budesonide multi-matrix (MMX) 9 mg/day for patients that are intolerant or non-responsive to oral and/or rectal and oral 5-ASA at appropriate doses • Moderately active disease: ○ Oral budesonide multi-matrix (MMX) 9 mg/day for induction of remission • Moderately to severely active disease: ○ Oral systemic corticosteroids, TNF inhibitors (i.e., adalimumab, golimumab, or infliximab), tofacitinib, or vedolizumab to induce remission ○ Combination of infliximab with thiopurine therapy when using infliximab for induction ○ Switch to tofacitinib or vedolizumab for induction in patients that have failed TNF inhibitors ○ Patients with initial response to TNF inhibitors that lose response should have antibody levels and serum drug levels tested to assess reason for loss of response. If serum levels are adequate, use of another TNF inhibitor is not likely to be of benefit. <u>Maintenance of remission</u>: • Previously mildly active disease: ○ Rectal 5-ASA at a dose of 1 g/day in patients with ulcerative proctitis ○ Oral 5-ASA at a dose of at least 2 g/day in patients with left-sided or extensive UC • Previously moderately to severely active disease: ○ Thiopurines in patients that achieved remission due to corticosteroid induction ○ Continue TNF inhibitors (i.e., adalimumab, golimumab, or infliximab) for remission due to TNF induction ○ Continue vedolizumab for remission due to vedolizumab induction ○ Continue tofacitinib for remission due to tofacitinib induction The American Gastroenterology Association (AGA) published recommendations for the management of mild to moderate UC(38): • Use either standard-dose mesalamine (2-3 g/day) or diazo-bonded 5-ASA for patients with extensive UC for induction of remission and maintenance of remission

	• May add rectal mesalamine to oral 5-ASA in patients with extensive or left-sided UC for induction of remission and maintenance of remission
	• Use high dose mesalamine (greater than 3 g/day) with rectal mesalamine in patients with suboptimal response to standard-dose mesalamine, diazo-bonded 5-ASA, or with moderate disease activity for induction of remission and maintenance of remission
	• Add either oral prednisone or budesonide MMX in patients that are refractory to optimized oral and rectal 5-ASA regardless of disease extent
	
	The American Gastroenterology Association (AGA) published recommendations for the management of moderate to severe UC(48):
	
	• Standard of care is to continue agents initiated for induction therapy as maintenance therapy, if they are effective (excluding corticosteroids and cyclosporine)
	• Adult outpatients with moderate to severe UC:
	  ○ Infliximab, adalimumab, golimumab, vedolizumab, tofacitinib or ustekinumab are strongly recommended over no treatment
	  ○ Biologic naïve patients:
	  ▪ infliximab or vedolizumab are conditionally recommended over adalimumab for induction of remission
	  ▪ Recommend tofacitinib only be used in the setting of a clinical or registry study
	  ○ Previous exposure to infliximab, particularly those with primary non-response, ustekinumab or tofacitinib are conditionally recommended over vedolizumab or adalimumab for induction of remission
	  ○ Conditionally recommend against use of thiopurine monotherapy for induction, but may be used for maintenance of remission over no treatment

OTHER DISORDERS - Uveitis	Uveitis is characterized by inflammation of the uvea, which is the middle portion of the eye; the anterior portion of the uvea includes the iris and ciliary body, and the posterior portion of the uvea is known as the choroid.(39) Treatment of non-infectious uveitis depends on the location of inflammation. Anterior uveitis is generally treated with topical glucocorticoids, such as prednisolone ophthalmic drops.(22,39) Uveitis that is primarily posterior to the lens is generally not responsive to topical medication, although some experts are increasingly using difluprednate.(22) Oral corticosteroids continue to be the mainstay of treatment for noninfectious intermediate, posterior, and pan uveitis. Intraocular and

	periocular injections of triamcinolone or glucocorticoids are also options, although patients may decline the injections. Systemic treatment is generally reserved for resistant inflammation and may be indicated in patients with glaucoma who cannot be treated with local injection. If remission has been achieved for 6 to 12 months with systemic glucocorticoids, the maintenance dose may be gradually discontinued.(22,42) The American Academy of Ophthalmology recommends the use of immunosuppressive agents, such as methotrexate, azathioprine, mycophenolate, cyclosporine, and tacrolimus, for patients that are intolerant and/or resistant to systemic corticosteroids. TNF-inhibitors, such as adalimumab, are recommended if the patient is inadequately controlled by corticosteroids and non-corticosteroid systemic immunomodulatory therapies.(22,42)

OTHER DISORDERS - Giant Cell Arteritis (GCA)	Giant cell arteritis (GCA) is a blood vessel disease that commonly occurs with polymyalgia rheumatica. It is a type of vasculitis involving mostly the arteries of the scalp and head, especially the arteries over the temples. Eyesight can be affected if GCA spreads to the blood vessels that supply the eye. Treatment should begin as soon as possible to prevent loss of vision.(23)
	
	The American College of Rheumatology/Vasculitis Foundation guidelines recommend High-dose systemic glucocorticoids as the mainstay of therapy for GCA. The guidelines provide the following recommendations for the medical management of GCA(40):
	
	• Patients with newly diagnosed active GCA with visual symptoms/loss or critical cranial ischemia:
	  ○ High dose IV pulse corticosteroids followed by high dose oral corticosteroids with or without a non-corticosteroid immunosuppressive agent (i.e., methotrexate or tocilizumab)
	  ○ Taper oral corticosteroids in patients that achieve remission
	  ○ Consider adding on or changing non-corticosteroid immunosuppressive agent in patients that have not achieved remission
	• Patients with newly diagnosed active GCA without visual symptoms/loss or critical cranial ischemia:
	  ○ High dose oral corticosteroids with or without a non-corticosteroid immunosuppressive agent (i.e., methotrexate or tocilizumab)
	  ○ Taper oral corticosteroids in patients that achieve remission

	○ Consider adding on or changing non-corticosteroid immunosuppressive agent in patients that have not achieved remission
OTHER DISORDERS - Cryopyrin-Associated Periodic Syndromes (CAPS)/Neonatal-Onset Multisystem Inflammatory Disease (NOMID)	Cryopyrin-associated periodic syndrome (CAPS) is a rare autosomal dominant hereditary autoimmune disorder associated with a defect in the cryopyrin protein. CAPS syndrome is caused by a gain of function mutation in the NLRP3 gene leading to over secretion of fever causing cytokine IL-1B. The CAPS spectrum includes mild, moderate, and severe phenotypes. The mild phenotype is called familial cold autoinflammatory syndrome (FCAS), the moderate phenotype is also known as Muckle-Wells syndrome (MWS), the neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous articular syndrome (CINCA) describes the severe phenotype. CAPS is diagnosed clinically and genetically. There are more than 240 sequence variants of the NLRP3 gene and mutations in this gene are not inclusive of a CAPS diagnosis. The diagnostic criteria of CAPS recognize that all but a few patients with CAPS have detectable systemic inflammation and use unique CPS-specific clinical features along the whole disease spectrum to achieve reasonable specificity and sensitivity to aid clinicians in making the CAPS diagnosis. These diagnostic criteria do not include genetic confirmation, and therefore can be applied in places where genetic testing is not available. The diagnostic criteria for CAPS are as follows:(24) • Raised inflammatory markers (CRP/SAA) • The presence of at least two of the following signs/symptoms: • Urticaria-like rash • Cold/stress triggered episodes • Sensorineural hearing loss • Musculoskeletal symptoms of arthralgia/arthritis/myalgia • Chronic aseptic meningitis • Skeletal abnormalities of epiphyseal overgrowth/frontal bossing FCAS is characterized by episodes of rash, fever. and joint pain following generalized exposure to cold. Attacks usually occur 1-2 hours after exposure and last less than 24.(49) Patients experience urticaria, arthralgia, fever with chills, severe thirst, red-eyes, and headache after a general cold exposure, including air conditioning. In MWS, inflammation can occur spontaneously as well as from triggers, such as stress, cold, or exercise, with episodes lasting from one to three days. MWS shares the same characteristics as FCAS, but is also characterized by renal amyloidosis, sensorineural hearing loss, and conjunctivitis. Hearing loss, partial or complete, often develop by teenage years.(41)

	NOMID is a rare chronic inflammatory disease. NOMID is characterized by fever, urticarial rash, aseptic meningitis, deforming arthropathy, hearing loss, and intellectual disability. An urticaria-like rash develops within the first six weeks of life, and a characteristic bony overgrowth predominantly involving the knees develops in most affected children. Therapies are aimed at suppressing inflammation and have included high-dose corticosteroids, disease-modifying antirheumatic drugs, and biologic agent targeting tumor necrosis factor (TNF). Selective blockade of interleukin-1B is effective in the pathophysiology and organ-specific manifestations of NMOSD, in particular the CNS manifestations of the disease.(57) Treatment aims are to suppress systemic inflammation, to improve functionality, to prevent organ damage, and to increase patients' quality of life. To achieve these aims, cytokine targeting drugs are important and evidence-based treatment. Since IL-1 plays a central role in CAPS pathogenesis, the anti-IL1 treatments (anakinra, canakinumab, and rilonacept) are recommended for the whole CAPS spectrum.(24)
OTHER DISORDERS Deficiency of the IL-1 Receptor Antagonist (DIRA)	Systemic autoinflammatory diseases (SAIDs) are a group of multisystem immunodysregulatory disorders caused primarily by the dysfunction of the innate immune system. Currently, SAIDs are comprised of a wide range of disorders with systemic and organ-specific inflammation in the absence of infections or autoimmunity. In a subset of genetically defined SAIDs, the pathogenesis is driven by increased release or signaling of the pro-inflammatory cytokine IL-1.(51) Patients with DIRA present with early-onset pustular rashes that can be triggered by mechanical stress (pathergy), with sterile osteomyelitis, and nail changes (onychomadesis). Although inflammatory markers are typically highly elevated, fever may be absent. Vertebral involvement can include odontoid osteomyelitis resulting in destruction and neck instability, vertebral block formation and gibbus-like spinal changes that need to be screened for by MRI or CT. The differential diagnosis for DIRA includes chronic recurrent multifocal osteomyelitis (CRMO), synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome and pustular psoriasis. Genetic testing for monogenic defects with overlapping clinical features should include *LPIN2, FGR, FBLIM1* for *CRMO*, *CARD14* for CARD14-Mediated Psoriasis (CAMPS), *IL36RN* for Deficiency of IL-36 Receptor Antagonist (DITRA), *AP1S3* for other pustular psoriasis and *MEFV* for Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis (PAAND).(51) Aims of therapy are early control of disease activity, prevention of disease and treatment related damage, and optimal health-related quality of life. The ultimate

	goal of a treat-to-target approach is complete remission. In absence of a consensus definition of remission or minimal disease activity for these diseases, remission has been defined for clinical studies and clinical monitoring as an absence of clinical symptoms and normal inflammatory markers. Anakinra and rilonacept both block IL-1α and IL-1β and should be used for DIRA patients.(51)
OTHER DISORDERS-Systemic Sclerosis (Scleroderma)-Associated Interstitial Lung Disease (ILD)	Systemic sclerosis (SSc) is a connective tissue disease (CTD) that affects numerous organ systems, including skin, blood vessels, heart, lungs, kidneys, gastrointestinal, and musculoskeletal. Pulmonary disease is the leading cause of death in patients with systemic sclerosis, and ILD is a common manifestation that tends to occur early in the course of systemic sclerosis.(52) The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) collaborated on classification criteria for the diagnosis of systemic sclerosis, in which they note that systemic sclerosis-associated ILD is diagnosed when there is radiographic evidence of diffuse parenchymal lung disease in patients with systemic sclerosis. The ACR/EULAR criteria note that ILD is defined as pulmonary fibrosis seen on HRCT or chest radiography, most pronounced in the basilar portions of the lungs.(54) The American College of Rheumatology (ACR) published a treatment algorithm for systemic sclerosis and related conditions. The ACR recommends the following treatment options for ILD associated with systemic sclerosis:(53) Induction therapy: • Mycophenolate mofetil (MMF) as first line therapy • IV cyclophosphamide (CYC) as second line therapy • Rituximab as third line therapy • Lung transplant or hemopoietic stem cell transplant for select patients as fourth line therapy Maintenance therapy: • MMF as first line therapy • Azathioprine as second line therapy • IV or oral CYC as third line therapy Recent recommendations from the American College of Rheumatology suggest early first line treatment with tocilizumab based on the efficacy and safety from phase II and phase III clinical trials. MMF and CYC are alternative options, but do not have clinical trial data showing efficacy and safety for patients with subclinical ILD. Patients that have clinical evidence of skin and/or

	musculoskeletal manifestations and inactive disease, MMF, CYC, and nintedanib are the preferred first line options for patients with SSc-ILD. Patients with clinical evidence of skin and/or musculoskeletal manifestations and active disease, tocilizumab, MMF, and CYC are suggested as initial therapy. After treatment is initiated, patients should be followed up every 4 months until disease stabilization. Patients that achieve stabilization on first line therapy, should continue first line therapy for maintenance therapy.(70)
Efficacy	**Cosentyx** *Psoriatic Arthritis* The safety and efficacy of Cosentyx were assessed in 1999 patients, in 3 randomized, double-blind, placebo-controlled studies (PsA1, PsA2 and PsA3) in adult patients, age 18 years and older with active psoriatic arthritis (greater than or equal to 3 swollen and greater than or equal to 3 tender joints) despite non-steroidal anti-inflammatory drug (NSAID), corticosteroid or disease modifying anti-rheumatic drug (DMARD) therapy. In PsA1, patients treated with 150 mg or 300 mg Cosentyx demonstrated a greater clinical response, including ACR20, ACR50, and ACR70 compared to placebo at Week 24 (Table 6). Responses were similar in patients regardless of concomitant methotrexate treatment. Responses were seen regardless of prior anti-TNFα exposure. Patients on placebo who received Cosentyx without a loading regimen achieved similar ACR20 responses over time (data not shown).(3) In PsA3 Study, inhibition of progression of structural damage was assessed radiographically and expressed by the modified mTSS and its components, the Erosion Score (ES) and Joint Space Narrowing Score (JSN), at Week 24 compared to baseline. Cosentyx 150 mg without load, 150 mg with load and 300 mg with load treatment significantly inhibited progression of peripheral joint damage compared with placebo treatment as measured by change from baseline in mTSS at Week 24. The percentage of patients with no disease progression (defined as a change from baseline in mTSS of less than or equal to 0.0) from randomization to Week 24 was 75.7%, 70.9%, and 76.5% for Cosentyx 150 mg without load, 150 mg, 300 mg, respectively versus 68.2% for placebo. (3) Future 4 and Future 5 trials assessed the efficacy and safety of Cosentyx 150 mg with or without loading dose in patients with active psoriatic arthritis.(3) Future 4 trial was a randomized, double-blind, placebo-controlled phase 3 multicenter study of Cosentyx 150 mg, with and without a loading regimen, assessed the efficacy, safety and tolerability in patients with active psoriatic arthritis over 104 weeks. The primary end point was met by both secukinumab

treatment regimens (150 mg and 150 mg no-loading dose), demonstrating a significantly higher ACR20 response with secukinumab compared with placebo at week 16. Both secukinumab 150 mg and 150 mg no-loading dose regimens improved other clinically important end points including DAS28-CRP, PASI 75, SF36 PCS, ACR50, ACR70, PASI 90, MDA, FACIT-Fatigue and HAQ-DI response and resolution of enthesitis and dactylitis through 2 years.(3)

Future 4 Trial

Primary Endpoint	150 mg with loading dose		150 mg without loading dose	
	16 weeks	52 weeks	16 weeks	52 weeks
ACR 20	41.2%	60.5%	39.8%	57.5%
ACR 50	22.8%	40.4%	16.8%	22.8%
ACR 70	7.9%	32.7%	8.8%	18.6%

The Future 4 trial indicated that there was no statistically significant difference between the loading dose and non-loading dose for all primary and secondary endpoints.(68)

Future 5 was a double-blind, placebo-controlled, parallel-group phase III trial of Cosentyx 150 mg, with and without a loading regimen, and Cosentyx 300 mg, to assess the efficacy, safety and tolerability in patients with active psoriatic arthritis over 24 weeks. The primary endpoint, ACR20 response at week 16, was met for all secukinumab regimens, and secondary endpoints were significant for all secukinumab doses except for enthesitis and dactylitis resolution in the 150mg without LD group.

Future 5 Trial

Primary Endpoint	150 mg with loading dose		150 mg without loading dose	
	16 weeks	24 weeks	16 weeks	24 weeks
ACR 20	55.5%	53.2%	59.5%	53.2%
ACR 50	35.9%	39%	32.0%	36%
ACR 70	18.2%	24.1%	14.9%	18.5%

The Future 5 trial did not assess if there was statistically significant differences between the loading vs non-loading doses for any endpoints.(69)

Ankylosing Spondylitis

The safety and efficacy of Cosentyx were assessed in 816 patients in three randomized, double-blind, placebo-controlled studies (AS1, AS2, and AS3) in adult patients 18 years of age and older with active ankylosing spondylitis. In AS1, patients treated with 150 mg Cosentyx demonstrated greater improvements in ASAS20 and ASAS40 responses compared to placebo at Week 16. Responses were similar in patients regardless of concomitant therapies. Patients on placebo who received Cosentyx without a loading regimen achieved similar ASAS20 responses over time. At Week 16, the ASAS20 and ASAS40 responses were 58.1% and 40.5% for 150 mg and 60.5% and 42.1% for 300 mg, respectively. Cosentyx treated patients showed improvement compared to placebo-treated patients in health-related quality of life as assessed by ASQoL at Week 16.(3)

Non-Radiographic Axial Spondyloarthritis

The safety and efficacy of Cosentyx were assessed in 555 patients in one randomized, double-blind, placebo-controlled phase 3 study (nr-axSpA1, NCT02696031) in adult patients 18 years of age and older with active non-radiographic axial spondyloarthritis. Patients were treated with Cosentyx 150 mg subcutaneous treatment with load (Weeks 0, 1, 2, 3, and 4) or without a load (Weeks 0 and 4) followed by the same dose every 4 weeks or placebo. In nr-axSpA1 Study, treatment with Cosentyx 150 mg resulted in significant improvements in the measure of disease activity compared to placebo at Week 16 and Week 52.

Number of subjects with ASAS40 response (%)	Cosentyx 150 mg without load (n = 184)	Cosentyx 150 mg with load (n = 185)	Placebo (n = 186)	Difference from Placebo (95% CI)	
				Cosentyx 150 mg without load	Cosentyx 150 mg with load
Week 16	75 (41)	74 (40)	52 (28)	13 (3, 22)	12 (2, 22)
Week 52	70 (38)	62 (34)	36 (19)	19 (10, 28)	14 (5, 23)

	COSENTYX treated patients showed improvement in both load and without load arms compared to placebo-treated patients at Week 16 in health-related quality of life as measured by ASQoL (LS mean change: Week 16: -3.5 and -3.6 vs - 1.8, respectively).(3)
Safety	*Adalimumab(6,71,74,75,76,77,78,79,80,83,90)* Adalimumab products have the following boxed warnings: • Increased risk for developing serious infections that may lead to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections. Perform test for latent TB, and if positive, start treatment for TB prior to initiating therapy. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. • Lymphoma and other malignancies, some fatal have been reported in children and adolescent patients treated with TNF blockers. • Post marketing cases of hepatosplenic T-cell lymphoma have occurred in adolescents and young adults with inflammatory bowel disease treated with TNF blockers *Bimzelx(84)* Bimekizumab-bkzx has no FDA labeled contraindications. *Cimzia(2)* Certolizumab has the following boxed warnings: • Increased risk for developing serious infections that may lead to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections. Perform test for latent TB, and if positive, start treatment for TB prior to initiating therapy. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. • Lymphoma and other malignancies, some fatal have been reported in children and adolescent patients treated with TNF blockers. Cimzia is not indicated for use in pediatric patients.

	Certolizumab is contraindicated in patients with a severe hypersensitivity to certolizumab pegol or to any of the excipients. *Cosentyx(3)* Secukinumab is contraindicated in patients with a serious hypersensitivity reaction to secukinumab or to any of the excipients. *Enbrel(4)* Etanercept has the following boxed warnings: • Increased risk for developing serious infections that may lead to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections. Perform test for latent TB, and if positive, start treatment for TB prior to initiating therapy. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. • Lymphoma and other malignancies, some fatal have been reported in children and adolescent patients treated with TNF blockers. Etanercept is contraindicated for use in patients with sepsis. *Entyvio(5)* Vedolizumab is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to Entyvio or any of its excipients. *Kevzara(7)* Sarilumab has the following boxed warning: • Increased risk for developing serious infections that may lead to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections. Perform test for latent TB, and if positive, start treatment for TB prior to initiating therapy. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. Sarilumab is contraindicated in patients with a known hypersensitivity to sarilumab or any of the inactive ingredients.

	Kineret(8) Anakinra is contraindicated in patients with a known hypersensitivity to E.coli-derived proteins, anakinra, or any component of the product. *Litfulo(81)* Ritlecitinib is contraindicated in patients with known hypersensitivity to ritlecitinib or any of its excipients. *Olumiant(9)* Baricitinib has the following boxed warnings: • Increased risk of serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Interrupt treatment with Olumiant if serious infection occurs until the infection is controlled. Test for latent TB before and during therapy, and if positive, start treatment for TB prior to use. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. • Higher rate of all-cause mortality, including sudden cardiovascular death with another Janus Kinase (JAK) inhibitor vs tumor necrosis factor (TNF) blockers in RA patients • Malignancies have occurred in patients treated with Olumiant. Higher rate of lymphomas and lung cancers with another JAK inhibitor vs TNF blockers in RA patients • Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with another JAK inhibitor vs TNF blockers in RA patients • Thrombosis has occurred in patients treated with Olumiant. Increased incidence of pulmonary embolism, venous and arterial thrombosis with another JAK inhibitor vs TNF blockers. Baricitinib does not have any FDA labeled contraindications for use. *Omvoh(86)* Mirikizumab is contraindicated in patients with a history of serious hypersensitivity reaction to mirikizumab-mrkz or any of the excipients. *Orencia(10)*

	Abatacept does not have any FDA labeled contraindications for use. *Rinvoq(44)* Upadacitinib has the following boxed warnings: • Increased risk of serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Interrupt treatment with Rinvoq if serious infection occurs until the infection is controlled. Test for latent TB before and during therapy, and if positive, start treatment for TB prior to use. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. • Higher rate of all-cause mortality, including sudden cardiovascular death with another Janus Kinase (JAK) inhibitor vs tumor necrosis factor (TNF) blockers in RA patients • Malignancies have occurred in patients treated with Rinvoq. Higher rate of lymphomas and lung cancers with another JAK inhibitor vs TNF blockers in RA patients • Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with another JAK inhibitor vs TNF blockers in RA patients • Thrombosis has occurred in patients treated with Rinvoq. Increased incidence of pulmonary embolism, venous and arterial thrombosis with another JAK inhibitor vs TNF blockers. Upadacitinib is contraindicated in patients with known hypersensitivity to upadacitinib or any of its excipients. *Siliq(11)* Brodalumab has the following boxed warning: • Suicidal ideation and behavior, including completed suicides, have occurred in patients. *Simponi(12)* Golimumab has the following boxed warnings: • Increased risk for developing serious infections that may lead to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections. Perform test for latent

	TB, and if positive, start treatment for TB prior to initiating therapy. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. • Lymphoma and other malignancies, some fatal have been reported in children and adolescent patients treated with TNF blockers. *Skyrizi(43)* Risankizumab is contraindicated in patients with a history of serious hypersensitivity reaction to risankizumab-rzaa or any of the excipients. *Sotyktu(67)* Deucravacitinib is contraindicated in patients with a history of hypersensitivity reaction to deucravacitinib or to any of the excipients in Sotyktu. *Stelara(13)* Ustekinumab is contraindicated for use in patients with clinically significant hypersensitivity to ustekinumab or to any of the excipients. *Taltz(14)* Ixekizumab is contraindicated for use in patients with serious hypersensitivity reaction to ixekizumab or to any of the excipients. *Tocilizumab(1,50)* Tocilizumab has the following boxed warning: • Increased risk for developing serious infections that may lead to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections. Perform test for latent TB, and if positive, start treatment for TB prior to initiating therapy. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. Tocilizumab is contraindicated in patients with a known hypersensitivity reaction to tocilizumab. *Tremfya(15)*

	Guselkumab is contraindicated for use in patients with serious hypersensitivity reaction to guselkumab or to any of the excipients. *Velsipity(85)* Etrasimod is contraindicated in: • Patient who in the last 6 months, experienced myocardial infarction, unstable angina pectoris, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure • History or presence of Mobitz type II second-degree or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker *Xeljanz/Xeljanz XR(16)* Tofacitinib has the following boxed warnings: • Increased risk serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Interrupt treatment with Xeljanz/Xeljanz XR if serious infection occurs until the infection is controlled. Test for latent TB before and during therapy, and if positive, start treatment for TB prior to initiating therapy. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. • Higher rate of all-cause mortality, including sudden cardiovascular death with Xeljanz vs TNF blockers in RA patients • Higher rate of MACE (defined as cardiovascular death, myocardial infarction, and stroke) with Xeljanz vs TNF blockers in RA patients. • Thrombosis has occurred in patients treated with Xeljanz. Increased incidence of pulmonary embolism, venous and arterial thrombosis with Xeljanz vs TNF blockers in RA patients. • Malignancies have occurred in patients treated with Xeljanz. Higher rate of lymphomas and lung cancers with Xeljanz vs TNF blockers in RA patients. Tofacitinib does not have any FDA labeled contraindications for use. *Zymfentra(89)*

	Infliximab has the following boxed warnings: • Increased risk for developing serious infections that may lead to hospitalization or death, including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections. Perform test for latent TB, and if positive, start treatment for TB prior to initiating therapy. The risks and benefits of treatment should be carefully considered prior to initiating therapy in patient with chronic or recurrent infection. Monitor all patients for the development of signs and symptoms of infection during and after treatment, including possible development of active TB during treatment, even if initial latent TB test is negative. • Lymphoma and other malignancies, some fatal, have been reported in children and adolescent patients treated with TNF blockers. • Postmarketing cases of hepatosplenic T-cell lymphoma (HSTCL) have been reported in patients treated with TNF blockers, and almost all patients had received treatment with azathioprine or 6-mercaptopurine concomitantly at or prior to diagnosis. These cases have had a very aggressive disease course and have been fatal. The majority of reported cases have occurred in patients with Crohn's disease or ulcerative colitis and most were in young adult males. Zymfentra is contraindicated in patients with a history of a severe hypersensitivity reaction to infliximab-dyyb, other infliximab products, any of the inactive ingredients in Zymfentra, or any murine proteins. Reactions have included anaphylaxis.

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Adalimumab and Adalimumab Biosimilars	

Preferred Agent(s)	Non-Preferred Agent(s)
Hadlima (adalimumab-bwwd) **Simlandi** (adalimumab-ryvk)	**Abrilada** (adalimumab-afzb) **Adalimumab-aacf** **Adalimumab-adbm**

Module	Clinical Criteria for Approval

	Adalimumab-fkjp **Adalimumab-ryvk** **Amjevita** (adalimumab-atto) **Cyltezo** (adalimumab-adbm) **Hulio** (adalimumab-fkjp) **Hyrimoz** (adalimumab-adaz) **Idacio** (adalimumab-aacf) **Yuflyma** (adalimumab-aaty) **Yusimry** (adalimumab-aqvh)

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Agents Eligible for Continuation of Therapy
All target agents EXCEPT the following are eligible for continuation of therapy: Abrilada Adalimumab-ryvk Amjevita Cyltezo, Adalimumab-adbm

Module	Clinical Criteria for Approval
	Hulio, Adalimumab-fkjp Hyrimoz Idacio, Adalimumab-aacf Yuflyma Yusimry 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. ALL of the following: 1. The patient has an FDA labeled indication or an indication supported in compendia for the requested agent and route of administration AND ONE of the following: A. The patient has a diagnosis of moderately to severely active rheumatoid arthritis (RA) AND ONE of the following: 1. The patient has tried and had an inadequate response to maximally tolerated methotrexate (e.g., titrated to 25 mg weekly) after at least a 3-month duration of therapy **OR** 2. The patient has tried and had an inadequate response to another conventional agent (i.e., hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA after at least a 3-month duration of therapy **OR** 3. The patient has an intolerance or hypersensitivity to ONE of the following conventional agents (i.e., maximally tolerated methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** 4. The patient has an FDA labeled contraindication to ALL of the following conventional agents (i.e., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR**

Module	Clinical Criteria for Approval
	5. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of RA **OR** B. The patient has a diagnosis of active psoriatic arthritis (PsA) AND ONE of the following: 1. The patient has tried and had an inadequate response to ONE conventional agent (i.e., cyclosporine, leflunomide, methotrexate, sulfasalazine) used in the treatment of PsA after at least a 3-month duration of therapy **OR** 2. The patient has an intolerance or hypersensitivity to ONE of the conventional agents used in the treatment of PsA **OR** 3. The patient has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of PsA **OR** 4. The patient has severe active PsA (e.g., erosive disease, elevated markers of inflammation [e.g., ESR, CRP] attributable to PsA, long-term damage that interferes with function [i.e., joint deformities], rapidly progressive) **OR** 5. The patient has concomitant severe psoriasis (PS) (e.g., greater than 10% body surface area involvement, occurring on select locations [i.e., hands, feet, scalp, face, or genitals], intractable pruritus, serious emotional consequences) **OR** 6. The patient's medication history indicates use of another biologic immunomodulator agent OR Otezla that is FDA labeled or supported in compendia for the treatment of PsA **OR** C. The patient has a diagnosis of moderate to severe plaque psoriasis (PS) AND ONE of the following: 1. The patient has tried and had an inadequate response to ONE conventional agent (i.e., acitretin, anthralin, calcipotriene, calcitriol, coal tar products, cyclosporine, methotrexate, pimecrolimus, PUVA [phototherapy], tacrolimus, tazarotene, topical corticosteroids) used in the treatment of PS after at least a 3-month duration of therapy **OR** 2. The patient has an intolerance or hypersensitivity to ONE conventional agent used in the treatment of PS **OR** 3. The patient has an FDA labeled contraindication to ALL conventional agents used in the treatment of PS **OR**

Module	Clinical Criteria for Approval
	4. The patient has severe active PS (e.g., greater than 10% body surface area involvement, occurring on select locations [i.e., hands, feet, scalp, face, or genitals], intractable pruritus, serious emotional consequences) **OR** 5. The patient has concomitant severe psoriatic arthritis (PsA) (e.g., erosive disease, elevated markers of inflammation [e.g., ESR, CRP] attributable to PsA, long-term damage that interferes with function [i.e., joint deformities], rapidly progressive) **OR** 6. The patient's medication history indicates use of another biologic immunomodulator agent OR Otezla that is FDA labeled or supported in compendia for the treatment of PS **OR** D. The patient has a diagnosis of moderately to severely active Crohn's disease (CD) AND ONE of the following: 1. The patient has tried and had an inadequate response to ONE conventional agent (i.e., 6-mercaptopurine, azathioprine, corticosteroids [e.g., prednisone, budesonide EC capsule], methotrexate) used in the treatment of CD after at least a 3-month duration of therapy **OR** 2. The patient has an intolerance or hypersensitivity to ONE of the conventional agents used in the treatment of CD **OR** 3. The patient has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of CD **OR** 4. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of CD **OR** E. The patient has a diagnosis of moderately to severely active ulcerative colitis (UC) AND ONE of the following: 1. The patient has tried and had an inadequate response to ONE conventional agent (i.e., 6-mercaptopurine, azathioprine, balsalazide, corticosteroids, cyclosporine, mesalamine, sulfasalazine) used in the treatment of UC after at least a 3-month duration of therapy **OR** 2. The patient has severely active ulcerative colitis **OR** 3. The patient has an intolerance or hypersensitivity to ONE of the conventional agents used in the treatment of UC **OR** 4. The patient has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of UC **OR**

Module	Clinical Criteria for Approval
	5. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of UC **OR** F. The patient has a diagnosis of non-infectious intermediate uveitis, posterior uveitis, or panuveitis AND ONE of the following: 1. BOTH of the following: A. ONE of the following: 1. The patient has tried and had an inadequate response to oral corticosteroids used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis after at least a 2-week duration of therapy **OR** 2. The patient has tried and had an inadequate response to periocular or intravitreal corticosteroid injections in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis **OR** 3. The patient has an intolerance or hypersensitivity to oral corticosteroids OR periocular or intravitreal corticosteroid injections used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis **OR** 4. The patient has an FDA labeled contraindication to BOTH oral corticosteroids and periocular/intravitreal corticosteroids **AND** B. ONE of the following: 1. The patient has tried and had an inadequate response to ONE conventional systemic agent (i.e., azathioprine, mycophenolate, methotrexate, cyclosporine, tacrolimus) used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis after at least a 3-month duration of therapy **OR** 2. The patient has an intolerance or hypersensitivity to ONE conventional systemic agent used in the treatment of non-infectious

Module	Clinical Criteria for Approval
	intermediate uveitis, posterior uveitis, or panuveitis **OR** 3. The patient has an FDA labeled contraindication to ALL conventional systemic agents used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis **OR** 2. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis **OR** G. The patient has a diagnosis of active ankylosing spondylitis (AS) AND ONE of the following: 1. The patient has tried and had an inadequate response to TWO different NSAIDs used in the treatment of AS after at least a 4-week total trial **OR** 2. The patient has an intolerance or hypersensitivity to TWO different NSAIDs used in the treatment of AS **OR** 3. The patient has an FDA labeled contraindication to ALL NSAIDs used in the treatment of AS **OR** 4. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of AS **OR** H. The patient has a diagnosis of active non-radiographic axial spondyloarthritis (nr-axSpA) AND ONE of the following: 1. The patient has tried and had an inadequate response to TWO different NSAIDs used in the treatment of nr-axSpA after at least a 4-week total trial **OR** 2. The patient has an intolerance or hypersensitivity to TWO different NSAIDs used in the treatment of nr-axSpA **OR** 3. The patient has an FDA labeled contraindication to ALL NSAIDs used in the treatment of nr-axSpA **OR** 4. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of nr-axSpA **OR** I. The patient has a diagnosis of moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA) AND ONE of the following:

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	1. The patient has tried and had an inadequate response to ONE conventional agent (i.e., methotrexate, leflunomide) used in the treatment of PJIA after at least a 3-month duration of therapy **OR** 2. The patient has an intolerance or hypersensitivity to ONE conventional agent used in the treatment of PJIA **OR** 3. The patient has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of PJIA **OR** 4. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of PJIA **OR** J. The patient has a diagnosis of moderate to severe hidradenitis suppurativa (HS) AND ONE of the following: 1. The patient has tried and had an inadequate response to ONE conventional agent (i.e., oral tetracyclines [doxycycline, minocycline, tetracycline]; oral contraceptives [females only]; metformin [females only]; finasteride [females only]; spironolactone [females only]; intralesional corticosteroids [triamcinolone]; clindamycin in combination with rifampin; combination of rifampin, moxifloxacin, and metronidazole; cyclosporine; oral retinoids) used in the treatment of HS after at least a 3-month duration of therapy **OR** 2. The patient has an intolerance or hypersensitivity to ONE conventional agent used in the treatment of HS **OR** 3. The patient has an FDA labeled contraindication to ALL conventional agents used in the treatment of HS **OR** 4. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of HS **OR** K. The patient has a diagnosis not mentioned previously **AND** 2. If the client has preferred agents, then ONE of the following (reference preferred agents table): A. The requested agent is a preferred agent **OR** B. The patient has tried and had an inadequate response to THREE preferred agents after at least a 3-month trial per agent (medical records required) **OR** C. The patient has an intolerance or hypersensitivity to THREE of the preferred agents that is not expected to occur with the requested agent (medical records required) **OR**

Module	Clinical Criteria for Approval
	D. The patient has an FDA labeled contraindication to ALL of the preferred agents that is not expected to occur with the requested agent (medical records required) **OR** E. BOTH of the following (medical records required): 1. ALL of the preferred agents are not clinically appropriate for the patient **AND** 2. The prescriber has provided a complete list of previously tried agents **AND** 3. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., rheumatologist for JIA, PsA, RA; gastroenterologist for CD, UC; dermatologist for PS) or has consulted with a specialist in the area of the patient's diagnosis **AND** 3. ONE of the following (please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (submitted copy of clinical trials, phase III studies, guidelines required) **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The patient has been tested for latent tuberculosis (TB) when required by the prescribing information for the requested agent AND if positive the patient has begun therapy for latent TB **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 12 months for all agents EXCEPT adalimumab containing products for ulcerative colitis (UC), and the agents with indications that require loading doses for new starts. NOTE: For agents that require a loading dose for a new start, approve the loading dose based on FDA labeling AND the maintenance dose for the remainder of the length of approval. Adalimumab containing products for UC may be approved for 12 weeks.

Module	Clinical Criteria for Approval
	NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. If the client has preferred agents, then ONE of the following (reference preferred agents table): A. The requested agent is a preferred agent **OR** B. The patient has tried and had an inadequate response to THREE preferred agents after at least a 3-month trial per agent (medical records required) **OR** C. The patient has an intolerance or hypersensitivity to THREE of the preferred agents that is not expected to occur with the requested agent (medical records required) **OR** D. The patient has an FDA labeled contraindication to ALL of the preferred agents that is not expected to occur with the requested agent (medical records required) **OR** E. BOTH of the following (medical records required): 1. ALL of the preferred agents are not clinically appropriate for the patient **AND** 2. The prescriber has provided a complete list of previously tried agents **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., rheumatologist for JIA, PsA, RA; gastroenterologist for CD, UC; dermatologist for PS) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. ONE of the following (please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (submitted copy of clinical trials, phase III studies, guidelines required) **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>Compendia Allowed: AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use

Length of Approval: 12 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.</td></tr>
<tr><td>All other Target Agents</td><td>Step Table
<table>
<tr><th rowspan="2">Disease State</th><th colspan="2">Step 1</th><th rowspan="2">Step 2 (Directed to ONE step 1 agent)</th><th rowspan="2">Step 3a (Directed to TWO step 1 agents)</th><th rowspan="2">Step 3b (Directed to TWO agents from step 1 and/or step 2)</th><th rowspan="2">Step 3c (Directed to THREE step 1 agents)</th></tr>
<tr><th>Step 1a</th><th>Step 1b (Directed to ONE TNF inhibitor) NOTE: Please see Step 1a for preferred TNF inhibitors</th></tr>
<tr><td colspan="7">Rheumatoid Disorders</td></tr>
<tr><td>Ankylosing Spondylitis (AS)</td><td>SC: adalimumab product(s)**, Cosentyx, Enbrel</td><td>Oral: Rinvoq, Xeljanz, Xeljanz XR</td><td>N/A</td><td>SC: Cimzia, Simponi, Taltz</td><td>N/A</td><td>SC: Bimzelx</td></tr>
</table></td></tr>
</table>

Module	Clinical Criteria for Approval						
	Nonradiographic Axial Spondyloarthritis (nr-axSpA)	SC: Cimzia, Cosentyx	Oral: Rinvoq	N/A	SC: Taltz	N/A	SC: Bimzelx
	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	SC: adalimumab product(s)**, Enbrel	Oral: Rinvoq, Rinvoq LQ, Xeljanz	SC: Tyenne (an adalimumab product** is a required Step 1 agent)	N/A	SC: Actemra (an adalimumab product** AND Tyenne are required Step agents) Orencia	SC: Cimzia, Kevzara
	Psoriatic Arthritis (PsA)	SC: adalimumab product(s)**, Cosentyx, Enbrel, Skyrizi, Stelara, Tremfya Oral: Otezla	Oral: Rinvoq, Rinvoq LQ, Xeljanz, Xeljanz XR	N/A	SC: Cimzia, Orencia, Simponi, Taltz	N/A	SC: Bimzelx
	Rheumatoid Arthritis (RA)	SC: adalimumab product(s)**, Enbrel	Oral: Rinvoq, Xeljanz, Xeljanz XR	SC: Tyenne (an adalimumab product** is a required Step 1 agent)	Oral: Olumiant SC: Cimzia, Kevzara, Orencia, Simponi	SC: Actemra (an adalimumab product** AND Tyenne are required Step agents)	SC: Kineret
	Systemic Juvenile Idiopathic	SC: Tyenne	N/A	SC: Actemra	N/A	N/A	N/A

Module	Clinical Criteria for Approval						
	Arthritis (SJIA)						
	Dermatological Disorder						
	Hidradenitis Suppurativa (HS)	SC: adalimumab product(s)**, Cosentyx	N/A	N/A	N/A	N/A	N/A
	Psoriasis (PS)	SC: adalimumab product(s)**, Cosentyx, Enbrel, Skyrizi, Stelara, Tremfya Oral: Otezla, Sotyktu	N/A	N/A	SC: Cimzia, Ilumya	N/A	SC: Bimzelx, Siliq, Taltz
	Inflammatory Bowel Disease						
	Crohn's Disease (CD)	SC: adalimumab product(s)**, Entyvio, Skyrizi, Stelara	Oral: Rinvoq	N/A	SC: Cimzia (an adalimumab product** is a required Step 1 agent) Zymfentra	N/A	N/A

Module	Clinical Criteria for Approval						
	Ulcerative Colitis (UC)	SC: adalimumab product(s)**, Entyvio, Skyrizi, Stelara, Tremfya	Oral: Rinvoq, Xeljanz, Xeljanz XR	SC: Omvoh Simponi (an adalimumab product** is a required Step 1 agent)	SC: Zymfentra Oral: Zeposia	N/A	Oral: Velsipity
	Other						
	Giant Cell Arteritis (GCA)	SC: Tyenne	N/A	SC: Actemra	N/A	N/A	N/A
	Systemic Sclerosis-associated Interstitial Lung Disease (SSc-ILD)	SC: Tyenne	N/A	SC: Actemra	N/A	N/A	N/A
	Uveitis	SC: adalimumab product(s)**	N/A	N/A	N/A	N/A	N/A
	Indications Without Prerequisite Biologic Immunomodulators Required						
	Alopecia Areata (AA) Atopic Dermatitis (AD) Deficiency of IL-1 Receptor	N/A	N/A	N/A	N/A	N/A	N/A

Module	Clinical Criteria for Approval

Antagonist (DIRA) Enthesitis Related Arthritis (ERA) Juvenile Psoriatic Arthritis (JPsA) Neonatal-Onset Multisystem Inflammatory Disease (NOMID) Polymyalgia Rheumatica (PMR)						

****Allowable preferred adalimumab product(s)**
Hadlima, Simlandi

Note: For Xeljanz products (Xeljanz and Xeljanz XR) and Rinvoq products (Rinvoq and Rinvoq LQ), a trial of either or both dosage forms collectively counts as ONE product

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The request is NOT for use of Olumiant or Actemra in the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) *NOTE: This indication is not covered under the pharmacy benefit **AND**
2. If the request is for use in Alopecia Areata and Alopecia Areata is NOT restricted from coverage under the patient's benefit **AND**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
3. ONE of the following:
A. The requested agent is eligible for continuation of therapy AND ONE of the following:

<table>
<tr><th>Agents Eligible for Continuation of Therapy</th></tr>
<tr><td>All target agents EXCEPT the following are eligible for continuation of therapy:

Actemra</td></tr>
</table>

1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days OR
2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed OR
B. ALL of the following:
1. The patient has an FDA labeled indication or an indication supported in compendia for the requested agent and route of administration AND ONE of the following:
A. The patient has a diagnosis of moderately to severely active rheumatoid arthritis (RA) AND BOTH of the following:
1. ONE of the following:
A. The patient has tried and had an inadequate response to maximally tolerated methotrexate (e.g., titrated to 25 mg weekly) after at least a 3-month duration of therapy OR
B. The patient has tried and had an inadequate response to another conventional agent (i.e., hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA after at least a 3-month duration of therapy OR
C. The patient has an intolerance or hypersensitivity to ONE of the following conventional agents (i.e., maximally tolerated methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA OR
</td></tr>
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Module	Clinical Criteria for Approval
	D. The patient has an FDA labeled contraindication to ALL of the following conventional agents (i.e., methotrexate, hydroxychloroquine, leflunomide, sulfasalazine) used in the treatment of RA **OR** E. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of RA **AND** 2. If the request is for Simponi, ONE of the following: A. The patient will be taking the requested agent in combination with methotrexate **OR** B. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to methotrexate **OR** B. The patient has a diagnosis of active psoriatic arthritis (PsA) AND ONE of the following: 1. The patient has tried and had an inadequate response to ONE conventional agent (i.e., cyclosporine, leflunomide, methotrexate, sulfasalazine) used in the treatment of PsA after at least a 3-month duration of therapy **OR** 2. The patient has an intolerance or hypersensitivity to ONE of the conventional agents used in the treatment of PsA **OR** 3. The patient has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of PsA **OR** 4. The patient has severe active PsA (e.g., erosive disease, elevated markers of inflammation [e.g., ESR, CRP] attributable to PsA, long-term damage that interferes with function [i.e., joint deformities], rapidly progressive) **OR** 5. The patient has concomitant severe psoriasis (PS) (e.g., greater than 10% body surface area involvement, occurring on select locations [i.e., hands, feet, scalp, face, or genitals], intractable pruritus, serious emotional consequences) **OR** 6. The patient's medication history indicates use of another biologic immunomodulator agent OR Otezla that is FDA labeled or supported in compendia for the treatment of PsA **OR** C. The patient has a diagnosis of moderate to severe plaque psoriasis (PS) AND ONE of the following:

Module	Clinical Criteria for Approval
	1. The patient has tried and had an inadequate response to ONE conventional agent (i.e., acitretin, anthralin, calcipotriene, calcitriol, coal tar products, cyclosporine, methotrexate, pimecrolimus, PUVA [phototherapy], tacrolimus, tazarotene, topical corticosteroids) used in the treatment of PS after at least a 3-month duration of therapy **OR** 2. The patient has an intolerance or hypersensitivity to ONE conventional agent used in the treatment of PS **OR** 3. The patient has an FDA labeled contraindication to ALL conventional agents used in the treatment of PS **OR** 4. The patient has severe active PS (e.g., greater than 10% body surface area involvement, occurring on select locations [i.e., hands, feet, scalp, face, or genitals], intractable pruritus, serious emotional consequences) **OR** 5. The patient has concomitant severe psoriatic arthritis (PsA) (e.g., erosive disease, elevated markers of inflammation [e.g., ESR, CRP] attributable to PsA, long-term damage that interferes with function [i.e., joint deformities], rapidly progressive) **OR** 6. The patient's medication history indicates use of another biologic immunomodulator agent OR Otezla that is FDA labeled or supported in compendia for the treatment of PS **OR** D. The patient has a diagnosis of moderately to severely active Crohn's disease (CD) AND ONE of the following: 1. The patient has tried and had an inadequate response to ONE conventional agent (i.e., 6-mercaptopurine, azathioprine, corticosteroids [e.g., prednisone, budesonide EC capsule], methotrexate) used in the treatment of CD after at least a 3-month duration of therapy **OR** 2. The patient has an intolerance or hypersensitivity to ONE of the conventional agents used in the treatment of CD **OR** 3. The patient has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of CD **OR** 4. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of CD **OR**

Module	Clinical Criteria for Approval
	E. The patient has a diagnosis of moderately to severely active ulcerative colitis (UC) AND ONE of the following: 1. The patient has tried and had an inadequate response to ONE conventional agent (i.e., 6-mercaptopurine, azathioprine, balsalazide, corticosteroids, cyclosporine, mesalamine, sulfasalazine) used in the treatment of UC after at least a 3-month duration of therapy **OR** 2. The patient has severely active ulcerative colitis **OR** 3. The patient has an intolerance or hypersensitivity to ONE of the conventional agents used in the treatment of UC **OR** 4. The patient has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of UC **OR** 5. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of UC **OR** F. The patient has a diagnosis of non-infectious intermediate uveitis, posterior uveitis, or panuveitis AND ONE of the following: 1. BOTH of the following: A. ONE of the following: 1. The patient has tried and had an inadequate response to oral corticosteroids used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis after at least a 2-week duration of therapy **OR** 2. The patient has tried and had an inadequate response to periocular or intravitreal corticosteroid injections in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis **OR** 3. The patient has an intolerance or hypersensitivity to oral corticosteroids OR periocular or intravitreal corticosteroid injections used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis **OR** 4. The patient has an FDA labeled contraindication to BOTH oral corticosteroids and periocular/intravitreal corticosteroids **AND**

Module	Clinical Criteria for Approval
	B. ONE of the following: 1. The patient has tried and had an inadequate response to ONE conventional systemic agent (i.e., azathioprine, mycophenolate, methotrexate, cyclosporine, tacrolimus) used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis after at least a 3-month duration of therapy **OR** 2. The patient has an intolerance or hypersensitivity to ONE conventional systemic agent used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis **OR** 3. The patient has an FDA labeled contraindication to ALL conventional systemic agents used in the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis **OR** 2. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of non-infectious intermediate uveitis, posterior uveitis, or panuveitis **OR** G. The patient has a diagnosis of giant cell arteritis (GCA) AND ONE of the following: 1. The patient has tried and had an inadequate response to systemic corticosteroids (e.g., prednisone, methylprednisolone) used in the treatment of GCA after at least a 7-10 day duration of therapy **OR** 2. The patient has an intolerance or hypersensitivity to systemic corticosteroids used in the treatment of GCA **OR** 3. The patient has an FDA labeled contraindication to ALL systemic corticosteroids **OR** 4. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of GCA **OR** H. The patient has a diagnosis of active ankylosing spondylitis (AS) AND ONE of the following:

Module	Clinical Criteria for Approval
	1. The patient has tried and had an inadequate response to TWO different NSAIDs used in the treatment of AS after at least a 4-week total trial **OR** 2. The patient has an intolerance or hypersensitivity to TWO different NSAIDs used in the treatment of AS **OR** 3. The patient has an FDA labeled contraindication to ALL NSAIDs used in the treatment of AS **OR** 4. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of AS **OR** I. The patient has a diagnosis of active non-radiographic axial spondyloarthritis (nr-axSpA) AND ONE of the following: 1. The patient has tried and had an inadequate response to TWO different NSAIDs used in the treatment of nr-axSpA after at least a 4-week total trial **OR** 2. The patient has an intolerance or hypersensitivity to TWO different NSAIDs used in the treatment of nr-axSpA **OR** 3. The patient has an FDA labeled contraindication to ALL NSAIDs used in the treatment of nr-axSpA **OR** 4. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of nr-axSpA **OR** J. The patient has a diagnosis of moderately to severely active polyarticular juvenile idiopathic arthritis (PJIA) AND ONE of the following: 1. The patient has tried and had an inadequate response to ONE conventional agent (i.e., methotrexate, leflunomide) used in the treatment of PJIA after at least a 3-month duration of therapy **OR** 2. The patient has an intolerance or hypersensitivity to ONE conventional agent used in the treatment of PJIA **OR** 3. The patient has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of PJIA **OR** 4. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of PJIA **OR** K. The patient has a diagnosis of moderate to severe hidradenitis suppurativa (HS) AND ONE of the following:

Module	Clinical Criteria for Approval
	1. The patient has tried and had an inadequate response to ONE conventional agent (i.e., oral tetracyclines [doxycycline, minocycline, tetracycline]; oral contraceptives [females only]; metformin [females only]; finasteride [females only]; spironolactone [females only]; intralesional corticosteroids [triamcinolone]; clindamycin in combination with rifampin; combination of rifampin, moxifloxacin, and metronidazole; cyclosporine; oral retinoids) used in the treatment of HS after at least a 3-month duration of therapy **OR** 2. The patient has an intolerance or hypersensitivity to ONE conventional agent used in the treatment of HS **OR** 3. The patient has an FDA labeled contraindication to ALL conventional agents used in the treatment of HS **OR** 4. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of HS **OR** L. BOTH of the following: 1. The patient has a diagnosis of systemic sclerosis associated interstitial lung disease (SSc-ILD) **AND** 2. The patient's diagnosis has been confirmed on high-resolution computed tomography (HRCT) or chest radiography scans **OR** M. The patient has a diagnosis of active enthesitis related arthritis (ERA) and ONE of the following: 1. The patient has tried and had an inadequate response to TWO different NSAIDs used in the treatment of ERA after at least a 4-week total trial **OR** 2. The patient has an intolerance or hypersensitivity to TWO different NSAIDs used in the treatment of ERA **OR** 3. The patient has an FDA labeled contraindication to ALL NSAIDs used in the treatment of ERA **OR** 4. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of ERA **OR** N. The patient has a diagnosis of moderate-to-severe atopic dermatitis (AD) AND ALL of the following: 1. ONE of the following: A. The patient has at least 10% body surface area involvement **OR**

Module	Clinical Criteria for Approval
	B. The patient has involvement of body sites that are difficult to treat with prolonged topical corticosteroid therapy (e.g., hands, feet, face, neck, scalp, genitals/groin, skin folds) **OR** C. The patient has an Eczema Area and Severity Index (EASI) score greater than or equal to 16 **OR** D. The patient has an Investigator Global Assessment (IGA) score greater than or equal to 3 **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to at least a medium-potency topical corticosteroid used in the treatment of AD after at least a 4-week duration of therapy **OR** B. The patient has an intolerance or hypersensitivity to at least a medium-potency topical corticosteroid used in the treatment of AD **OR** C. The patient has an FDA labeled contraindication to ALL medium-, high-, and super-potency topical corticosteroids used in the treatment of AD **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response to a topical calcineurin inhibitor (e.g., Elidel/pimecrolimus, Protopic/tacrolimus) used in the treatment of AD after at least a 6-week duration of therapy **OR** B. The patient has an intolerance or hypersensitivity to a topical calcineurin inhibitor used in the treatment of AD **OR** C. The patient has an FDA labeled contraindication to ALL topical calcineurin inhibitors used in the treatment of AD **AND** 4. The prescriber has documented the patient's baseline (prior to therapy with the requested agent) pruritus and other symptom severity (e.g., erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and/or lichenification) **OR** O. BOTH of the following: 1. The patient has a diagnosis of severe alopecia areata (AA) **AND**

Module	Clinical Criteria for Approval
	2. The patient has at least 50% scalp hair loss that has lasted 6 months or more **OR** P. The patient has a diagnosis of polymyalgia rheumatica (PMR) AND ONE of the following: 1. The patient has tried and had an inadequate response to systemic corticosteroids at a dose equivalent to at least 7.5 mg/day of prednisone used in the treatment of PMR after at least an 8-week duration of therapy **OR** 2. The patient is currently treated with systemic corticosteroids at a dose equivalent to at least 7.5 mg/day of prednisone and cannot tolerate a corticosteroid taper **OR** Q. The patient has a diagnosis of juvenile psoriatic arthritis (JPsA) AND ONE of the following: 1. The patient has tried and had an inadequate response to ONE conventional agent (i.e., methotrexate, leflunomide, sulfasalazine) used in the treatment of JPsA after at least a 3-month duration of therapy **OR** 2. The patient has an intolerance or hypersensitivity to ONE conventional agent used in the treatment of JPsA **OR** 3. The patient has an FDA labeled contraindication to methotrexate **OR** 4. The patient has severe active JPsA (e.g., erosive disease, elevated markers of inflammation [e.g., ESR, CRP] attributable to JPsA, long-term damage that interferes with function [i.e., joint deformities], rapidly progressive) **OR** 5. The patient has concomitant severe psoriasis (PS) (e.g., greater than 10% body surface area involvement, occurring on select locations [i.e., hands, feet, scalp, face, or genitals], intractable pruritus, serious emotional consequences) **OR** 6. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of JPsA **OR** R. The patient has a diagnosis not mentioned previously **AND** 2. ONE of the following (reference Step Table): A. The requested indication does NOT require any prerequisite biologic immunomodulator agents **OR** B. The requested agent is a Step 1a agent for the requested indication **OR**

Module	Clinical Criteria for Approval
	C. If the requested agent is a Step 1b agent for the requested indication, then ONE of the following: 1. The patient has tried and had an inadequate response to ONE Tumor Necrosis Factor (TNF) inhibitor for the requested indication after at least a 3-month duration of therapy (See Step 1a for preferred TNF inhibitors) **OR** 2. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to therapy with a TNF inhibitor for the requested indication **OR** 3. The patient has an FDA labeled contraindication to ALL TNF inhibitors for the requested indication **OR** 4. BOTH of the following: A. ALL TNF inhibitors are not clinically appropriate for the patient **AND** B. The prescriber has provided a complete list of previously tried agents for the requested indication **OR** D. If the requested agent is a Step 2 agent for the requested indication, then ONE of the following: 1. The patient has tried and had an inadequate response to ONE of the required Step 1 agents for the requested indication after at least a 3-month duration of therapy (See Step 2) **OR** 2. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to ONE of the required Step 1 agents for the requested indication **OR** 3. The patient has an FDA labeled contraindication to ALL required Step 1 agents for the requested indication **OR** 4. BOTH of the following: A. ALL of the required Step 1 agents are not clinically appropriate for the patient **AND** B. The prescriber has provided a complete list of previously tried agents for the requested indication **OR** E. If the requested agent is a Step 3a agent for the requested indication, then ONE of the following (medical records required):

Module	Clinical Criteria for Approval
	1. The patient has tried and had an inadequate response to TWO of the Step 1 agents for the requested indication after at least a 3-month trial per agent (See Step 3a) **OR** 2. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to TWO of the Step 1 agents for the requested indication **OR** 3. The patient has an FDA labeled contraindication to ALL of the Step 1 agents for the requested indication **OR** 4. BOTH of the following: A. ALL of the Step 1 agents are not clinically appropriate for the patient **AND** B. The prescriber has provided a complete list of previously tried agents for the requested indication **OR** F. If the requested agent is a Step 3b agent for the requested indication, then ONE of the following (medical records required): 1. The patient has tried and had an inadequate response to TWO agents from Step 1 and/or Step 2 for the requested indication after at least a 3-month trial per agent (See Step 3b) **OR** 2. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to TWO agents from Step 1 and/or Step 2 for the requested indication **OR** 3. The patient has an FDA labeled contraindication to ALL of the Step 1 AND Step 2 agents for the requested indication **OR** 4. BOTH of the following: A. ALL of the Step 1 AND Step 2 agents are not clinically appropriate for the patient **AND** B. The prescriber has provided a complete list of previously tried agents for the requested indication **OR** G. If the requested agent is a Step 3c agent for the requested indication, then ONE of the following (medical records required): 1. The patient has tried and had an inadequate response to THREE of the Step 1 agents for the requested indication after at least a 3-month trial per agent (See Step 3c) **OR**

Module	Clinical Criteria for Approval
	2. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to THREE of the Step 1 agents for the requested indication **OR** 3. The patient has an FDA labeled contraindication to ALL of the Step 1 agents for the requested indication **OR** 4. BOTH of the following: A. ALL of the Step 1 agents are not clinically appropriate for the patient **AND** B. The prescriber has provided a complete list of previously tried agents for the requested indication **AND** 3. If Cosentyx 300 mg is requested as maintenance dosing, then ONE of the following: A. The patient has a diagnosis of moderate to severe plaque psoriasis with or without coexistent active psoriatic arthritis AND the requested dose is 300 mg every 4 weeks **OR** B. The patient has a diagnosis of hidradenitis suppurativa AND ONE of the following: 1. The requested dose is 300 mg every 4 weeks **OR** 2. The requested dose is 300 mg every 2 weeks AND the patient has tried and had an inadequate response to Cosentyx 300 mg every 4 weeks after at least a 3-month duration of therapy **OR** C. The patient has a diagnosis of active psoriatic arthritis or active ankylosing spondylitis AND BOTH of the following: 1. The requested dose is 300 mg every 4 weeks **AND** 2. The patient has tried and had an inadequate response to Cosentyx 150 mg every 4 weeks after at least a 3-month duration of therapy **AND** 4. If Omvoh is requested for the treatment of ulcerative colitis, then ONE of the following: A. The patient has received Omvoh IV for induction therapy **OR** B. The patient is new to therapy and will receive Omvoh IV for induction therapy **AND** 5. If Entyvio is requested for the treatment of ulcerative colitis or Crohn's disease, then ONE of the following: A. The patient has received at least 2 doses of Entyvio IV therapy **OR**

Module	Clinical Criteria for Approval
	B. The patient is new to therapy and will receive at least 2 doses of Entyvio IV therapy **AND** 6. If Skyrizi is requested for the treatment of Crohn's disease or ulcerative colitis, then ONE of the following: A. The patient received Skyrizi IV for induction therapy **OR** B. The patient is new to therapy and will receive Skyrizi IV for induction therapy **AND** 7. If an ustekinumab product is requested for the treatment of Crohn's disease or ulcerative colitis, then ONE of the following: A. The patient received an ustekinumab IV product for induction therapy **OR** B. The patient is new to therapy and will receive an ustekinumab IV product for induction therapy **AND** 8. If Zymfentra is requested for the treatment of Crohn's disease or ulcerative colitis, then ONE of the following: A. The patient received an infliximab IV product for induction therapy **OR** B. The patient is new to therapy and will receive an infliximab IV product for induction therapy **AND** 9. If Tremfya is requested for the treatment of ulcerative colitis, then ONE of the following: A. The patient received Tremfya IV for induction therapy **OR** B. The patient is new to therapy and will receive Tremfya IV for induction therapy **AND** 10. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 4. If an ustekinumab 90 mg product is requested, then ONE of the following: A. The patient has a diagnosis of psoriasis AND weighs >100kg **OR** B. The patient has a dual diagnosis of psoriasis AND psoriatic arthritis AND the patient is >100kg **OR** C. The patient has a diagnosis of Crohn's disease or ulcerative colitis **AND** 5. If Actemra is requested for a diagnosis of systemic sclerosis associated interstitial lung disease, the request is for the Actemra syringe (NOTE: Actemra ACTpen is not approvable for SSc-ILD) **AND** 6. If Kevzara is requested for a diagnosis of polyarticular juvenile idiopathic arthritis (pJIA), the patient weighs 63 kg or greater **AND**

Module	Clinical Criteria for Approval
	7. If the patient has a diagnosis of moderate-to-severe atopic dermatitis (AD), then BOTH of the following: A. The patient is currently treated with topical emollients and practicing good skin care **AND** B. The patient will continue the use of topical emollients and good skin care practices in combination with the requested agent **AND** 8. The prescriber is a specialist in the area of the patient's diagnosis (e.g., rheumatologist for JIA, PsA, RA; gastroenterologist for CD, UC; dermatologist for PS, AD; pulmonologist, radiologist, pathologist, rheumatologist for SSc-ILD; allergist, immunologist for AD) or has consulted with a specialist in the area of the patient's diagnosis **AND** 9. ONE of the following (please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (submitted copy of clinical trials, phase III studies, guidelines required) **AND** 10. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 11. The patient has been tested for latent tuberculosis (TB) when required by the prescribing information for the requested agent AND if positive the patient has begun therapy for latent TB **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 12 months for all agents EXCEPT Rinvoq for atopic dermatitis (AD), Siliq for plaque psoriasis (PS), Xeljanz and Xeljanz XR for induction therapy for UC, and the agents with indications that require loading doses for new starts. NOTE: For agents that require a loading dose for a new start, approve the loading dose based on FDA labeling AND the maintenance dose for the remainder of the length of approval. Rinvoq for AD may be approved for 6 months, Siliq for PS may be approved for 16 weeks, and Xeljanz and Xeljanz XR for UC may be approved for 16 weeks. **NOTE: Cosentyx for the diagnoses of AS, nr-axSpA, and PSA loading doses are not approvable. NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Clinical Criteria for Approval
	Renewal Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The request is NOT for use of Olumiant or Actemra in the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) *NOTE: This indication is not covered under the pharmacy benefit **AND** 2. The request is for use in Alopecia Areata and Alopecia Areata is NOT restricted from coverage under the patient's benefit **AND** 3. The patient has been previously approved for the requested agent through the plan's Prior Authorization process (*please note ustekinumab product renewal must be for the same strength as the initial approval) [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 4. ONE of the following: A. The patient has a diagnosis of moderate to severe atopic dermatitis AND BOTH of the following: 1. The patient has had a reduction or stabilization from baseline (prior to therapy with the requested agent) of ONE of the following: A. Affected body surface area **OR** B. Flares **OR** C. Pruritus, erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and/or lichenification **OR** D. A decrease in the Eczema Area and Severity Index (EASI) score **OR** E. A decrease in the Investigator Global Assessment (IGA) score **AND** 2. The patient will continue standard maintenance therapies (e.g., topical emollients, good skin care practices) in combination with the requested agent **OR** B. The patient has a diagnosis of polymyalgia rheumatica AND BOTH of the following: 1. The patient has had clinical benefit with the requested agent **AND** 2. If the requested agent is Kevzara, the patient does NOT have any of the following: A. Neutropenia (ANC less than 1,000 per mm^3 at the end of the dosing interval) **AND** B. Thrombocytopenia (platelet count is less than 100,000 per mm^3) **AND** C. AST or ALT elevations 3 times the upper limit of normal **OR**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
C. The patient has a diagnosis other than moderate to severe atopic dermatitis or polymyalgia rheumatica AND the patient has had clinical benefit with the requested agent AND
5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., rheumatologist for JIA, PsA, RA; gastroenterologist for CD, UC; dermatologist for PS, AD; pulmonologist, radiologist, pathologist, rheumatologist for SSc-ILD; allergist, immunologist for AD) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND
6. ONE of the following (please refer to "Agents NOT to be used Concomitantly" table):
A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) OR
B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following:
1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent AND
2. There is support for the use of combination therapy (submitted copy of clinical trials, phase III studies, guidelines required) AND
7. ONE of the following:
A. The requested agent is eligible for continuation of therapy OR
<table>
<tr><th>Agents Eligible for Continuation of Therapy</th></tr>
<tr><td>All target agents EXCEPT the following are eligible for continuation of therapy:

Actemra</td></tr>
</table>
B. ONE of the following (reference Step table):
1. The requested indication does NOT require any prerequisite biologic immunomodulator agents OR
2. The requested agent is a Step 1a agent for the requested indication OR
3. If the requested agent is a Step 1b agent for the requested indication, then ONE of the following:
A. The patient has tried and had an inadequate response to ONE Tumor Necrosis Factor (TNF) inhibitor for the requested indication after at least a 3-month duration of therapy (See Step 1a for preferred TNF inhibitors) OR
B. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or
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Module	Clinical Criteria for Approval
	hypersensitivity to therapy with a TNF inhibitor for the requested indication **OR** C. The patient has an FDA labeled contraindication to ALL TNF inhibitors for the requested indication **OR** D. BOTH of the following: 1. ALL TNF inhibitors are not clinically appropriate for the patient **AND** 2. The prescriber has provided a complete list of previously tried agents for the requested indication **OR** 4. If the requested agent is a Step 2 agent for the requested indication, then ONE of the following: A. The patient has tried and had an inadequate response to ONE of the required Step 1 agents for the requested indication after at least a 3-month duration of therapy (See Step 2) **OR** B. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to ONE of the required Step 1 agents for the requested indication **OR** C. The patient has an FDA labeled contraindication to ALL required Step 1 agents for the requested indication **OR** D. BOTH of the following: 1. ALL of the required Step 1 agents are not clinically appropriate for the patient **AND** 2. The prescriber has provided a complete list of previously tried agents for the requested indication **OR** 5. If the requested agent is a Step 3a agent for the requested indication, then ONE of the following (medical records required): A. The patient has tried and had an inadequate response to TWO of the Step 1 agents for the requested indication after at least a 3-month trial per agent (See Step 3a) **OR** B. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to TWO of the Step 1 agents for the requested indication **OR** C. The patient has an FDA labeled contraindication to ALL of the Step 1 agents for the requested indication **OR** D. BOTH of the following: 1. ALL of the Step 1 agents are not clinically appropriate for the patient **AND**

Module	Clinical Criteria for Approval
	2. The prescriber has provided a complete list of previously tried agents for the requested indication **OR** 6. If the requested agent is a Step 3b agent for the requested indication, then ONE of the following (medical records required): A. The patient has tried and had an inadequate response to TWO agents from Step 1 and/or Step 2 for the requested indication after at least a 3-month trial per agent (See Step 3b) **OR** B. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to TWO agents from Step 1 and/or Step 2 for the requested indication **OR** C. The patient has an FDA labeled contraindication to ALL of the Step 1 AND Step 2 agents for the requested indication **OR** D. BOTH of the following: 1. ALL of the Step 1 AND Step 2 agents are not clinically appropriate for the patient **AND** 2. The prescriber has provided a complete list of previously tried agents for the requested indication **OR** 7. If the requested agent is a Step 3c agent for the requested indication, then ONE of the following (medical records required): A. The patient has tried and had an inadequate response to THREE of the Step 1 agents for the requested indication after at least a 3-month trial per agent (See Step 3c) **OR** B. The patient has an intolerance (defined as an intolerance to the drug or its excipients, not to the route of administration) or hypersensitivity to THREE of the Step 1 agents for the requested indication **OR** C. The patient has an FDA labeled contraindication to ALL of the Step 1 agents for the requested indication **OR** D. BOTH of the following: 1. ALL of the Step 1 agents are not clinically appropriate for the patient **AND** 2. The prescriber has provided a complete list of previously tried agents for the requested indication **AND** 8. If Cosentyx 300 mg is requested as maintenance dosing, then ONE of the following: A. The patient has a diagnosis of moderate to severe plaque psoriasis with or without coexistent active psoriatic arthritis AND the requested dose is 300 mg every 4 weeks **OR** B. The patient has a diagnosis of hidradenitis suppurativa AND ONE of the following:

Module	Clinical Criteria for Approval
	1. The requested dose is 300 mg every 4 weeks **OR** 2. The requested dose is 300 mg every 2 weeks AND the patient has tried and had an inadequate response to Cosentyx 300 mg every 4 weeks after at least a 3-month duration of therapy **OR** C. The patient has a diagnosis of active psoriatic arthritis or active ankylosing spondylitis AND BOTH of the following: 1. The requested dose is 300 mg every 4 weeks **AND** 2. The patient has tried and had an inadequate response to Cosentyx 150 mg every 4 weeks after at least a 3-month duration of therapy **AND** 9. If Actemra is requested for a diagnosis of systemic sclerosis associated interstitial lung disease, the request is for the Actemra syringe (NOTE: Actemra ACTpen is not approvable for SSc-ILD) **AND** 10. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 12 months **NOTE: Cosentyx for the diagnoses of AS, nr-axSpA, and PSA loading doses are not approvable. NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Ops Set Up	Validation Options	Other Explanation
Adalimumab and Adalimumab Biosimilars	Documentation: Requirements as noted within the policy;Validation: Apply Baseline and go to Validation Options	Age Verification;Continuation of Therapy;Contraind., intolerance, or hypersensitivity to prereq.;Diagnosis;Other (see Other explanation field)	*Review info and claims: use of another biologic immunomodulator agent FDA approved or compendia supported for the requested indication *Review medical records and claims - preferred agent requirements: accept medical records or claims history with indefinite lookback for "tried and had an inadequate response"

Module	Ops Set Up	Validation Options	Other Explanation
			criteria requirement. If new to claims, medical records are required. *Review the requested agent's prescribing information: prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent
All other Target Agents	Documentation: Requirements as noted within the policy;Validation: Apply Baseline and go to Validation Options	Age Verification;Continuation of Therapy;Contraind., intolerance, or hypersensitivity to prereq.;Diagnosis;Other (see Other explanation field)	*Review info and claims: use of another biologic immunomodulator agent FDA approved or compendia supported for the requested indication *Review info: contraindication, intolerance, or hypersensitivity to concurrent use of methotrexate *Review info - Step 1b, 2, and 3 agent requirements: support for why the Step 1 AND Step 2 agents are not clinically appropriate for the patient *Review info - Step 1b, 2, and 3 agent requirements: complete list of previously tried agents for the requested indication *Review medical records and claims - Step 3 agent requirements: for Step 3 agents only, accept medical records or claims history with indefinite lookback for "tried and had an inadequate response" criteria

Module	Ops Set Up	Validation Options	Other Explanation
			requirement. If new to claims, medical records are required. *Review the requested agent's prescribing information: prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent *UM Writer to select one of the following [] options for the requirement "If the request is for use in alopecia areata AND alopecia areata is NOT restricted from coverage under the patient's benefit": [ ] Cover alopecia areata (remove this criteria point from the question set) [ ] Restrict alopecia areata (keep this criteria point in the question set)

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL All Program Type	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. The requested agent is Xeljanz/Xeljanz XR for a diagnosis of ulcerative colitis, AND BOTH of the following: 1. There is support for therapy for the dose exceeding the quantity limit (e.g., patient has lost response to the FDA labeled maintenance dose [i.e., 5 mg

Module	Clinical Criteria for Approval
	twice daily or 11 mg once daily] during maintenance treatment; requires restart of induction therapy) (medical records required) **AND** 2. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit **OR** B. The requested agent is Xeljanz oral solution for a diagnosis of polyarticular course juvenile idiopathic arthritis, AND ONE of the following: 1. BOTH of the following: A. The requested quantity (dose) does not exceed the maximum FDA labeled dose (i.e., 5 mg twice daily) NOR the maximum compendia supported dose for the requested indication **AND** B. There is support for why the patient cannot take Xeljanz 5 mg tablets **OR** 2. The requested quantity (dose) exceeds the maximum FDA labeled dose but does NOT exceed the maximum compendia supported dose for the requested indication **OR** 3. BOTH of the following: A. The requested quantity (dose) exceeds the maximum FDA labeled dose AND the maximum compendia supported dose for the requested indication **AND** B. There is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required) **OR** C. The requested agent is NOT Xeljanz/Xeljanz XR for a diagnosis of ulcerative colitis or polyarticular course juvenile idiopathic arthritis, AND ONE of the following: 1. The patient has an FDA labeled indication for the requested agent, AND ONE of the following: A. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does NOT exceed the program quantity limit **OR** B. ALL of the following: 1. The requested quantity (dose) exceeds the FDA maximum labeled dose for the requested indication **AND** 2. The patient has tried and had an inadequate response to at least a 3 month trial of the maximum FDA labeled dose for the requested indication (medical records required) **AND**

Module	Clinical Criteria for Approval
	3. ONE of the following: A. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum compendia supported dose for the requested indication **AND** 2. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength/and or package size that does NOT exceed the program quantity limit **OR** B. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose AND the maximum compendia supported dose for the requested indication **AND** 2. There is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required) **OR** 2. The patient has a compendia supported indication for the requested agent, AND ONE of the following: A. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum compendia supported dose for the requested indication **AND** 2. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength/and or package size that does NOT exceed the program quantity limit **OR** B. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum compendia supported dose for the requested indication **AND** 2. There is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required) **OR** 3. The patient does NOT have an FDA labeled indication NOR a compendia supported indication for the requested agent AND BOTH of the following: A. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength and/or package size that does not exceed the program quantity limit **AND**

Module	Clinical Criteria for Approval
	B. There is support for therapy with a higher dose or shortened dosing interval for the requested indication (submitted copy of clinical trials, phase III studies, guidelines required) **Compendia Allowed**: AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** **Initial Approval with PA:** up to 12 months for all agents EXCEPT adalimumab containing products for ulcerative colitis (UC), Rinvoq for atopic dermatitis (AD), Siliq for plaque psoriasis (PS), Xeljanz and Xeljanz XR for induction therapy for UC, and the agents with indications that require loading doses for new starts. NOTE: For agents that require a loading dose for a new start, approve the loading dose based on FDA labeling AND the maintenance dose for the remainder of the length of approval. Adalimumab containing products for UC may be approved for up to 12 weeks, Rinvoq for AD may be approved for up to 6 months, Siliq for PS may be approved for up to 16 weeks, and Xeljanz and Xeljanz XR for UC may be approved for up to 16 weeks. **Renewal Approval with PA:** up to 12 months **Standalone QL approval:** up to 12 months or through the remainder of an existing authorization, whichever is shorter **NOTE: Cosentyx for the diagnoses of AS, nr-axSpA, and PSA loading doses are not approvable.

CONTRAINDICATION AGENTS

Contraindicated as Concomitant Therapy
Agents NOT to be used Concomitantly Abrilada (adalimumab-afzb) Actemra (tocilizumab) Adalimumab Adbry (tralokinumab-ldrm) Amjevita (adalimumab-atto) Arcalyst (rilonacept) Avsola (infliximab-axxq) Benlysta (belimumab) Bimzelx (bimekizumab-bkzx) Cibinqo (abrocitinib)

Contraindicated as Concomitant Therapy
Cimzia (certolizumab)
Cinqair (reslizumab)
Cosentyx (secukinumab)
Cyltezo (adalimumab-adbm)
Dupixent (dupilumab)
Enbrel (etanercept)
Entyvio (vedolizumab)
Fasenra (benralizumab)
Hadlima (adalimumab-bwwd)
Hulio (adalimumab-fkjp)
Humira (adalimumab)
Hyrimoz (adalimumab-adaz)
Idacio (adalimumab-aacf)
Ilaris (canakinumab)
Ilumya (tildrakizumab-asmn)
Inflectra (infliximab-dyyb)
Infliximab
Kevzara (sarilumab)
Kineret (anakinra)
Leqselvi (deuruxolitinib)
Litfulo (ritlecitinib)
Nemluvio (nemolizumab-ilto)
Nucala (mepolizumab)
Olumiant (baricitinib)
Omvoh (mirikizumab-mrkz)
Opzelura (ruxolitinib)
Orencia (abatacept)
Otezla (apremilast)
Pyzchiva (ustekinumab-ttwe)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rinvoq (upadacitinib)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Saphnelo (anifrolumab-fnia)
Selarsdi (ustekinumab-aekn)
Siliq (brodalumab)

Contraindicated as Concomitant Therapy
Simlandi (adalimumab-ryvk)
Simponi (golimumab)
Simponi ARIA (golimumab)
Skyrizi (risankizumab-rzaa)
Sotyktu (deucravacitinib)
Spevigo (spesolimab-sbzo) subcutaneous injection
Stelara (ustekinumab)
Taltz (ixekizumab)
Tezspire (tezepelumab-ekko)
Tofidence (tocilizumab-bavi)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tyenne (tocilizumab-aazg)
Tysabri (natalizumab)
Velsipity (etrasimod)
Wezlana (ustekinumab-auub)
Xeljanz (tofacitinib)
Xeljanz XR (tofacitinib extended release)
Xolair (omalizumab)
Yuflyma (adalimumab-aaty)
Yusimry (adalimumab-aqvh)
Zeposia (ozanimod)
Zymfentra (infliximab-dyyb)

Buprenorphine, Buprenorphine/Naloxone for Opioid Dependence

Quantity Limit

ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
Buprenorphine SL							
65200010100760		Buprenorphine HCl SL Tab 2 MG (Base Equiv)	2 MG	Quantity limit per 90 days is to allow for a single course of induction treatment			
65200010100780		Buprenorphine HCl SL Tab 8 MG (Base Equiv)	8 MG	Quantity limit per 90 days is to allow for a single course of induction treatment			

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. If the requested agent is buprenorphine sublingual tablets, then ONE of the following:

Module	Clinical Criteria for Approval
	1. The patient is pregnant **OR** 2. The patient has a documented intolerance, FDA labeled contraindication, or hypersensitivity to naloxone or naltrexone **OR** B. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** C. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** D. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** • Buprenorphine sublingual tablets: Approve for up to 12 months. For increased quantities, the quantity requested up to a maximum dose of 32 mg buprenorphine may be approved. • Buprenorphine/naloxone sublingual tablets and films: Approve for up to 6 months NOTE: For increased quantities, the quantity requested up to a maximum dose of 32 mg buprenorphine may be approved. • Zubsolv: Approve for up to 6 months NOTE: For increased quantities, the quantity requested up to a maximum dose of 22.8 mg buprenorphine may be approved.

Cablivi

Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Cablivi® (caplacizumab-yhdp) Injection for intravenous or subcutaneous use	Treatment of adult patients with acquired thrombotic thrombocytopenia purpura (aTTP), in combination with plasma exchange and immunosuppressive therapy		1

CLINICAL RATIONALE

Acquired/immune-mediated thrombotic thrombocytopenic purpura (aTTP/iTTP)	Thrombotic thrombocytopenic purpura (TTP) is a rare medical emergency that is almost always fatal if appropriate treatment is not quickly started. TTP is caused by severely reduced activity of the von Willebrand factor-cleaving protease ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 repeats, member 13). Hereditary or congenital TTP (cTTP) accounts for less than 5 percent of cases and is inherited by mutations of the ADAMTS13 gene. More commonly, TTP is acquired and due to ADAMTS13 autoantibodies that inhibit plasma ADAMTS13 activity and is referred to as immune-mediated TTP (iTTP) or acquired TTP (aTTP). More than 95% of all TTP cases are aTTP/iTTP. Patients with TTP present with thrombocytopenia, microangiopathic hemolytic anemia with schistocytes on the blood smear, and various degrees of organ damage.(2,3) Rapid recognition of TTP is crucial to initiate appropriate treatment. The first-line therapy for acute TTP is based on daily therapeutic plasma exchange (PEX) supplying deficient ADAMTS13, with or without steroids. Additional immune modulators targeting ADAMTS13 autoantibodies are mainly based on steroids

	and the humanized anti-CS20 monoclonal antibody rituximab. In refractory or unresponsive TTP, more intensive therapies including twice-daily PEX; pulses of cyclophosphamide, vincristine, or cyclosporine A; or salvage splenectomy are considered.(3) Complications of TTP may include neurological problems, fever, abnormal kidney function, abdominal pain, and heart problems. An episode of TTP usually occurs suddenly and lasts days or weeks, but may continue for months. Relapses (or flareups) can occur in up to 60 percent of people with aTTP/iTTP. The ADAMTS13 enzyme normally helps control the activity of certain blood clotting factors.(4) Distinguishing TTP from other thrombotic microangiopathy (TMA) syndromes is crucial because patients with severe ADAMTS13 deficiency are likely to respond to empirical therapeutic PEX, while those without ADAMTS13 severe deficiency often require treatments other than PEX. To definitely identify TTP out of the other diagnoses is also necessary because it has a specific outcome requiring a well-defined follow-up.(3) Screening for ADAMTS13 activity is the first test to be performed. If ADAMTS 13 activity is less than 10% TTP diagnosis is confirmed. Reference methods for ADAMTS13 activity remain homemade manual methods requiring substantial skill to provide enough reliability for diagnostic use, especially because of preanalytical and analytical limitations. These methods are time-consuming requiring several labor-intensive hours for turnaround results. As a consequence, these reference methods are limited to expert laboratories (usually 1 or 2 laboratories per country worldwide centralizing ADAMTS13 biology and networking with clinical centers involved in the management of patients with TMA). Rapid commercial ELISA assays for ADAMTS13 activity manageable in local laboratories have been developed, but they do not have the accuracy and reliability of the reference methods. These assays are secondary, but in the acute setting, when positive, they reinforce the diagnosis of TTP.(3)

	Because of these reasons, reliable results of ADAMTS13 investigation usually cannot be available in an emergency. In a large majority of cases, the unavailability of ADAMTS13 data in an emergency is not a limitation to initial management. Urgent therapeutic management is usually decided on the basis of TTP clinical symptoms and not on the basis of ADAMTS13 results. However, ADAMTS13 investigation remains crucial to definitely confirm TTP diagnosis.(3) The International Society on Thrombosis and Haemostasis (ISTH) developed guidelines for diagnosing TTP and prioritizing the initial diagnostic steps involved in confirming TTP during the first acute episode, for the purpose of providing optimal initial treatment to the appropriate patient population. Three diagnostic pathways were identified for a full appraisal:(2) • Scenario A: a pathway where ADAMTS13 activity measurement is readily available (i.e., within 72 hours) • Scenario B: a pathway where ADAMTS13 measurement is NOT available • Scenario C: a pathway where WDAMTS13 activity measurement is available with a delay (i.e., after 72 hours but less than 7 days) The patients with suspected TTP are defined as: patients with thrombocytopenia (platelets less than 100 X 10^9/L), microangiopathic hemolytic anemia (e.g., hemoglobin and hematocrit below the lower limit of the reference range, low haptoglobin, elevated lactase dehydrogenase, the presence of schistocytes in peripheral blood smear), and relatively preserved renal function. The panel discussed the additional value of using a clinical risk assessment model such as the PLASMIC score or the French score but felt it was out of scope for the guidelines at this time.(2) PLASMIC score or French score predictions of likelihood of severe ADAMTS13 deficiency in suspected TTP(2)

Parameters	French Score (points accrued)	PLASMIC Score (points accrued)
Platelet count	Less than 30 X 10^9/L (+1)	Less than 30 X 10^9/L (+1)
Serum creatinine level	Less than 2.26 mg/dL (+1)	Less than 2.0 mg/dL (+1)
Hemolysis • Indirect bilirubin greater than 2 mg/dL • Or reticulocyte count greater than 2.5% Or undetectable haptoglobin	*	(+1)
No active cancer in previous year	*	(+1)
No history of solid organ or stem cell transplant	*	(+1)
INR	*	Less than 1.5 (+1)
MCV	NA	(+1)

Likelihood of severe deficiency of ADAMTS13 activity (i.e., less than 10%)	0:2% 1: 70% 2: 94%	0-4: 0-4% 5: 5%-24% 6-7: 62%-82%

Note: each item is associated with 1 point (+1) as noted
* French score considered patients with thrombotic microangiopathy that included hemolysis and schistocytes in their definition and assumed that there was no history or clinical evidence for associated cancer, transplantation, or disseminated intravascular coagulation. Therefore, these items were intrinsic to the scoring system. NA in MCV: not incorporated in the French score

For patients with iTTP experiencing a first acute event, the ISTH panel gives a strong recommendation for the addition of corticosteroids to PEX over PEX alone. The panel was unable to make a more detailed recommendation on a preferred dosage and type of corticosteroid (e.g., prednisone, methylprednisolone) given the known cardiac, endocrine, and neuropsychiatric adverse effects of corticosteroids on the susceptible patient that will be administered these agents. The panel gave a conditional recommendation for the addition of rituximab to corticosteroids and PEX over corticosteroids and PEX alone.(5)

For patients with iTTP experiencing a relapse, the ISTH panel gives a strong recommendation for the addition of corticosteroids to PEX over PEX alone. The panel made a strong recommendation despite very low certainty evidence because the recommended intervention may moderately reduce the mortality in a life-threatening situation, and its adverse events are not prohibitive over a short term. The panel made a conditional recommendation for the addition of rituximab to corticosteroids and PEX over corticosteroids and PEX alone.(5)

For patients with iTTP experiencing an acute event (first event or relapse), the

	ISTH panel gave a conditional recommendation for using caplacizumab over not using caplacizumab. The data informing this recommendation was of moderate certainty, based on two published randomized controlled trials (one of which was double-blinded). Data was not available to differentiate the caplacizumab's effect on the first and relapsed events, so these patients are considered together. The panel noted that the mortality rate was low in both control and caplacizumab arms in both randomized controlled trials. This might not be reflective of the true mortality rates in other TTP studies or patient populations, suggesting the possibility of selection bias meaning the patients in these studies may have had less severe disease. Patients receiving caplacizumab showed a clinically and statistically significant reduction in the number of exacerbations (defined as disease recurrence during therapy or within 30 days after completion of PEX); however, these patients also had a clinically and statistically significant increase in the number of relapses (defined as disease recurrence occurring more than 30 days after completion of PEX therapy) at 12 months. Caplacizumab may leave patients prone to experience a later recurrence owing to the unresolved ADAMTS13 deficiency and inhibitors. The panel also noted that patients on caplacizumab experienced clinically important bleeding side effects.(5)
	
	More specific conditional recommendations were made by the ISTH panel depending on ADAMTS13 testing availability:(2)
	
	• In settings with a timely access to plasma ADAMTS13 activity testing (scenario A or scenario C) and for patients with a high clinical suspicion (greater than or equal to 90% pretest probability) of iTTP (e.g., based on clinical assessment or a formal clinical risk assessment method):
	  • Step 1: Acquire a plasma sample for ADAMTS13 testing before an initiation of PEX or use of any blood product
	  • Step 2: Start PEX and corticosteroids without waiting for the results of ADAMTS13 testing

	• Step 3: Consider early administration of caplacizumab before receiving plasma ADAMTS13 activity results • Step 4: When the results of plasma ADAMTS13 activity is available, continue caplacizumab if ADAMTS13 activity is less than 10 IU/dL (or 10% of normal) (a positive result) or stop caplacizumab and consider other diagnoses if ADAMTS13 activity is greater than 20 IU/dL (or greater than 20% of normal) (a negative test) • Step 5: For patients with plasma ADAMTS13 activity less than 10 IU/dL (or less than 10% of normal), also consider adding rituximab as early as possible, as a majority of these adult patients (greater than 95%) • In settings with a timely access to plasma ADAMTS13 testing (scenario A or scenario C) and for patients with patients with intermediate or low clinical suspicion of iTTP (e.g., based on clinical assessment or a formal clinical risk assessment method): • Step 1: Acquire a plasma sample for ADAMTS13 testing before an initiation of PEX or use of any blood product • Step 2: Consider starting PEX and corticosteroids, depending on the clinician's judgment and assessment of the individual patient • Step 3: Do not start caplacizumab until the result of plasma ADAMTS13 activity becomes available • Step 4: When the results of plasma ADAMTS13 activity testing is available, consider adding caplacizumab and rituximab if ADAMTS13 activity is less than 10 IU/dL (or less than 10% of normal) with inhibitors or an elevated level of anti-ADAMTS13 IgG (a positive result) do not start caplacizumab and consider other diagnoses if ADAMTS13 activity is greater than 20IU/dL (or greater than 20% of normal (a negative result)

	• In settings of no reasonable access to plasma ADMTS13 activity testing (scenario B) do not use caplacizumab regardless of the pretest probability of TTP
Efficacy	The efficacy of Cablivi for the treatment of adult patients with acquired thrombotic thrombocytopenic purpura (aTTP) in combination with plasma exchange (PEX) and immunosuppressive therapy was established in a pivotal multicenter, randomized, double-blind, placebo- controlled trial (HERCULES) (NCT02553317). 72 patients were randomized to receive Cablivi and 73 patients received placebo. Patients in both groups received PEX and immunosuppressive therapy. The efficacy of Cablivi in patients with aTTP was established based on time to platelet count response (platelet count greater than or equal to 150,000/µL followed by cessation of daily PEX within 5 days). Time to platelet count response was shorter among patients treated with Cablivi compared to placebo. Treatment with Cablivi resulted in a lower number of patients with TTP-related death, recurrence of TTP, or at least one treatment-emergent major thromboembolic event (a composite endpoint) during the treatment period. Recurrence of TTP was defined as a new decrease in platelet count after initial normalization, requiring PEX therapy to be reinitiated. A recurrence within 30 days after completion of PEX therapy was defined as an 'exacerbation'. A recurrence occurring more than 30 days after completion of PEX therapy was defined as a 'relapse'.(1) During the treatment period and 28-day follow-up, treatment with caplacizumab was associated with a significantly shorter time to platelet normalization, compared with placebo: 2.69 days (95% CI 1.89-2.83] versus 2.88 days (95% CI 2.68-3.56; p=0.01). The authors also reported that caplacizumab-treated patients were 1.55 times more likely than placebo-treated patients to have a normalization of the platelet count at any time point (p= 0.01).(6) Caplacizumab significantly outperformed standard-of-care alone in other secondary outcomes, including:(3)

	• composite of TTP-related death, TTP recurrence, or a thromboembolic event: 12% vs. 49% (p less than 0.001) • recurrence of TTP at any time: 12% vs. 38% (p less than 0.001) Disease exacerbation occurred in 31 patients (28 in the placebo group and 3 in the caplacizumab group). Of these, 28 had an unresolved autoimmune disease that may have been the underlying culprit, the researchers noted.(6) Health-care resource use also appeared lower in the caplacizumab group: In the placebo group, patients required an average of 9.4 days of plasma-exchange therapy, compared with 5.8 days in the caplacizumab group. This represented a 38-percent shorter duration of treatment and a 41-percent lower volume of PEX (p values not reported). Duration of hospitalization and intensive care unit stays were reduced, as well.(6)
Safety	Cablivi is contraindicated in patients with a previous severe hypersensitivity reaction to caplacizumab-yhdp or any of its excipients. (1) Cablivi should be discontinued if the patient experiences more than 2 recurrences of aTTP, while on Cablivi.(1)

REFERENCES

Number	Reference
1	Cablivi prescribing information. Genzyme Corporation. April 2023.
2	Zheng, X. L., Vesely, S. K., Cataland, S. R., Coppo, P., Geldziler, B., Iorio, A., Matsumoto, M., Mustafa, R. A., Pai, M., Rock, G., Russell, L., Tarawneh, R., Valdes, J., & Peyvandi, F. (2020). ISTH guidelines for the diagnosis of thrombotic thrombocytopenic purpura. *Journal of Thrombosis and Haemostasis*, *18*(10), 2486–2495. https://doi.org/10.1111/jth.15006

Number	Reference
3	Joly, B. S., Coppo, P., & Veyradier, A. (2017). Thrombotic thrombocytopenic purpura. *Blood*, *129*(21), 2836–2846. https://doi.org/10.1182/blood-2016-10-709857
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5	Zheng, X. L., Vesely, S. K., Cataland, S. R., Coppo, P., Geldziler, B., Iorio, A., Matsumoto, M., Mustafa, R. A., Pai, M., Rock, G., Russell, L., Tarawneh, R., Valdes, J., & Peyvandi, F. (2020). ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. *Journal of Thrombosis and Haemostasis*, *18*(10), 2496–2502. https://doi.org/10.1111/jth.15010
6	ASH Publications. (2019, March). Ashpublications.org. Clinical News. Bleeding disorders. https://ashpublications.org/ashclinicalnews/news/4356/Caplacizumab-Improves-Platelet-Normalization-Time

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL Standalone	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. BOTH of the following A. The patient had at least one occurrence of acquired thrombotic thrombocytopenic purpura (aTTP) during the current course of therapy **AND** B. The patient has NOT had more than 2 occurrences of aTTP while using the requested agent during the current course of therapy **OR**

Module	Clinical Criteria for Approval
	2. The patient had a relapse/recurrence of aTTP after completion of a course of therapy and requires an additional course of therapy **Length of Approval:** Occurrence of aTTP on current course of therapy - requested number of vials up to 58 vials/365 days; Relapse of aTTP - 58 vials/365 days

Camzyos

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Camzyos® (mavacamten) Capsule	Treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and symptoms		1

CLINICAL RATIONALE

HCM	Hypertrophic cardiomyopathy (HCM) is a common genetic heart disease reported in populations globally. Inherited in an autosomal dominant pattern, the distribution is equal by sex, although women are diagnosed less commonly than men. The prevalence of unexplained asymptomatic hypertrophy in young adults in the United States has been reported to range from 1:200 to 1:500. Symptomatic hypertrophy based on medical claims data has been estimated at <1:3000 adults in the United States; however, the true burden is much higher when unrecognized disease in the general population is considered. Clinical evaluation for HCM may be triggered by occurrence of symptoms, a cardiac event, detection of a heart murmur, an abnormal 12-lead electrocardiogram (ECG) identified on routine examinations, or through cardiac imaging during family screening studies.(2)
Efficacy	Mavacamten is a reversible inhibitor selective for cardiac myosin. Mavacamten modulates the number of myosin heads that can enter “on actin” (power-generating) states, thus reducing the probability of force-producing (systolic) and residual (diastolic) cross-bridge formation. Excess myosin actin cross-bridge formation and dysregulation of the super-relaxed state are mechanistic hallmarks of HCM. In HCM patients, myosin inhibition with mavacamten reduces dynamic left ventricular outflow tract (LVOT) obstruction and improves cardiac filling pressures.(1) The efficacy of Camzyos was evaluated in EXPLORER-HCM, a phase 3, double-

	blind, randomized, placebo-controlled, multicenter, international, parallel group trial in 251 adults with symptomatic NYHA class II and III obstructive HCM, LVEF greater than or equal to 55%, and Valsalva LVOT peak gradient greater than or equal to 50 mmHg at rest or with provocation. Patients on dual therapy with beta blocker and calcium channel blocker treatment or monotherapy with disopyramide or ranolazine were excluded. Patients with a known infiltrative or storage disorder causing cardiac hypertrophy that mimicked obstructive HCM, such as Fabry disease, amyloidosis, or Noonan syndrome with left ventricular hypertrophy, were also excluded. Patients were randomized in a 1:1 ratio to receive either a starting dose of 5 mg of Camzyos or placebo once daily for 30 weeks. Treatment assignment was stratified by baseline disease severity NYHA functional class, baseline use of beta blockers, and type of ergometer (treadmill or exercise bicycle). Groups were well matched with respect to age (mean 59 years), BMI (mean 30 kg/m), heart rate (mean 62 bpm), blood pressure (mean 128/76 mmHg), and race (90% Caucasian). Males comprised 54% of the Camzyos group and 65% of the placebo group. At baseline, approximately 73% of the randomized patients were NYHA class II and 27% were NYHA class III. The mean LVEF was 74%, and the mean Valsalva LVOT gradient was 73 mmHg. About 10% had prior septal reduction therapy, 75% were on beta 2 blockers, 17% were on calcium channel blockers, and 14% had a history of atrial fibrillation. All patients were initiated on Camzyos 5 mg (or matching placebo) once daily, and the dose was periodically adjusted to optimize patient response (decrease in LVOT gradient with Valsalva maneuver) and maintain LVEF greater to or equal to 50%. The primary composite functional endpoint, assessed at 30 weeks, was defined as the proportion of patients who achieved either improvement of mixed peak oxygen consumption (pVO2) by greater than or equal to 1.5 mL/kg/min plus improvement in NYHA class by at least 1 or improvement of pVO2 by greater than or equal to 3.0 mL/kg/min plus no worsening in NYHA class. A greater proportion of patients met the primary endpoint at Week 30 in the Camzyos group compared to the placebo group (37% vs. 17%, respectively, p=0.0005).(1)
Safety	Camzyos has a boxed warning for the risk of heart failure. Camzyos reduces left ventricular ejection fraction (LVEF) and can cause heart failure due to systolic dysfunction.(1) Echocardiogram assessments of LVEF are required prior to and during treatment with Camzyos. Initiation of Camzyos in patients with LVEF <55% is not recommended. Interrupt Camzyos if LVEF is <50% at any visit or if the patient experiences heart failure symptoms or worsening clinical status.(1) Concomitant use of Camzyos with certain cytochrome P450 inhibitors or discontinuation of certain cytochrome P450 inducers may increase the risk of

	heart failure due to systolic dysfunction; therefore, the use of Camzyos is contraindicated with the following:(1) • Moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors • Moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers Because of the risk of heart failure due to systolic dysfunction, Camzyos is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called Camzyos REMS Program.(1)

REFERENCES

Number	Reference
1	Camzyos prescribing information. Bristol Meyers Squibb. June 2023.
2	Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients with Hypertrophic Cardiomyopathy. *Circulation (New York, NY)*. 2020;142(25). doi:10.1161/cir.0000000000000937

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** B. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR**

Module	Clinical Criteria for Approval
	C. The patient has a diagnosis of symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) AND ALL of the following: 1. The patient has a left ventricular ejection fraction (LVEF) of greater than or equal to 55% **AND** 2. The patient has a left ventricular outflow tract (LVOT) peak gradient greater than or equal to 50 mmHg at rest or with provocation (Valsalva or post-exercise) **AND** 3. The patient does not have a known infiltrative or storage disorder causing cardiac hypertrophy that mimics obstructive HCM (e.g., Fabry disease, amyloidosis, Noonan syndrome with left ventricular hypertrophy) **AND** 4. ONE of the following: A. The patient has tried and had an inadequate response to a beta blocker **OR** B. The patient has an intolerance or hypersensitivity to therapy with beta blockers **OR** C. The patient has an FDA labeled contraindication to ALL beta blockers **AND** 5. ONE of the following A. The patient has tried and had an inadequate response to a calcium channel blocker **OR** B. The patient has an intolerance or hypersensitivity to therapy with calcium channel blockers **OR** C. The patient has an FDA labeled contraindication to ALL calcium channel blockers **OR** D. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Clinical Criteria for Approval
	Renewal Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. Patient has a left ventricular ejection fraction (LVEF) of greater than or equal to 50% **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR**

Module	Clinical Criteria for Approval
	C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Cannabidiol

Prior Authorization

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Epidiolex® (cannabidiol) Oral solution	Treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients 1 year of age and older		1

CLINICAL RATIONALE

Lennox-Gastaut Syndrome	Lennox-Gastaut syndrome (LGS) is a severe form of epilepsy involving several seizure types, with an onset during infancy or early childhood. Many causes of LGS have been identified, including genetic disorders, trauma, cortical malformations, perinatal hypoxia, and meningitis. Tonic, atonic, and atypical absence seizures are the most common seizure types associated with LGS. Clinical features that may be present include cognitive dysfunction, behavioral abnormalities, and neurodevelopmental impairment. Management of LGS is difficult because it is refractory to many treatments, and no specific therapy is effective for all patients. Valproate is generally considered first-line therapy, and if monotherapy is ineffective another drug such as lamotrigine or rufinamide is added to valproate therapy.(4,10) Alternative adjunctive antiseizure medications include topiramate, clobazam, cannabidiol, fenfluramine, or felbamate.(10) Additional therapies, for patients who do not respond to antiseizure medications, include the ketogenic diet and vagal nerve stimulation.(4,10)
Dravet Syndrome	Dravet syndrome (DS) is a severe form of epilepsy with an onset of recurrent, prolonged seizures in infancy that are often triggered by fever or overheating. DS is characterized by lifelong comorbidities, including neurodevelopmental problems and intellectual disability.(7,8,9,15) Mutations in the alpha-1 subunit of the voltage-gated sodium channel (SCN1A) gene are identified in at least 80% of patients with DS.(7,9,15) Status epilepticus is common and is one of the leading causes of premature mortality seen with DS. Patients with DS have an elevated

	risk of premature mortality, with the most common cause being sudden unexpected death in epilepsy (SUDEP).(7,8,9) Other types of seizures appear before age 5 years and include myoclonic, focal, and atypical absence seizures.(7,9,15) Valproate is considered first-line therapy, with clobazam added if needed.(7,8,9,15) Additional agents include stiripentol, topiramate, cannabidiol, and fenfluramine.(7,8,15) For patients with symptoms refractory to drug therapy, ketogenic diet and vagal nerve stimulation may be beneficial.(7,8,9,15)
Tuberous Sclerosis Complex	Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder caused by a mutation in either the TSC1 gene or the TSC2 gene. TSC is characterized by the development of a variety of benign tumors in multiple organs, including the brain, heart, skin, eyes, kidney, lung, and liver. Seizures are the most frequent presenting neurologic feature of TSC, with more than 80% of patients developing seizures during childhood.(12) Often infantile spasms occur in children with TSC, and vigabatrin is recommended as first-line therapy. Adrenocorticotropic hormone (ACTH), synthetic ACTH, or prednisolone may be used as second-line therapy if an inadequate response to vigabatrin is seen after 2 weeks.(14) Anticonvulsants may be prescribed, with the specific drug being dependent on the type of seizure. Patients with intractable seizures may benefit from a ketogenic diet or vagal nerve stimulation.(11,12,14)
Efficacy	Cannabidiol was studied for treatment of seizures associated with LGS in two published randomized, double-blind, placebo-controlled trials in patients age 2 to 55. Study 1 (GWPCARE4, N=171) compared cannabidiol 20 mg/kg/day vs. placebo.(2) Study 2 (GWPCARE3, N=225) compared cannabidiol 10 mg/kg/day and 20 mg/kg/day vs. placebo.(3) In both studies, LGS patients were inadequately controlled on at least one anti-epileptic drug (AED), with or without vagal nerve stimulation and/or ketogenic diet. In both trials, patients were required to have a minimum of 8 drop seizures (greater than or equal to 2 drop seizures per week) during a 4-week baseline evaluation period. The baseline period was followed by a 2-week titration period and a 12-week maintenance period.(2,3) During Study 1, 94% of patients were taking greater than 2 concomitant AEDs. Most frequently used concomitant AEDs (greater than 25%) were clobazam (49%), valproate (40%), lamotrigine (37%), levetiracetam (34%), and rufinamide (27%).(2) During Study 2, 94% of patients were taking greater than 2 concomitant AEDs. Most frequently used concomitant AEDs (greater than 25%) were clobazam (49%), valproate (38%), levetiracetam (31%), lamotrigine (30%), and rufinamide (29%).(3) In both studies, the primary endpoint was percent change from baseline in frequency (per 28 days) of drop seizures (atonic, tonic, or tonic-clonic seizures) over 14-weeks of treatment. In both studies, median percent change from baseline (reduction) in the frequency of

	drop seizures was significantly greater for cannabidiol vs. placebo: A reduction in drop seizures was observed within 4 weeks of initiating cannabidiol treatment; the reduction remained generally consistent over the 14-week treatment period. Median percent changes from baseline in drop seizure frequency per 28-day period (cannabidiol vs. placebo):(2,3) • Study 1- 20 mg/kg/day [-44%]; placebo [-22%] (p equal to 0.01) • Study 2- 10 mg/kg/day [-37%], 20 mg/kg/day [-42%], placebo [-17%] (both doses p less than 0.01) An open-label extension study (GWPCARE5, N=366), evaluating the long-term safety and efficacy of cannabidiol, was conducted in patients with LGS who completed either GWPCARE3 or GWPCARE4. Sustained reductions in median drop seizure frequency (48-71%) and median total seizure frequency (48-68%) were observed in 12 week intervals through 156 weeks. Notably, 87-93% of patients/caregivers reported an improvement in the patient's overall condition per the patient-reported Subject/Caregiver Global Impression of Change (S/CGIC) scale over the 156 week period at various intervals (7 total assessments, with the first assessment at week 24 and the last assessment at week 156).(5) A single, published, randomized, double-blind, placebo-controlled trial compared cannabidiol 20 mg/kg/day vs. placebo in patients ages 2-18 (N=120) with treatment-resistant DS, inadequately controlled with at least one concomitant AED, with or without vagal nerve stimulation or ketogenic diet. During a 4-week baseline period, patients were required to have greater than 4 convulsive seizures while on stable AED therapy. The baseline period was followed by a 2-week titration period and a 12-week maintenance period. During this study, 93% of patients were taking greater than 2 concomitant AEDs; most commonly used concomitant AEDs (greater than 25%) were clobazam (65%), valproate (57%), stiripentol (43%), levetiracetam (28%), and topiramate (26%). Baseline median convulsive seizure frequency was 13 per 28 days for the combined groups. The primary endpoint was the percent change from baseline in the frequency (per 28 days) of convulsive seizures (all countable atonic, tonic, clonic, and tonic-clonic seizures) over the 14-week treatment period. The median percent change in total convulsive seizure frequency per 28-day period (cannabidiol vs. placebo): 20 mg/kg/day [-39%], placebo [-13%]; p equal to 0.01. A reduction in convulsive seizures was observed within 4 weeks of initiating cannabidiol treatment; effect remained generally consistent over the 14-week treatment period.(6) A randomized, double-blind, placebo-controlled trial compared cannabidiol 25 mg/kg/day and 50 mg/kg/day (two times the recommended maintenance dosage) vs. placebo in patients aged 1-65 years (N=224) with treatment-resistant

	TSC, inadequately controlled with at least one concomitant AED, with or without vagal nerve stimulation or ketogenic diet. During a 4-week baseline period, patients were required to have greater than or equal to 8 seizures while on stable AED therapy. The baseline period was followed by a 4-week titration period and a 12-week maintenance period. During this study, all patients but one were taking 1-2 concomitant AEDs; most commonly used concomitant AEDs (greater than 25%) were valproate (45%), vigabatrin (33%), levetiracetam (29%), and clobazam (27%). Baseline median convulsive seizure frequency was 57 per 28 days for the combined groups. The primary efficacy measure was the percent change from baseline (reduction) in the frequency (per 28 days) of TSC-associated seizures over the 16-week treatment period. The median percentage change in total convulsive seizure frequency per 28-day period (cannabidiol vs. placebo): 25 mg/kg/day [-43%], placebo [-20%]; p less than 0.01. A reduction in convulsive seizures was observed within 4 weeks of initiating cannabidiol treatment; effect remained generally consistent over the 12-week maintenance period.(1)
Safety	Epidiolex carries no boxed warnings. Epidiolex is contraindicated in patients with hypersensitivity to cannabidiol or any of the ingredients in Epidiolex.(1)

REFERENCES

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3	Devinsky O, Patel AD, Cross JH, et al. Effect of Cannabidiol on Drop Seizures in the Lennox–Gastaut Syndrome. N Engl J Med. 2018;378:1888-1897.
4	Wheless JW. Lennox-Gastaut Syndrome. National Organization for Rare Disorders (NORD). Last updated June 2020. Available at https://rarediseases.org/rare-diseases/lennox-gastaut-syndrome/.

Number	Reference
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6	Devinsky O, Cross JH, Laux L, et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med. 2017;376:2011-2020.
7	Sullivan J, Knupp K, Wirrell E, et al. Dravet Syndrome. National Organization for Rare Disorders (NORD). Last updated July 2020. Available at https://rarediseases.org/rare-diseases/dravet-syndrome-spectrum/.
8	Andrade DM, Nascimento FA, et al. Dravet Syndrome: Management and Prognosis. UpToDate. Last updated November 2022. Literature review current through December 2023.
9	Wirrell EC, Laux L, Donner E, et al. Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations from a North American Consensus Panel. Pediatr Neurol. 2017;68:18-34.
10	Wilfong A, et al. Lennox-Gastaut syndrome. UpToDate. Last updated June 2023. Literature review current through December 2023.
11	Randle S, et al. Tuberous Sclerosis Complex: Management and Prognosis. UpToDate. Last updated December 2023. Literature review current through December 2023.
12	DiMario FJ, et al. Tuberous Sclerosis. National Organization for Rare Disorders (NORD). Last updated May 2023. Available at https://rarediseases.org/rare-diseases/tuberous-sclerosis/.
13	Reference no longer used.
14	Northrup H, Aronow ME, Bebin EM, et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatric Neurology. 2021;123:50-66.
15	Wirrell E, Hood V, Knupp KG, et al. International consensus on diagnosis and management of Dravet syndrome. Epilepsia. 2022;63(7):1761-1777.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of seizures associated with ONE of the following: A. Lennox-Gastaut syndrome (LGS) **OR** B. Dravet syndrome (DS) **OR** C. Tuberous sclerosis complex (TSC) **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The requested agent will NOT be used as monotherapy for seizure management **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The requested agent will NOT be used as monotherapy for seizure management **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months

Carbaglu (carglumic acid)

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Carbaglu® (carglumic acid) Tablet for oral suspension*	Adjunctive therapy to standard of care in pediatric and adult patients for the treatment of acute hyperammonemia due to deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) Maintenance therapy in pediatric and adult patients for the treatment of chronic hyperammonemia due to deficiency of the hepatic enzyme N-acetylglutamate synthase (NAGS) Adjunctive therapy to standard of care in pediatric and adult patients for the treatment of acute hyperammonemia due to propionic acidemia (PA) or methylmalonic acidemia (MMA)	* generic available	1

CLINICAL RATIONALE

Urea Cycle Disorders	Urea cycle disorders (UCDs) are rare genetically inherited metabolic deficiencies that result from defects in the metabolism of waste nitrogen from the breakdown of protein and other nitrogen-containing molecules. Severe deficiency, or total absence, of any of the enzymes in the urea cycle (carbamoyl phosphate synthetase I [CPS1], ornithine transcarbamylase [OTC], argininosuccinic acid synthetase [ASS1], argininosuccinic acid lyase [ASL], arginase [ARG1]) or the cofactor producer (N-acetyl glutamate synthetase [NAGS]) results in the accumulation of ammonia (hyperammonemia) during the first few days of life. In severe disease, infants rapidly develop cerebral edema and signs of lethargy, anorexia, hyper- or hypoventilation, hypothermia, seizures, neurologic posturing, and coma whereas milder disease and the associated accumulation of ammonia may be triggered by illness or stress.(2,3,4) The most important diagnostic step in UCDs is clinical suspicion of hyperammonemia. Laboratory data useful in the diagnosis of UCD includes, but is not limited to, plasma ammonia, anion gap, and plasma glucose. A normal

	anion gap and normal blood glucose in the presence of a plasma ammonia concentration of 150 micromol/L (greater than 260 micrograms/dL) or higher in neonates and greater than 100 micromol/L (175 micrograms/dL) in older children and adults is indicative of UCD. The diagnosis of a specific UCD can be confirmed by genetic testing. Specifically, NAGS, OTC, and CPSI deficiencies can be confirmed by liver biopsy.(2,3,4) Pharmacologic therapy for acute hyperammonemia consists of initial IV administration of a combination preparation of sodium phenylacetate and sodium benzoate, ideally while the dialysis is being arranged and the diagnostic workup is under way. If chronic therapy is warranted, the patient can then be switched to nitrogen scavengers such as sodium phenylbutyrate, glycerol phenylbutyrate, and carglumic acid.(3,4,5) NAG is an essential cofactor of CPS1, the enzyme that catalyzes the first step of the urea cycle. A deficiency, or absence, of NAGS results in deficiency of NAG, leading to a defect in the urea cycle resulting in toxic ammonia accumulation.(3) Carglumic acid (Carbaglu) is a synthetic structural analog of NAG thereby removing the block in the urea cycle and facilitating ammonia detoxification and urea production. During acute hyperammonemic episodes, concomitant administration of carglumic acid with other ammonia lowering therapies, such as alternate pathway medications, hemodialysis, and dietary protein restriction, is recommended. During maintenance therapy, the concomitant use of other ammonia lowering therapies and protein restriction may be needed based on plasma ammonia levels.(1) Long term management options to prevent hyperammonemia includes dietary modification and nutritional oversight (e.g., protein restriction, limitation of alcohol intake, essential amino acid supplementation if clinically appropriate).(3,4,5) Not all adult patients who recover from a hyperammonemic episode require chronic nitrogen scavengers, but they ought to be considered since many of these patients can become brittle as time goes on.(3,4)
Organic Acidemias	Methylmalonic acidemia (MMA) and propionic acidemia (PA) are inborn errors of metabolism characterized by accumulation of methylmalonic acid or propionic acid, respectively, due to deficiency of methylmalonyl-CoA mutase (MUT) or propionyl-CoA carboxylase (PCC). MMA has an estimated incidence of ~ 1:50,000 and PA of ~ 1:150,000.(6) Patients present either shortly after birth with acute deterioration, metabolic acidosis and hyperammonemia, or later at any age with a more heterogeneous clinical picture, leading to early death or to severe neurological handicap in many survivors. Mental outcome tends to be worse in PA and late complications include chronic kidney disease almost exclusively in MMA and cardiomyopathy mainly in PA. Except for vitamin B12 responsive forms

	of MMA, the outcome remains poor despite the existence of apparently effective therapy with a low protein diet and carnitine. This may be related to under recognition and delayed diagnosis due to nonspecific clinical presentation and insufficient awareness of health care professionals because of disease rarity.(6,7,8) In the classical, neonatal onset form of MMA or PA, symptoms start as early as the second day of life with acute deterioration of the general clinical condition, vomiting, dehydration, weight loss, temperature instability, neurological involvement with muscular hypo- or hypertonia, irritability, lethargy progressing to coma and seizures. At presentation, laboratory findings include severe and persistent metabolic acidosis and ketosis, elevated anion gap, and hyperammonemia.(6,7,8) One of the most severe life-threatening events in MMA and PA is hyperammonemia. The acute management differs depending on whether the cause of hyperammonemia is known or not. The differential diagnosis should include urea cycle defects and some other inherited disorders. The start of ammonia detoxification and measures to reverse catabolism must not be delayed. Therapy mirrors that for hyperammonemia due to NAGS deficiency (see section above, regarding pharmacologic therapy for acute hyperammonemia). Carglumic acid (Carbaglu) has been utilized in MMA and PA for its ability to antagonize propionyl-CoA induced hyperammonemia.(6,7,8) In a randomized, double-blind, placebo-controlled, multicenter clinical trial evaluating the efficacy of Carbaglu in the treatment of hyperammonemia in patients with PA and MMA, eligible patients had a hyperammonemic episode(s), defined as an admission to the hospital with a plasma ammonia level greater than or equal to 70 micromol/L. Patients were randomized 1:1 to receive either Carbaglu or placebo for 7 days or until hospital discharge, whichever occurred earlier. All patients received standard of care; the median patient age was 8 years (range 4 days to 29 years). The primary endpoint was the time from the first dose of drug to the earlier of plasma ammonia level less than or equal to 50 micromol/L (normal range) or hospital discharge. The median time to reach the primary endpoint was 1.5 days in the Carbaglu group compared to 2.0 days in the placebo group, a difference of 0.5 days (95% confidence interval: -1.2, 0.1), driven exclusively by an effect on plasma ammonia normalization.(1)
Safety	Carbaglu (carglumic acid) has no boxed warnings or contraindications.(1)

REFERENCES

Number	Reference
1	Carbaglu prescribing information. Recordati Rare Diseases Inc. January 2024.
2	Ah Mew N, Simpson KL, Gropman AL, et al. Urea Cycle Disorders Overview. April 2003 [Updated June 2017]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2024. Available at: http://www.ncbi.nlm.nih.gov/books/NBK1217/.
3	Rare Diseases Clinical Research Network. Urea Cycle Disorders Consortium. Urea Cycle Disorders Treatment Guidelines. Available at: https://www.rarediseasesnetwork.org/cms/ucdc/Healthcare-Professionals/Urea-Cycle-Treatment-Guidelines.
4	Summar M. Urea Cycle Disorders. National Organization for Rare Disorders (NORD). Available at: https://rarediseases.org/physician-guide/urea-cycle-disorders/.
5	Haberle J, Burlina A, Chakrapani A, et al. Suggested Guidelines for the Diagnosis and Management of Urea Cycle Disorders: First Revision. J Inherit Metab Dis. 2019;42(6):1041-1230.
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8	Jurecki E, Ueda K, Frazier D, et al. Nutrition Management Guideline for Propionic Acidemia: An Evidence- and Consensus-Based Approach. Mol Genet Metab. 2019 Apr;126(4):341-354.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. ALL of the following:

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
1. The patient has a diagnosis of N-acetylglutamate synthase (NAGS) deficiency confirmed by enzyme analysis (via liver biopsy) OR genetic testing AND
2. The patient has a diagnosis of hyperammonemia AND ALL of the following:
A. The patient has elevated ammonia levels according to the patient's age [Neonate: plasma ammonia level 150 micromol/L (greater than 260 micrograms/dL) or higher; Older child or adult: plasma ammonia level greater than 100 micromol/L (175 micrograms/dL)] AND
B. The patient has a normal anion gap AND
C. The patient has a normal blood glucose level AND
3. The patient is unable to maintain a plasma ammonia level within the normal range with the use of a protein restricted diet and, when clinically appropriate, essential amino acid supplementation OR
B. ALL of the following:
1. ONE of the following:
A. The patient has a diagnosis of methylmalonic acidemia (MMA) OR
B. The patient has a diagnosis of propionic acidemia (PA, PROP) AND
2. The requested drug will be used as adjunctive therapy to standard of care for the treatment of acute hyperammonemia AND
3. The patient was hospitalized with a plasma ammonia level greater than or equal to 70 micromol/L AND
2. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:
<table>
<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Carbaglu</td><td>carglumic acid</td></tr>
</table>
A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
C. There is support for the use of the requested brand agent over the generic equivalent AND
3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., nephrologist, metabolic disorders) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent AND
</td></tr>
</table>

Module	Clinical Criteria for Approval
	5. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** Methylmalonic acidemia (MMA) or propionic acidemia (PA): 1 month NAGS deficiency: 12 months **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review; Carbaglu for methylmalonic acidemia [MMA] or propionic acidemia [PA] should always be reviewed under Initial Evaluation] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., nephrologist, metabolic disorders) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months

Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Kalydeco® (ivacaftor) Oral granules Tablets	Treatment of cystic fibrosis (CF) in patients age 1 month and older who have at least one mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or *in vitro* assay data. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.		1
Orkambi® (lumacaftor/ivacaftor) Oral granules Tablet	Treatment of cystic fibrosis (CF) in patients aged 1 year and older who are homozygous for the *F508del* mutation in the *CFTR* gene. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the *F508del* mutation on both alleles of the *CFTR* gene. Limitations of use: The efficacy and safety of Orkambi have not been established in patients with CF other than those homozygous for the *F508del* mutation.		2
Symdeko®	Treatment of patients with cystic fibrosis (CF) age 6 years and older who are homozygous for the *F508del* mutation or who have at least one		3

Agent(s)	FDA Indication(s)	Notes	Ref#
(tezacaftor/ivacaftor and ivacaftor co-packaged) Tablet	mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to tezacaftor/ ivacaftor based on *in vitro* data and/or clinical evidence. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of a *CFTR* mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use.		
Trikafta® (elexacaftor/tezacaftor/ivacaftor and ivacaftor co-packaged) Oral granules Tablet	Treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one F508del mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on in vitro data. If the patient's genotype is unknown, an FDA-cleared CF mutation test should be used to confirm the presence of at least one F508del mutation or a mutation that is responsive based on in vitro data.		8

CLINICAL RATIONALE

Cystic Fibrosis	Cystic fibrosis (CF) is the most common life-threatening autosomal recessive disease among Caucasian populations. CF is a multisystem disorder caused by mutations in the gene for the CF transmembrane conductance regulator (CFTR), which encodes an ion channel protein. Defects in the ion channel protein cause deranged transport of chloride and other CFTR-affected ions (e.g., sodium and bicarbonate), which leads to thick, viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract, and to increased salt content in sweat gland secretions.(5) Pulmonary disease remains the leading cause of morbidity and mortality in patients with CF.(6)

	Diagnosis of CF is based upon compatible clinical findings with biochemical or genetic confirmation. Both of the following criteria must be met to diagnose CF:(4,5)
	
	• Clinical symptoms consistent with CF in at least one organ system, OR positive newborn screen, OR history of CF in a sibling
	AND
	• Evidence of CFTR dysfunction (i.e., elevated sweat chloride greater than or equal to 60 mmol/L, two mutations on separate alleles known to cause CF, abnormal nasal potential difference)
	
	Treatment of CF requires a multidisciplinary approach to care that is best provided at one of more than 120 CF Care Centers (accredited by the CF Foundation), most of which have dedicated programs for both children and adults. Patients treated at these centers are seen by physicians, nurses, dietitians, respiratory therapists, physical therapists, and social workers with special competence in CF care.(4) Sinus infection, nutritional status, glucose control, and psychosocial issues should be assessed at regular intervals. Antibiotics, bronchodilators, anti-inflammatory agents, agents that promote airway secretion clearance, nutritional support, and CFTR modulators are possible therapies for CF patients.(6)
	
	CFTR modulators are a new class of drugs that act by improving production, intracellular processing, and/or function of the defective CFTR protein. These drugs represent an important advance in management of CF because they target the defective CFTR protein rather than its downstream consequences. Indications and efficacy of CFTR drugs depend upon the CFTR mutations in the individual patient. Therefore, all CF patients should undergo CFTR genotyping to determine if they carry a mutation that makes them eligible for CFTR modulator therapy.(7,9,10)
	
	The following approach is recommended for CFTR modulators, guided by both genotype and age:(7)
	
	• F508del homozygotes:
	  ○ Age 1 to less than 2 years – lumacaftor/ivacaftor (LUM/IVA)
	  ○ Age greater than or equal to 2 years – elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)
	• F508del heterozygotes
	  ○ Age greater than or equal to 1 month to less than 2 years - IVA (only if the second mutation is responsive to this therapy)
	  ○ Age greater than or equal to 2 years - ELZ/TEZ/IVA

	• If a patient has a genotype that is eligible for more than one therapy, start on the maximal therapy available for their age group (i.e., triple therapy before dual therapy before monotherapy) • For patients with no gating mutations, residual function mutations, or F508del mutations, CFTR therapy should be used in the setting of a clinical trial.
Efficacy	Ivacaftor was the first approved CFTR modulator therapy. It was originally approved for patients 12 years or older with a G551D mutation in at least one of their CFTR genes. A phase 3 multicenter randomized trial studied the effect of 48 weeks of ivacaftor, 150 mg twice daily, compared with placebo in 161 subjects aged 12 years or older with at least one G551D mutation. The FEV1 increased 10.4% from baseline in the treated patients compared with −0.2% for those receiving placebo at 24 weeks (*p* less than 0.001). Subjects receiving ivacaftor were 55% less likely to have a pulmonary exacerbation than those receiving placebo (p less than 0.001). There were significant improvements in QOL, as measured by Cystic Fibrosis Questionnaire Revised (CFQ-R), as well as nutritional status. The authors observed a 48.1 mmol/L decrease in sweat chloride concentration in treated patients compared with placebo (p less than 0.001), reflecting the impact of the drug on the basic defect in CF.(1,7,9) Other trials have evaluated the efficacy of ivacaftor in patients with CF and mutations in additional CFTR genes (e.g., G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, S549R, R117H) and have showed beneficial results similar to those reported for patients with the G551D mutation.(1,7,10) Further clinical trials and in vitro studies with ivacaftor have expanded the approved label to 6 years of age and additional CFTR mutations. However, even with the expanded indication only about 10% of patients with CF in the United States carry mutations responsive to ivacaftor.(7,10) The most common CFTR mutation that causes CF is F508del; 50% of CF patients with CF are homozygous, and another 40% are heterozygous.(5,10) Ivacaftor alone is ineffective in treating F508del mutation since these mutations result in decreased CFTR expression (due to incorrect CFTR protein folding) at the respiratory epithelial cell surface, whereas ivacaftor's mechanism of action is augmentation of ion conductance via gating channel.(1,9,10) Combination lumacaftor and ivacaftor has shown improvements in pulmonary function and reduced the risk of pulmonary exacerbations in CF patients who are homozygous for the F580del mutation.(2,7,10) Lumacaftor partially corrects the CFTR misfolding while ivacaftor improves the gating abnormality. Neither drug is effective as monotherapy for F508del homozygotes.(7,10)

	The efficacy of lumacaftor-ivacaftor in patients with CF who are homozygous for the F508del mutation in the CFTR gene was evaluated in two randomized, double-blind, placebo-controlled, 24-week clinical trials. The primary efficacy endpoint in both trials was change in lung function as determined by absolute change from baseline in percent predicted FEV1 (ppFEV1) at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24. In both trials, treatment with lumacaftor-ivacaftor resulted in a statistically significant improvement in ppFEV1.(2,7,10) Key secondary efficacy variables included relative change from baseline in ppFEV1 at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24; absolute change from baseline in BMI at Week 24; absolute change from baseline in CFQ-R score at Week 24, a measure of respiratory symptoms relevant to patients with CF such as cough, sputum production, and difficulty breathing; proportion of patients achieving greater than or equal to 5% relative change from baseline in ppFEV1 using the average of Week 16 and Week 24; and number of pulmonary exacerbations through Week 24. For the purposes of these trials, a pulmonary exacerbation was defined as a change in antibiotic therapy (IV, inhaled, or oral) as a result of 4 or more of 12 pre-specified sino-pulmonary signs/symptoms.(2,10) In patients who are heterozygous for the F508del mutation, lumacaftor-ivacaftor does not appear to have clinically meaning benefit.(2,7) Tezacaftor-ivacaftor combination has shown modest improvements in pulmonary function and reduced the risk of pulmonary exacerbations for individuals who are homozygous for the F508del mutation or a heterozygous F508del mutation in combination with a residual function mutation. Tezacaftor partially corrects the CFTR misfolding, while ivacaftor is a potentiator that improves the gating abnormality.(7) A trial involving F508del homozygotes resulted in modest improvement in FEV1 (absolute change, 4 percentage points versus placebo) and modest improvement in CFQ-R score (5.1 points versus placebo). The rate of pulmonary exacerbations was 35 percent lower in the treatment group compared with placebo (hazard ratio [HR] 0.64, 95% CI 0.46-0.88).(2,7) The October 2019 Priority Review FDA approval of Trikafta (elexacaftor-tezacaftor-ivacaftor combination) brought another CFTR agent to the market with additional benefit for the 50% of CF patients with homozygous F508del mutation, but particularly the 40% of CF patients with heterozygous F508del mutation who were previously unable to be treated unless their other CFTR mutation was an approved mutation for Kalydeco or Symdeko. The efficacy of Trikafta was demonstrated in two trials. The first trial was a 24-week, randomized, double-blind, placebo-controlled trial in 403 patients who had an F508del mutation and a mutation on the second allele that results in either no

	CFTR protein or a CFTR protein that is not responsive to ivacaftor or tezacaftor/ivacaftor alone. The second trial was a four-week, randomized, double-blind, active-controlled trial in 107 patients who had two identical F508del mutations. Trikafta increased the ppFEV1 in both trials (Trial 1 increased mean ppFEV1 13.8% from baseline compared to placebo; Trial 2 increased mean ppFEV1 10% from baseline compared to tezacaftor/ivacaftor). In the first trial, treatment with Trikafta also resulted in improvements in sweat chloride, number of pulmonary exacerbations (worsening respiratory symptoms and lung function), and body mass index (weight-to-height ratio) compared to placebo.(8) The safety of elexacaftor-tezacaftor-ivacaftor in younger children was evaluated in a 24-week open-label study in 66 children 6 to 11 years old who were homozygous for F508del or heterozygous for F508del with a second minimal function mutation. The safety profile and pharmacokinetics were similar to those in older individuals, and patients experience improvement in percent predicted FEV1 (10.2 percentage points; 95% CI 7.9-12.6), respiratory symptoms, sweat chloride, and body weight.(7,11) On the basis of this study, the drug combination was approved for this age group in June 2021.(8)
Safety	Kalydeco, Orkambi, Symdeko, and Trikafta do not have any boxed warnings nor contraindications.(1,2,3,8)

REFERENCES

Number	Reference
1	Kalydeco prescribing information. Vertex Pharmaceuticals Incorporated. August 2023.
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3	Symdeko prescribing information. Vertex Pharmaceuticals Incorporated. August 2023.
4	Farrell PM, White TB, Ren CL, et al. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. J Pediatr. 2017 Feb;181S:S4-S15.e1.
5	Katkin JP, et al. Cystic Fibrosis: Clinical Manifestations and Diagnosis. UpToDate. Last updated March 2023. Literature review current through August 2023.

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6	Simon RH, et al. Cystic Fibrosis: Overview of the Treatment of Lung Disease. UpToDate. Last updated June 2023. Literature review current through August 2023.
7	Simon RH, et al. Cystic Fibrosis: Treatment with CFTR Modulators. UpToDate. Last updated May 2023. Literature review current through August 2023.
8	Trikafta prescribing information. Vertex Pharmaceuticals Incorporated. August 2023.
9	Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al, of the Pulmonary Clinical Practice Guidelines Committee. Cystic Fibrosis Pulmonary Guidelines: Chronic Medications for Maintenance of Lung Health. Am J Respir Crit Care Med. 2013 Apr;187(7):680-689.
10	Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Pulmonary Guidelines: Use of CFTR Modulator Therapy in Patients with Cystic Fibrosis. Ann Am Thorac Soc. 2018 Mar;15(3):271-280.
11	Zemanick ET, Taylor-Cousar JL, Davies J, et al. A Phase 3 Open-Label Study of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 through 11 Years of Age with Cystic Fibrosis and at Least One F508del Allele. Am J Respir Crit Care Med. 2021;203(12):1522.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. ALL of the following: 1. The patient has a diagnosis of cystic fibrosis **AND** 2. Information has been provided that indicates the patient has a CFTR gene mutation(s), confirmed by genetic testing, according to the FDA label for the requested agent (medical records required) **AND** 3. If the requested agent is Kalydeco, the patient does NOT have F508del mutation on BOTH alleles of CFTR gene (NOT homozygous) **OR** B. The patient has another FDA approved indication for the requested agent **AND**

Module	Clinical Criteria for Approval
	2. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 3. The patient will NOT be using the requested agent in combination with another CFTR modulator agent for the requested indication **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cystic fibrosis, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. ONE of the following: A. If the patient has a diagnosis of cystic fibrosis, the prescriber has provided information that the patient has had clinical improvement or stabilization with the requested agent from baseline (prior to treatment with the requested agent) [e.g., improvement in FEV1, increase in weight/BMI, improvement in Cystic Fibrosis Questionnaire-Revised (CFQ-R) Respiratory Domain score, improvements in respiratory symptoms related to patients with CF (cough, sputum production, and difficulty breathing), and/or reduced number of pulmonary exacerbations] **OR** B. If the patient has another FDA approved indication for the requested agent, the patient has had clinical benefit with the requested agent **AND** 3. The patient will NOT be using the requested agent in combination with another CFTR modulator agent for the requested indication **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cystic fibrosis, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**

Module	Clinical Criteria for Approval
	5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. The prescriber has provided information in support of therapy with a higher dose for the requested indication **Length of Approval**: Initial: 6 months; Renewal: 12 months

Continuous Glucose Monitor (CGM)

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Dexcom G6®			
Dexcom G7®			
Freestyle Libre 2®			
Freestyle Libre®			
Freestyle Libre 3®			

CLINICAL RATIONALE

Continuous Glucose Monitoring (CGM)	Glucose measurements are critical to effective diabetes management. While measurement of glycated hemoglobin (HbA_{1c}) has been the traditional method for assessing glycemic control, it does not reflect intra- and interday glycemic excursions that may lead to acute events (such as hypoglycemia) or postprandial hyperglycemia. These events have been linked to both microvascular and macrovascular complications. While self-monitoring of blood glucose (SMBG) has been shown to improve glycemic control and quality of life in patients, it cannot predict impending hypoglycemia or alert for hypoglycemia. Real-time continuous glucose monitoring (rtCGM) and intermittently viewed CGM (iCGM) address many of the limitations inherent in HcA_{1c} testing and SMBG. rtCGM uniformly tracks the glucose concentrations in the body's interstitial fluid, providing near real-time glucose data; iCGM uses similar methodology to show continuous glucose measurements retrospectively at the time of checking. Both rtCGM and iCGM facilitate monitoring of time spent in the target glucose range ("time in range"). However, only rtCGM can warn users if glucose is trending

	toward hypoglycemia or hyperglycemia. With iCGM, these trends can only be viewed after physically scanning the sensor.(1) CGM affords 2 major benefits over the current standard of SMBG coupled with A_{1c} testing. First, a vast increase in the quantity of blood glucose information, which provides a more comprehensive view of glycemic control. Rather than snapshots in time, continuous information allows us to capture important metrics like time in range, time in hypoglycemia, glucose variability, and many other emerging "glycometrics." These additional metrics cannot be captured with SMBG, even in the most diligent patients. A CGM recording blood glucose every 5 minutes will record 105,120 BG readings per year compared with between just 1000 to 2000 for a person doing frequent SMBG. Second is the ability of CGM systems to provide real-time biofeedback. With real-time data now seamlessly available on a user's mobile device and the internet, easily visible trends and trajectories can help a person understand their own glycemic response in a more meaningful way. Patients can observe which foods and exercises affect them the most. Iterative exposure to this immediate biofeedback allows patients to learn about their own bodies and physiologic responses.(2) Numerous studies have shown that use of rtCGM improves glycemic control and quality of life in both children and adults with type 1 diabetes treated with either continuous subcutaneous insulin infusion or multiple daily insulin injection therapy, improving HbA_{1c}, shortening the time spent in hypoglycemia and hyperglycemia, and reducing moderate-to-severe hypoglycemia. Benefits of rtCGM use have also been reported in individuals with type 2 diabetes who are managed with or without intensive insulin treatment. There is limited data regarding the benefit of rtCGM as an outcome measure for individuals with gestational diabetes mellitus and type 2 diabetes, especially for those who do not use insulin. The benefit of rtCGM is directly correlated to persistence and frequency of use. A meta-analysis found that every 1-day increase of sensor usage per week increased the effect of CGM; the effect on HbA_{1c} is more pronounced the higher the initial HbA_{1c}.(1) High costs and uncertainty over efficacy and necessity have kept CGM from widespread use in people with type 2 diabetes. However, the newest CGM models, the Abbott Freestyle Libre and Dexcom G6, have begun to overcome many of these technical barriers to use of CGM systems. The sensors are inserted painlessly, are small enough to fit easily under clothing, can remain in place for 10 to 14 days, and are FDA approved as sufficiently accurate to use in lieu of fingersticks to make insulin-dosing decisions. Overcoming another

	significant barrier to use, data can now be seamlessly and continuously uploaded wirelessly to the cloud via a user's smartphone.(2) Technology is rapidly changing, but there is no "one-size-fits-all" approach to technology use in people with diabetes. Patient interest in devices and willingness for adoption can vary. Use of technology should be individualized based on a person's specific needs, preferences, and skill level. In general, no device used in diabetes management works optimally without education, training, and ongoing support.(3) In their 2023 Guidelines, the American Diabetes Association published a recommendation that rtCGM should be offered for diabetes management in adults with diabetes on basal insulin who are capable of using devices safely.(3)

REFERENCES

Number	Reference
1	Danne T, Nimri R, Barrelino T, et al. "International Consensus on Use of Continuous Glucose Monitoring". Diabetes Care 2017 Dec;40(12): 1631-1640. Available at: https://care.diabetesjournals.org/content/40/12/1631.
2	Kompala T, and Neinstein A. "A New Era: Increasing Continuous Glucose Monitoring Use in Type 2 Diabetes". Evidence-based Diabetes Management. March 2019, Volume 25, Issue 4. Available at: https://www.ajmc.com/view/a-new-era-increasing-continuous-glucose-monitoring-use-in-type-2-diabetes.
3	American Diabetes Association Professional Practice Committee; 7. Diabetes Technology: Standards of Care in Diabetes-2024. Diabetes Care 1 January 2024; 47 (Supplement_1): S126–S144. https://doi.org/10.2337/dc24-S007.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL Standalone	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR**

Module	Clinical Criteria for Approval
	2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Calcitonin Gene-Related Peptide (CGRP)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Aimovig® (erenumab-aooe) Subcutaneous autoinjector Subcutaneous prefilled syringe	Preventive treatment of migraine in adults		1
AJOVY® (fremanezumab-vfrm) Subcutaneous autoinjector Subcutaneous prefilled syringe	Preventive treatment of migraine in adults		2
Emgality® (galcanezumab-gnlm) Subcutaneous prefilled pen Subcutaneous prefilled syringe	Preventive treatment of migraine in adults Treatment of episodic cluster headache in adults		3
Nurtec ODT® (rimegepant sulfate) Orally disintegrating tablet	Acute treatment of migraine with or without aura in adults Preventive treatment of episodic migraine in adults		19

Agent(s)	FDA Indication(s)	Notes	Ref#
QULIPTA® (atogepant) Tablet	Preventive treatment of migraine in adults		21
UBRELVY® (ubrogepant) Tablet	Acute treatment of migraine with or without aura in adults Limitations of Use: UBRELVY is not indicated for the preventive treatment of migraine.		20
Zavzpret™ (zavegepant) Nasal spray	Acute treatment of migraine with or without aura in adults Limitations of Use: Zavzpret is not indicated for the preventive treatment of migraine.		23

CLINICAL RATIONALE

Migraine and Cluster Headache Management	Migraine is a common disabling primary headache disorder with high prevalence, ranking second globally in terms of years lost to disability.(7) Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia. Migraines can present with or without aura, unilateral fully reversible visual, sensory, or other central nervous system symptoms that usually develop gradually and are most-often followed by headache and associated migraine symptoms.(5) The International Classification of Headache Disorders 3rd Edition (ICHD-3) Diagnostic Criteria:(5)

Indication	Diagnostic Criteria
Migraine without aura	A. At least five attacks fulfilling criteria B-D

		B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated) C. Headache has at least TWO of the following: 1. unilateral location 2. pulsating quality 3. moderate to severe pain intensity 4. aggravation by causing avoidance of routine physical activity D. During headache at least ONE of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia E. Not better accounted for by another ICHD-3 diagnosis
	Migraine with aura	A. At least two attacks fulfilling criteria B and C B. One or more of the following fully reversible aura symptoms: 1. visual 2. sensory 3. speech and/or language 4. motor 5. brainstem 6. retinal C. At least THREE of the following: 1. at least one aura symptom spreads gradually over 5 minutes or more

		2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5-60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive 6. the aura is accompanied, or followed within 60 minutes, by headache D. Not better accounted for by another ICHD-3 diagnosis
	Chronic Migraine	A. Headache (migraine-like or tension-type-like) on greater than or equal to 15 days/month for greater than 3 months AND fulfilling B and C B. Occurring in patient who has had at least 5 attacks fulfilling 1. criteria B-D for migraine without aura (noted above) and/or 2. criteria B and C for migraine with aura (noted above) C. On greater than or equal to 8 days/month for greater than 3 months, fulfilling any of the following: 1. criteria C and D for migraine without aura (noted above) 2. criteria B and C for migraine with aura (noted above)

		3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative D. Not better accounted for by another ICHD-3 diagnosis
	Cluster Headache	A. At least 5 attacks fulfilling criteria B-D B. Severe to very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (untreated) C. At least one of the following: 1. At least one of the following signs or symptoms, ipsilateral to the headache a. conjunctival injection and/or lacrimation b. nasal congestion and/or rhinorrhea c. eyelid edema d. forehead and facial sweating e. miosis and/or ptosis 2. Sense of restlessness or agitation D. Occurring with frequency between one every other day and 8 per day E. Not better accounted for by another ICHD-3 diagnosis

Episodic Cluster Headache	A. Attacks fulfilling criteria for Cluster Headache (noted above) occurring in bouts (cluster periods) B. At least two cluster periods lasting 7 days to 1 years (untreated) and separated by pain-free remission periods of at least 3 months

The IHS notes that cluster periods usually last between 2 weeks and 3 months.(5)

The 2024 American Headache Society (AHS) position statement update states that for those with episodic migraine (4-14 monthly migraine days) based on ICHD-3 with at least moderate disability (Migraine Disability Assessment [MIDAS] score greater than or equal to 11 or Headache Impact Test [HIT-6] score greater than 50), and those with chronic migraine (greater than or equal to 15 headache days/month) based on ICDH-3, CGRP-targeting agents are a first line migraine prevention treatment options and initiation of CGRP-targeting agents should not require the trial and failure of other migraine preventative medications.(6)

The 2021 American Headache Society Consensus Statement recommends the following indications for initiating treatment acute treatment with gepants and ditans agents:(22)

- Prescribed by a licensed clinician
- Patient is at least 18 years of age
- Diagnosis of ICHD-3 migraine with aura, migraine without aura, or chronic migraine
- Either of the following:
    - Contraindication to or inability to tolerate triptans
    - Inadequate response to two or more oral triptans, as determined by either of the following:
        - Validated acute treatment patient-reported outcoming questionnaire (mTOQ, Migraine-ACT, PPMQ-R, FIS, PGIC)
        - Clinician attestation

Lasmiditan is a selective serotonin 5HT-1F receptor agonist that lacks vasoconstrictor activity. Lasmiditan is structurally different than triptans and therefore constitutes a new class of drugs called “ditans”.(22) Ditans are

	selective for the 5HT-1F receptor and its mechanism of action is neuronal without evidence of vasoactive effects.(27) Triptans non-specifically bind to the 5HT-1B and 5HT-1D receptors and with varying affinity bind the 5HT-1F receptors, causing direct vascular vasoconstriction. The safety, tolerability, and efficacy of co-administering lasmiditan with a triptan or a gepant has not been assessed.(22) Patients who do not respond to initial therapy with a triptan, may benefit from a second triptan or different therapy such as use of a gepant (ubrogepant or rimegepant) or a ditan (lasmiditan).(7) The Medical Letter Treatment Guidelines (2023) and Institute for Clinical Systems Improvement Guideline Diagnosis and Treatment of Migraine Headache - Drugs for Migraine states that a triptan is the drug of choice for moderate to severe migraine. The short-acting oral serotonin (5-HT1B/1D) receptor agonists (triptans) sumatriptan (IMITREX, and others), almotriptan (Axert, and generics), eletriptan (RELPAX), rizatriptan (Maxalt, and generics), and zolmitriptan (Zomig, and generics) are similar in efficacy.(24,25) Onset of pain relief generally occurs 30-60 minutes after administration. The longer-acting oral triptans naratriptan (Amerge, and generics) and frovatriptan (Frova, and generics) have a slower onset of action and lower initial response rate than other triptans, but they are better tolerated. Patients with migraine who have nausea or vomiting may not be able to take an oral triptan. Intranasal triptan formulations have a more rapid onset of action than oral tablets, but their efficacy is partially dependent on GI absorption of the portion of the dose that is swallowed. Use of sumatriptan nasal powder (ONZETRA Xsail) results in a faster rise in sumatriptan plasma concentrations and higher peak concentrations than use of a similar dose of sumatriptan nasal spray, suggesting that a larger portion of the dose is absorbed intranasally with the powder. Subcutaneously administered sumatriptan relieves pain faster (in about 10 minutes) and more effectively than other triptan formulations, but it causes more adverse effects.(25) American Headache Society (AHS) (2015): Triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan [oral, nasal spray, injectable, transcutaneous patch], zolmitriptan [oral and nasal spray]) are effective (Level A) and considered by AHS guidelines (2015) to be the gold standard for acute treatment of moderate to severe migraine headaches.(8) Dihydroergotamine is recommended for use as a second- or third-line therapy for select patients or for those with refractory migraine. Intranasal dihydroergotamine has strong evidence of effectiveness but more adverse effects than triptans because of its decreased receptor specificity.(18) An assessment of new migraine treatments by the AHS (2018; updated 2021) reaffirms previous migraine guidelines. The update lists triptans, dihydroergotamine, the oral gepants (Nurtec ODT

	[rimegepant] and UBRELVY [ubrogepant]), and REYVOW (lasmiditan) as effective treatment of moderate or severe acute attacks and mild to moderate attacks that respond poorly to non-specific nonsteroidal anti-inflammatory drugs (NSAIDs), non-opioid analgesics, acetaminophen, or caffeinated combinations (e.g., aspirin/acetaminophen/caffeine). The recommendation remains that prescribers must consider medication efficacy and potential medication-related adverse effects, potential adverse events, patient-specific contraindications to use with a particular medication, and drug-drug interactions when prescribing acute medications for migraine.(7,8,22) The American Academy of Neurology (AAN) 2010 Guideline: Acute and preventive pharmacologic treatment of Cluster Headache (CH) state that sumatriptan subcutaneous injection and zolmitriptan nasal spray are first line-options for acute treatment of CH.(12,24) Since the publication of the 2010 AAN review, and re-reviewed in 2016, there is no new data from randomized, double-blind, controlled trials that contribute to determining the efficacy or safety for a number of acute treatments, including specifically sumatriptan and zolmitriptan. For acute treatment, sumatriptan subcutaneous, zolmitriptan nasal spray, and high flow oxygen remain the treatments with a Level A recommendation.(26) Guidelines suggest that prophylactic therapy should be started and continued for the duration of the CH period. Prophylactic pharmacological therapy includes verapamil, corticosteroids, lithium, topiramate, melatonin, gabapentin, valproic acid, ergotamine, and capsaicin. Verapamil is commonly considered the first option for prophylactic therapy in practice.(10,11,12) Corticosteroids can be used as transitional or bridging therapy until another prophylaxis agent is established.(10) Corticosteroids may be used by some practitioners for short periods of CH.(11,12) The American Academy Neurology lists the following agents as option that maybe considered or should be advised as preventative treatments: • Civamide • Suboccipital steroid injection • Melatonin • Verapamil • Lithium The European Headache Federation and WHO consensus article (2019) states the following:(13) • Individuals with migraine headaches should always be managed in primary care with the exception being chronic migraine, which likely requires specialist management

	• Any headache not responding satisfactorily in primary care or chronic migraine, should be referred to a specialist
	• In adults and children, regular high frequency use (greater than 2 day/week) of acute medication risks the development of MOH
	• Treatment of episodic acute migraine headaches should be approached in a step wise manner and should treat three attacks at each step before moving to the next step if needed:
	  ○ Step 1:
	  ▪ Use non-opioid analgesics, plus an antiemetic when needed
	  ○ Step 2 for adults:
	  ▪ Use triptan products
	  ▪ Triptans should not be used regularly for 10 or more days per month to avoid the risk of MOH
	  ▪ Triptan efficacy is highly variable between individuals, so patients should try different triptans and formulations. Sumatriptan subcutaneous injection should be considered when all other triptans are ineffective.
	  ▪ When vomiting is present, zolmitriptan nasal spray or sumatriptan subcutaneous injection may be preferred
	  ○ Step 2 for children and adolescents:
	  ▪ Failure of Step 1 in children should lead to specialist referral. No specific anti-migraine drugs have shown efficacy in children under 12 years of age.
	  ▪ Failure of Step 2 in adolescents (12-17 years of age), the following have shown efficacy and are approved:
	  • Sumatriptan nasal spray
	  • Zolmitriptan nasal spray
	• Episodic migraine prophylaxis:
	  ○ Indication for migraine prophylaxis include:
	  ▪ Attacks cause disability on two or more days per month, and
	  ▪ Acute therapy has been optimized but does not prevent this, or is poorly tolerated, or there is a risk of over-frequent use of acute therapy, even when it is effective, and
	  ▪ Patient is willing to take daily medication
	  ▪ Failure of acute therapy is an indication for migraine prophylaxis
	  ▪ For children, frequent absence from school is an additional indication for prophylaxis

	○ Migraine prophylaxis agents may take 2-3 months to show efficacy ○ Children requiring prophylactic medication should be referred to a specialist ○ Medications which are effective in adult prophylaxis of episodic migraine include: ▪ Beta blockers: • Atenolol, bisoprolol, metoprolol, propranolol ▪ Amitriptyline ▪ Topiramate ▪ Candesartan ▪ Sodium valproate ▪ Flunarizine ▪ CGRP ○ Onabotulinum toxin A is not effective in episodic migraine and not recommended ○ When prophylaxis therapy fails: ▪ May be due to subtherapeutic dosage or duration of therapy ▪ Failure of one therapy does not predict the failure of another therapy in a different class ▪ Review of the following are recommended: • Diagnosis • Adherence • Other medications, especially for MOH causes ▪ The prophylaxis therapy should be discontinued if it fails to show clear benefit ▪ If all prophylaxis therapies fail, a specialist should be referred • Chronic migraine management: ○ Chronic migraine patients should be referred to a specialist ○ Medications with efficacy in chronic migraine include: ▪ Topiramate ▪ Onabotulinum A ▪ CGRP • Cluster Headache management: ○ Patients should be referred to a specialist ○ Acute therapies include: ▪ Triptans: • Sumatriptan subcutaneous injection • Sumatriptan nasal spray

	• Zolmitriptan nasal spray ▪ Oxygen ○ Transition and maintenance therapies include: ▪ Prednisone ▪ Greater occipital nerve blockade ▪ Verapamil ▪ Lithium carbonate ▪ Topiramate ○ Neuromodulation is another treatment option ○ Failure of one prophylactic therapy does not predict the failure of other therapies ○ Combination prophylaxis therapy can be considered though the potential for toxicity is high ○ Long-term prophylaxis therapy may need to be continued The European Headache Federation guideline states the following on combining migraine prophylaxis therapy:(14) • In episodic migraine, guidelines suggest to stop oral prophylaxis migraine agents before starting CGRPs, unless the patient previously had chronic migraine prior to prophylaxis. In such patients, the suggestion is to add CGRP to the ongoing oral prophylaxis therapy • In chronic migraine, guidelines suggest to add CGRP to ongoing oral prophylaxis therapy • In chronic migraine patients on onabotulinum A therapy and are receiving inadequate treatment response, guidelines suggest to stop onabotulinum A therapy before starting CGRPs • In patients with chronic migraine who are on treatment with CGRP and may benefit from additional prevention, guidelines suggest to add on oral preventative agents • In patients with medication overuse, guidelines suggest to use CGRPs before or after withdrawal of acute medications The clinical trials referenced in FDA labeled package inserts for the preventative CGRP agents excluded patients that had received botulinum toxin within 4 months prior to receiving the CGRP agent.(15,16,17) However the 2021 American Headache Society consensus statement states that CGRP monoclonal antibody treatment (e.g., eptinezumab-jjmr, erenumab, fremanezumab, galcanezumab) may be added to greater than or equal to one established preventative treatment, based on clinical judgement, in adults who meet the ICHD-3 criteria for migraines.(5,22)

Safety	Atogepant is contraindicated in patients with a history of hypersensitivity to atogepant or to any of the components of QULIPTA.(21) Erenumab-aooe is contraindicated in patients with serious hypersensitivity to erenumab-aooe or to any of the excipients.(1) Fremanezumab-vfrm is contraindicated in patients with serious hypersensitivity to fremanezumab-vfrm to any of the excipients.(2) Galcanezumab-gnlm is contraindicated in patients with serious hypersensitivity to galcanezumab-gnlm to any of the excipients.(3) Rimegepant is contraindicated in patients with a history of hypersensitivity reaction to rimegepant, Nurtec ODT, or to any of its components.(19) Ubrogepant is contraindicated in the following:(20) • Concomitant use with strong CYP3A4 inhibitors • History of serious hypersensitivity to ubrogepant or any components of UBRELVY Zavegepant is contraindicated in patients with a history of hypersensitivity reaction to zavegepant or to any of the components of Zavzpret.(23)

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ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
677020353 0D520	Emgality	Galcanezumab-gnlm Subcutaneous Soln Auto-Injector 120 MG/ML	120 MG/ML	Loading dose is 2 injections (2 mL/30 days)			
677020353 0E520	Emgality	Galcanezumab-gnlm Subcutaneous Soln Prefilled Syr 120 MG/ML	120 MG/ML	Loading dose is 2 injections (2 mL/30 days)			

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval

Indication	Preferred Agent(s)	Non-Preferred Agent(s)	Stand Alone Target Agent(s)

Module	Clinical Criteria for Approval

Chronic Migraine Prophylaxis	Aimovig, AJOVY, Emgality, QULIPTA		
Episodic Migraine Prophylaxis	Aimovig, AJOVY, Emgality, Nurtec, QULIPTA		
Episodic Cluster Headaches	Emgality		
Acute Migraine Treatment	Nurtec, Ubrelvy		Zavzpret

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
    A. The requested agent is being used for migraine prophylaxis AND ALL of the following:
        1. ONE of the following:
            A. The patient has at least 15 headache days per month of migraine-like or tension-like headache for a minimum of 3 months (chronic migraine) AND ALL of the following:
                1. The patient has at least 8 migraine headache days per month for a minimum of 3 months **AND**
                2. The patient will NOT be using the requested agent in combination with another prophylactic use CGRP **AND**
                3. The requested agent and strength are FDA labeled for chronic migraine prophylaxis **OR**
            B. The patient has 4-14 monthly migraine days (episodic migraine) AND ALL of the following:
                1. The patient has experienced at least moderate disability due to migraines as indicated by ONE of the following:
                    A. Migraine Disability Assessment (MIDAS) score greater than or equal to 11 **OR**
                    B. Headache Impact Test (HIT-6) greater than 50 **AND**

Module	Clinical Criteria for Approval
	2. The patient will NOT be using the requested agent in combination with another prophylactic use CGRP agent **AND** 3. The requested agent and strength are FDA labeled for episodic migraine prophylaxis **AND** 2. If the client has a preferred agent, then ONE of the following: A. The requested agent is a preferred agent or a stand-alone agent for the requested indication **OR** B. The patient has ONE of the following to a preferred agent for the requested indication: 1. A trial and inadequate response **OR** 2. An intolerance or hypersensitivity **OR** C. The patient has an FDA labeled contraindication to ALL preferred agent(s) for the requested indication B. The requested agent is being used for the treatment of episodic cluster headache AND ALL of the following: 1. The patient has had at least 5 cluster headache attacks **AND** 2. The patient has at least two cluster periods lasting 7-365 days **AND** 3. The patient's cluster periods are separated by a pain-free remission period of greater than or equal to 3 months **AND** 4. ONE of the following: A. The patient has ONE of the following to at least one prerequisite agent (verapamil, melatonin, corticosteroids, topiramate, OR lithium): 1. A trial and inadequate response **OR** 2. An intolerance or hypersensitivity **OR** B. The patient has an FDA labeled contraindication to ALL prerequisite agents (verapamil, melatonin, corticosteroid, topiramate, AND lithium) **AND** 5. The requested agent and strength are FDA labeled for episodic cluster headache treatment **OR** C. The requested agent is being used for acute migraine treatment AND ALL of the following: 1. ONE of the following: A. The patient has ONE of the following to at least one triptan agent 1. A trial and inadequate response **OR** 2. An intolerance or hypersensitivity **OR** B. The patient has an FDA labeled contraindication to ALL triptan agents **AND** 2. The patient will NOT be using the requested agent in combination with another acute migraine therapy (i.e., 5HT-1F, acute use CGRP, ergotamine, triptan) **AND**

Module	Clinical Criteria for Approval
	3. If the client has a preferred agent, then ONE of the following: A. The requested agent is a preferred agent or a stand-alone agent for the requested indication **OR** B. The patient has ONE of the following to a preferred agent for the requested indication: 1. A trial and inadequate response **OR** 2. An intolerance or hypersensitivity **OR** C. The patient has an FDA labeled contraindication to ALL preferred agent(s) for the requested indication **AND** 4. The requested agent and strength are FDA labeled for acute migraine treatment **OR** D. The patient has another FDA labeled indication for the requested agent and route of administration **OR** E. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The patient does not have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** Cluster headache treatment - 6 months; migraine prophylaxis - 6 months; all other indications - 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been approved for the requested agent previously through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. ONE of the following: A. BOTH of the following: 1. ONE of the following:

Module	Clinical Criteria for Approval
	A. The requested agent is being used for migraine prophylaxis AND ALL of the following: 1. The patient has had improvement in migraine prevention (e.g., reduced migraine headache days, reduced migraine frequency, reduced use of acute abortive migraine medication) with the requested agent **AND** 2. The patient will NOT be using the requested agent in combination with another prophylactic use CGRP for the requested indication **AND** 3. ONE of the following: A. BOTH of the following: 1. The patient has at least 15 days per month of migraine-like or tension-like headache (chronic migraine) **AND** 2. The requested agent and strength are FDA labeled for chronic migraine **OR** B. BOTH of the following: 1. The patient has 4-14 monthly migraine days (episodic migraine) **AND** 2. The requested agent and strength are FDA labeled for episodic migraine **OR** B. The requested agent is being used for episodic cluster headache treatment AND BOTH of the following: 1. The patient has had improvement in cluster headaches management with the requested agent **AND** 2. The requested agent and strength are FDA labeled for episodic cluster headache treatment **OR** C. The requested agent is being used for acute migraine treatment AND ALL of the following: 1. The patient has had improvement in acute migraine management with the requested agent **AND** 2. The patient will NOT be using the requested agent in combination with another acute migraine therapy (i.e., 5HT-1F, acute use CGRP, ergotamine, triptan) for the requested indication **AND** 3. The requested agent and strength are FDA labeled for acute migraine treatment **OR**

Module	Clinical Criteria for Approval
	B. The requested agent is being used for an indication other than migraine prophylaxis, episodic cluster headache treatment, or acute migraine treatment AND has had clinical benefit with the requested agent **AND** 3. The patient does not have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL	**Quantity limit for Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. ALL of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. If the requested agent is being used for treatment of acute migraine, then ONE of the following: A. The patient is currently being treated with a migraine prophylactic medication (i.e., anticonvulsants [i.e., divalproex,

Module	Clinical Criteria for Approval
	valproate, topiramate], beta blockers [i.e., atenolol, metoprolol, nadolol, propranolol, timolol], antidepressants [i.e., amitriptyline, venlafaxine], candesartan, prophylactic use CGRP [e.g., Aimovig, AJOVY, Emgality, Nurtec, QULIPTA, Vyepti], onabotulinum toxin A [Botox]) **OR** B. The patient has an intolerance or hypersensitivity to therapy with migraine prophylactic medication (i.e., anticonvulsants [i.e., divalproex, valproate, topiramate], beta blockers [i.e., atenolol, metoprolol, nadolol, propranolol, timolol], antidepressants [i.e., amitriptyline, venlafaxine], candesartan, prophylactic use CGRP [e.g., Aimovig, AJOVY, Emgality, Nurtec, QULIPTA, Vyepti], OR onabotulinum toxin A [Botox]) **OR** C. The patient has an FDA labeled contraindication to ALL migraine prophylactic medications (i.e., anticonvulsants [i.e., divalproex, valproate, topiramate], beta blockers [i.e., atenolol, metoprolol, nadolol, propranolol, timolol], antidepressants [i.e., amitriptyline, venlafaxine], candesartan, prophylactic use CGRP [e.g., Aimovig, AJOVY, Emgality, Nurtec, QULIPTA, Vyepti], AND onabotulinum toxin A [Botox]) **OR** D. There is support that the patient's migraine is manageable with acute therapy alone **AND** 3. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months. NOTE: For agents that require a loading dose for a new start, approve the loading dose based on FDA labeling AND the maintenance dose for the remainder of approval up to 12 months.

Cholestasis Pruritus

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Bylvay® (odevixibat) Oral pellet Capsule	Treatment of cholestatic pruritus in patients 12 months of age and older with Alagille syndrome (ALGS) Treatment of pruritus in patients 3 months of age and older with progressive familial intrahepatic cholestasis (PFIC) Limitation of Use: May not be effective in PFIC type 2 patients with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3).		1
Livmarli® (maralixibat) Oral solution	Treatment of cholestatic pruritus in patients 3 months of age and older with Alagille syndrome (ALGS) Treatment of cholestatic pruritus in patients 5 years of age and older with progressive familial intrahepatic cholestasis (PFIC) Limitations of Use: Livmarli is not recommended in a subgroup of PFIC type 2 patients with specific ABCB11 variants resulting in non-functional or complete absence of bile salt export pump (BSEP) protein.		10

CLINICAL RATIONALE

Progressive Familial Intrahepatic Cholestasis	Progressive familial intrahepatic cholestasis (PFIC) is a rare, hereditary, progressive, and life-threatening liver disorder affecting young children.(5) Impaired production and excretion of bile results in cholestatic liver disease, where biliary substances cannot be eliminated from the liver and thus reenter the circulation, build up in the liver cells, cause elevated bile serum levels and deposition of bilirubin pigments in the tissues as skin, sclerae, mucous membranes and so on (jaundice).(4,15) Cholestasis can damage the liver, causing cirrhosis and liver failure within the first ten years of life. (7)

	The three common subtypes of PFIC are PFIC1, PFIC2 and PFIC3. Other subtypes of PFIC have been identified and all present with cholestasis.(4,5) PFIC1 and PFIC2 onset occurs very early in childhood, early after birth to a young age, and may progress to end stage rapidly, especially PFIC2. PFIC3 typically presents in the first years of childhood with progressive cholestasis, although disease manifestation and cirrhosis in young adulthood has also been described most recently.(7) Patients with PFIC1 and PFIC2 have normal gamma-glutamyl transferase (GGT) levels, while patients with PFIC3 have increased GGT levels. All 3 subtypes of PFIC are caused by defects in bile secretion from hepatocyte to canaliculi and have increased serum bile acid levels. In PFIC1 and PFIC2, bile acid secretion is depleted, while in PFIC3, bile phospholipid secretion is impaired. PFIC2 occurs due to a mutation of the major canalicular BSEP gene on chromosome 2 (BSEP/ABCB11). Expression of this gene is limited to the liver. Therefore, although the clinical course of PFIC2 is similar to that for PFIC1, extrahepatic manifestations are absent.(15) Cholestatic pruritus is one of the main symptoms of cholestasis in many patients. Pruritus is often out of proportion to the level of jaundice which is often low-grade and can wax and wane. The itching may be very disabling and often does not respond consistently to medications.(5) Chronic pruritus can cause severe sleep deprivation and exhaustion, resulting in fatigue, depression, and even suicidal ideas. Thus, therapy-refractory persistent pruritus can represent an indication for liver transplantation, even in the absence of liver failure.(2) Liver transplantation is generally curative for patients with PFIC1 and PFIC2. However, patients with PFIC1 may have ongoing disease due to the extrahepatic expression of familial intrahepatic cholestasis type 1 (FIC1).(8) Several possible transmitters and mechanisms have been suggested as possible causes of cholestatic pruritus, including biliary components, endogenous opioids, and the auto-taxin-lysophosphatidic acid (ATX-LPA) axis. However, no definitive correlation between itch intensity and levels of bile salts in serum, urine, or skin has been established to date.(2) No medical therapy of proven benefit for the long-term prognosis of PFIC exists. According to the European Association for the Study of the Liver (EASL) guidelines, ursodiol is the first line medication for cholestasis although it’s effect on pruritus varies. Ursodiol has been reported to improve biochemical tests in almost 50% of patients with PFIC3, but generally does not affect PFIC1 and PFIC2.(7) Rifampicin counteracts pruritus by increasing the metabolism of pruritogenic substances, prompting their renal elimination in hydroxylated forms. In addition, the antibacterial effect of rifampicin in the intestine may potentially modify the intestinal metabolism of pruritogenic substances. Because this

	treatment is well tolerated and its efficacy has been demonstrated, rifampicin is widely considered as the first-line treatment for cholestatic pruritus in children.(9) Oral antihistamines are commonly prescribed to patients with cholestatic pruritus drugs but do not attenuate itching in most cases.(2) The anion exchange resin cholestyramine was initially the only approved medication for cholestatic pruritus, however, its inconsistent efficacy and poor tolerance (nausea, constipation, diarrhea, acidosis) limits its use in children.(9) Bylvay is a systemic, reversible inhibitor of ileal bile acid transporter (IBAT), which decreases the reuptake of bile salts from the terminal ileum into the hepatic portal circulation. The therapy acts locally in the small intestine. The elimination of bile acids from the enterohepatic circulation reduces bile acid levels in serum and the liver. Bylvay may not be effective in PFIC2, a subtype of PFIC with mutations in the ABCB11 gene which causes deficiency of the bile salt export pump (BSEP) protein.(1) The current European guidelines suggest a stepwise approach to efficiently treat cholestatic pruritus and are listed in order: cholestyramine, rifampicin, bezafibrate, naltrexone, and sertraline. Sixth line therapy recommendations include the following experimental approaches: gabapentin, phenobarbital, UVB light 1–2 times/week, albumin dialysis and nasobiliary drainage.(2)
Alagille Syndrome	Alagille syndrome (ALGS) is a rare genetic disorder that can affect multiple organ systems of the body including the liver, heart, skeleton, eyes and kidneys. Some individuals may have mild forms of the disorder while others may have more serious forms. Most people with Alagille syndrome have mutations in one copy of the JAG1 gene with 2% of patients affected with mutations of the NOTCH2 gene. These mutations can be inherited in an autosomal dominant pattern, but in about half of cases, the mutation occurs as a new change in the individual and was not inherited from a parent. The current estimated incidence of ALGS is 1/30,000 –1/45,000.(11) Approximately 90 percent of individuals with Alagille syndrome have a reduced number of bile ducts within the liver. Because of the reduced number of bile ducts, individuals with Alagille syndrome can develop these common symptoms during the first 3 to 4 months of life: cholestasis, pruritus, jaundice, and poor weight gain and growth. Liver disease in Alagille syndrome, if present, may range in severity from jaundice or mild cholestasis to severe, progressive liver disease that can potentially result in liver failure. In severe cases of Alagille syndrome, liver transplantation may be required. Additional symptoms of ALGS include

	heart murmurs, congenital heart defects, vertebral differences, thickening of the ring that normally lines the cornea in the eye and distinctive facial features.(11) Specific treatment may be indicated for individuals with cholestatic liver disease. The drug ursodeoxycholic acid is given to help improve bile flow, which can lead to a reduction in some symptoms such as itching (pruritus) or cholesterol deposits (xanthomas). However, pruritus associated with Alagille syndrome often is resistant to therapy. Livmarli, a reversible inhibitor of the ileal bile acid transporter (IBAT), decreases the reabsorption of bile acids from the terminal ileum improving pruritus in patients with ALGS. Although the complete mechanism by which Livmarli improves pruritus is unknown, it may involve inhibition of the IBAT, which results in decreased reuptake of bile salts.(10) Additional drugs that have been used to treat pruritus include antihistamines, rifampin, cholestyramine, and naltrexone. Keeping the skin properly hydrated with moisturizers is also recommended. Cholestyramine may also be indicated for individuals with elevated cholesterol levels or xanthomas.(3,11-13)
Efficacy - Bylvay	*Progressive Familial Intrahepatic Cholestasis (PFIC)* The efficacy of Bylvay was evaluated in a 24-week, randomized, double-blind, placebo-controlled trial in 62 pediatric patients, aged 6 months to 17 years, with a confirmed molecular diagnosis of PFIC type 1 or type 2, and presence of pruritus at baseline. Patients with variants in the ABCB11 gene that predict non-function or complete absence of the bile salt export pump (BSEP) protein, who had experienced prior hepatic decompensation events, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT or total bilirubin was greater than 10-times the upper limit of normal, or who had received a liver transplant were excluded in Trial 1.(1) Patients were randomized to placebo, 40 mcg/kg, or 120 mcg/kg. A total of 13 patients discontinued from the trial prematurely either due to no improvement in pruritus (n=11) or due to adverse reactions (n=2). A total of 11 of the 13 patients rolled over to Trial 2 (PEDFIC II) to receive Bylvay 120 mcg/kg/day.(1) Patients treated with Bylvay demonstrated greater improvement in pruritus compared with placebo. Results showed that patients treated with odevixibat achieved a significant decline in itching or scratching and reduced serum bile acid responses. Around 53.5% of patients in the odevixibat arms showed a significant reduction in pruritus, compared to 28.7% in the placebo arm.(1) *Alagille Syndrome (ALGS)*

	The efficacy of Bylvay was evaluated in Trial 3 (NCT04674761), a 24-week, randomized, double blind, placebo-controlled trial. Trial 3 was conducted in 52 pediatric patients, aged 6 months to 15 years, with a confirmed diagnosis of ALGS and presence of pruritus at baseline. Patients who had decompensated liver disease, who had other concomitant liver disease, whose INR was greater than 1.4, whose ALT was greater than 10-times the upper limit of normal (ULN) at screening, whose total bilirubin was greater than 15-times the ULN at screening, or who had received a liver transplant were excluded from Trial 3.(1) Of the 52 patients, 52% were male and 83% were white; 92% of patients had the JAG1 mutation and 8% had the NOTCH2 mutation. The mean (standard deviation [SD]) scratching score in the 2 weeks prior to baseline was 2.9 (0.6). Baseline mean (SD) eGFR was 159 (51.4) mL/min/1.73 m^2. Baseline median (range) ALT, AST, and total bilirubin were 152 (39-403) U/L, 135 (57-427) U/L, and 2.0 (0.4-11.4) mg/dL, respectively. Given the patients' young ages, a single-item observer-reported outcome (ObsRO) was used to measure patients' scratching severity as observed by their caregiver twice daily (once in the morning and once in the evening). Scratching severity was assessed on a 5-point ordinal response scale, with scores ranging from 0 (no scratching) to 4 (worst possible scratching). Patients were included in Trial 3 if the average scratching score was greater than or equal to 2 (medium scratching) in the 14 days prior to baseline. The average scratching score for each patient for each month post-baseline was calculated by: (Step 1) averaging the morning scores and averaging the evening scores within a week; (Step 2) averaging the morning and evening weekly scores to yield a single weekly score; and finally (Step 3) averaging the 4 weekly scores within the month. The baseline average scratching score for each patient was calculated by averaging the weekly scores obtained in Step 2 across the 2 weeks prior to randomization and initiation of blinded treatment. Patients treated with Bylvay demonstrated greater improvement in pruritus compared with placebo.(1)
Efficacy - Livmarli	*Alagille Syndrome (ALGS)* The efficacy of Livmarli was assessed in Trial 1, enrolling 31 pediatric (ages 1 to 15, median age 5 years) ALGS patients with JAGGED1 mutation, cholestasis, and pruritus. Patients with surgical interruption of their enterohepatic circulation of bile acid, previous liver transplant, and with decompensated cirrhosis were not enrolled.(14) The study was divided into 6 parts: a 6-week open-label, dose escalation period, a 12-week open-label stable dosing period, a 4-week randomized, double-blind, placebo-controlled drug withdrawal period, a 26-week long-term stable dosing period, and a 52-week optional follow-up treatment period, and a long-term optional follow-up treatment period for eligible participants who choose to stay on treatment with Livmarli.(10)

	Patients (90.3%) were administered open-label treatment with Livmarli 380 mcg/kg once daily for 13 weeks after an initial 5-week dose-escalation period; two patients discontinued treatment. The 29 patients who completed the open-label treatment phase were then randomized to continue treatment with Livmarli or placebo during the 4-week drug withdrawal period at Weeks 19-22 (n=16 placebo, n=13 Livmarli). All 29 patients completed the withdrawal period and then received Livmarli at 380 mcg/kg once daily for an additional 26 weeks.(10) Given the patients' young age, an observer-reported outcome was used to measure patients' pruritus symptoms twice daily, each week, on the Itch Reported Outcome Instrument (ItchRO[Obs]). On average, patients administered Livmarli for 22 weeks maintained pruritus reduction whereas those in the placebo group who were withdrawn from Livmarli after Week 18 returned to baseline pruritus scores by Week 22. After re-entering the open-label treatment phase, both randomized treatment groups had similar mean pruritus scores by Week 28, the first week placebo patients received the full dosage of Livmarli after withdrawal. These observer-rated pruritus results are supported by similar results on patient-rated pruritus in patients 5 years of age and older who were able to self-report their itching severity.(10) *Progressive Familial Intrahepatic Cholestasis (PFIC)* The efficacy of Livmarli was assessed in Trial 2 (NCT03905330), a 26-week randomized, placebo-controlled trial. Efficacy was evaluated in 64 patients with documented molecular diagnosis of PFIC with presence of biallelic known pathogenic variants; this included 31 non-truncated PFIC2 patients (i.e., excluding patients with BSEP3) and 33 patients with PFIC1 (n=13), PFIC3 (n=9), PFIC4 (n=7), or PFIC6 (n=4). Additional patients with BSEP3 (n=9), prior surgical diversion (n=8), heterozygous subjects (n=2), or no variants associated with cholestasis (n=8) were included for evaluation in a supplemental cohort.(10) Patients were randomized to receive maralixibat orally 570 mcg/kg or placebo twice daily. 53% of pediatric patients were females. Most patients were on stable ursodeoxycholic acid (89.1%) or rifampicin (51.6%) therapy at baseline. The baseline mean (standard deviation [SD]) of liver test parameters were as follows: serum bile acid levels 263 (143) µmol/L, AST 113 (82) U/L, ALT 107 (87) U/L, and TB 4.1 (4.1) mg/dL, DB 3.0 (3.1) mg/dL.(10) Given the patients' young age, a single-item observer-reported outcome was used to measure patients' pruritus symptoms as observed by their caregiver twice daily (once in the morning and once in the evening) on the Itch Reported

	Outcome Instrument (ItchRO[Obs]). Pruritus symptoms were assessed on a 5-point ordinal response scale, with scores ranging from 0 (none observed or reported) to 4 (very severe). Patients were included in Trial 2 if their average pruritus score was greater than or equal to 1.5 in the 4 weeks prior to baseline. Patients treated with Livmarli demonstrated greater improvement in pruritus compared with placebo.(10)
Safety	Bylvay does not have any FDA labeled contraindications.(1) Livmarli is contraindications in patients with prior or active hepatic decompensation events (e.g., variceal hemorrhage, ascites, hepatic encephalopathy).(10)

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. BOTH of the following: 1. The patient has a diagnosis of progressive familial intrahepatic cholestasis (PFIC) with pruritus (medical records required) **AND**

Module	Clinical Criteria for Approval
	2. The patient does NOT have a diagnosis of PFIC2 with ABCB11 variants resulting in non-functional or complete absence of bile salt export pump protein (BSEP-3) **OR** B. The patient has a diagnosis of Alagille syndrome with pruritus (medical records required) **OR** C. The patient has another FDA labeled indication for the requested agent and route of administration **OR** D. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response to a standard cholestasis pruritus treatment agent (i.e., ursodiol, cholestyramine, naltrexone or rifampicin) **OR** B. The patient has an intolerance or hypersensitivity to therapy with a standard cholestasis pruritus treatment agent (i.e., ursodiol, cholestyramine, naltrexone, or rifampicin) **OR** C. The patient has an FDA labeled contraindication to ALL standard cholestasis pruritus treatment agents (i.e., ursodiol, cholestyramine, naltrexone, and rifampicin) **AND** 4. If the requested agent is Bylvay, then BOTH of the following: A. The patient's INR is less than 1.4 **AND** B. The patient has an ALT and total bilirubin that is less than 10-times the upper limit of normal **AND** 5. If the requested agent is Livmarli, then BOTH of the following: A. The patient does NOT have decompensated cirrhosis **AND** B. The patient has NOT had surgical interruption of the enterohepatic circulation of bile acid **AND** 6. The patient has a serum bile acid concentration above the upper limit of normal **AND** 7. ONE of the following: A. The patient has NOT had a liver transplant **OR** B. The patient has had a liver transplant and there is support for using the requested agent post liver transplant **AND** 8. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, hepatologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**

Module	Clinical Criteria for Approval
	9. The patient will NOT be using the requested agent in combination with another Ileal Bile Acid Transport (IBAT) inhibitor agent **AND** 10. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, hepatologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with another Ileal Bile Acid Transport (IBAT) inhibitor agent **AND** 5. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months

Cibinqo (abrocitinib)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Cibinqo® (abrocitinib) Tablet	Treatment of adults and pediatric patients 12 years of age and older with refractory, moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with other systemic drug products, including biologics, or when use of those therapies is inadvisable. Limitations of use: • Not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, or with other immunosuppressants		1

CLINICAL RATIONALE

Atopic Dermatitis	Atopic dermatitis (AD), also known as atopic eczema, is a chronic, pruritic inflammatory dermatosis affecting up to 25% of children and 1-5% of adults. AD follows a relapsing course and is associated with elevated serum immunoglobulin (IgE) levels and a personal or family history of type I allergies, allergic rhinitis, and/or asthma. Onset is most common between 3 and 6 months of age, with approximately 60% of patients developing the eruption in the first year of life and 90% by age 5. While the majority of affected individuals have resolution of disease by adulthood, 10 to 30% do not, and a smaller percentage first develop symptoms as adults. AD has a complex pathogenesis involving genetic, immunologic, and environmental factors, which lead to a dysfunctional skin barrier and dysregulation of the immune system. Clinical findings include erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and lichenification. These clinical findings vary by patient age and chronicity of lesions. Pruritus is a hallmark of the condition that is responsible for much of the disease burden borne by patients and their families. Typical patterns include

	facial, neck and extensor involvement in infants and children; flexure involvement in any age group, with sparing of groin and axillary regions.(2) Goals of treatment are to reduce symptoms (pruritus and dermatitis), prevent exacerbations, and minimize therapeutics risks.(6) Despite its relapsing and remitting nature, the majority of patients with AD can achieve clinical improvement and disease control with topical emollient/moisturizer use and conventional topical therapies (including corticosteroids and calcineurin inhibitors).(5,6) Moisturizers reduce signs, symptoms, and inflammation in AD, and can improve severity while also increasing time between flares. Moisturizers are considered generally safe and are strongly recommended to be used as part of a treatment regimen for AD, either as monotherapy or as concurrent use with pharmacologic treatments.(4) Topical therapies remain the mainstay of treatment due to their proven track record and generally favorable safety profile. They can be utilized individually or in combination with other topical, physical, and/or systemic treatments; as different classes of treatment have different mechanisms of action, combining therapies allows for the targeting of AD via multiple disease pathways. The American Academy of Dermatology (AAD) strongly recommends the following topical agents:(4) • Topical corticosteroids (TCS) • Calcineurin inhibitors (TCIs) (e.g., tacrolimus, pimecrolimus) • Topical PDE-4 inhibitors (e.g., crisaborole) [mild to moderate AD] • Topical JAK inhibitors (e.g., ruxolitinib) [mild to moderate AD] TCS are the most commonly utilized FDA-approved therapies in AD and are commonly used as first-line treatment for mild-to severe dermatitis in all skin regions. TCS target a variety of immune cells and suppress the release of proinflammatory cytokines. High to very high (super) potency TCS can be used to control flares and treat severe disease, while medium potency TCS are utilized for longer courses and as maintenance therapy. Lower potency TCS may be used, and it is important to consider the anatomical site (i.e., using lower potency agents on the face, neck, genitals, and body folds) and severity of the disease when choosing a steroid potency. Most studies of TCS in AD management involve twice daily application, but some studies (particularly for potent TCS) suggest once daily use may be sufficient. Traditionally, TCS were stopped once AD signs and symptoms of an AD flare were controlled. Maintenance in between AD flares with once to twice weekly use of TCS is another approach.(4)

	TCIs are a safe anti-inflammatory option for mild-to-severe AD, particularly when there is concern for adverse events secondary to corticosteroid use. Both tacrolimus and pimecrolimus have been shown to be effective in treating AD, but pimecrolimus may be more appropriate for patients who have milder disease or are sensitive to local reactions.(4) Prescribing information for pimecrolimus cream and tacrolimus ointment indicate evaluation after 6 weeks if symptoms of AD do not improve for adults and pediatrics.(8,9). When AD is more severe or refractory to topical treatment, advanced treatment with phototherapy or systemic medications can be considered. Phototherapy is conditionally recommended by the AAD as a treatment for AD based on low certainty evidence. The AAD strongly recommends the following systemic therapies:(5) • Monoclonal antibodies (biologics) (e.g., dupilumab, tralokinumab) • JAK inhibitors (e.g., upadacitinib, abrocitinib, baricitinib) In a change from the 2014 AAD AD guidelines, the use of systemic antimetabolites such as methotrexate, immunosuppressants such as systemic corticosteroids, mycophenolate mofetil, azathioprine, and cyclosporine are now conditionally recommended for AD only in a small number of select patients due to low or very low certainty of evidence and need for monitoring. The most favored first-line systemic is dupilumab.(5) There is no clear consensus on how to operationalize a definition of the FDA indication for treatment of patients with "moderate to severe" AD. The severity of AD can vary substantially over time and, from a patient's perspective, can include a complex combination of intensity of itch, location, body surface area (BSA) involvement, and degree of skin impairment. Given the variability of patient phenotype and lack of familiarity among clinicians with scoring systems used in clinical trials, it is advisable to create a broad clinically relevant definition inclusive of multiple specific measures of disease intensity for example:(11) One of the following: • Affected BSA greater than or equal to 10% • Investigator Global Assessment (IGA) greater than or equal to 3 • Eczema Area and Severity Index (EASI) greater than or equal to 16 OR

	One of the following: • Affected BSA greater than or equal to 10% • Involvement of body sites that are difficult to treat with prolonged topical corticosteroid therapy (e.g., hands, feet, face, neck, scalp, genitals/groin, skin folds) • Severe itch that has been unresponsive to topical therapies
Efficacy	The efficacy of Cibinqo as monotherapy and in combination with background topical corticosteroids was evaluated in 3 randomized, double-blind, placebo-controlled trials [Trial-AD-1 (NCT03349060), Trial-AD-2 (NCT03575871), and Trial-AD-3 (NCT03720470)] in 1615 subjects 12 years of age and older (Cibinqo is not approved for use in pediatric patients) with moderate-to-severe atopic dermatitis as defined by Investigator's Global Assessment (IGA) score greater than or equal to 3, Eczema Area and Severity Index (EASI) score greater than or equal to 16, body surface area (BSA) involvement greater than or equal to 10%, and Peak Pruritus Numerical Rating Scale (PP-NRS) greater than or equal to 4 at the baseline visit prior to randomization.(1) Overall, 53% of subjects were male, 69% of subjects were white, 64% of subjects had a baseline IGA score of 3 (moderate AD), and 36% of subjects had a baseline IGA score of 4 (severe AD). The baseline mean EASI score was 30. The baseline mean age was 36 years old with 8% of subjects 12 to less than 18 years old and 92% of subjects 18 years of age or older. Subjects in these trials were those who had inadequate response to previous topical therapy or were subjects for whom topical treatments were medically inadvisable, or who had received systemic therapies including dupilumab. In each of the trials, over 40% of subjects had prior exposure to systemic therapy. In Trial-AD-1 and Trial-AD-2, 6% of the subjects had received dupilumab, whereas prior use of dupilumab was not allowed in Trial-AD-3.(1) The proportion of subjects achieving PP-NRS4 at week 2 (defined as an improvement of greater than or equal to 4 points from baseline in PP-NRS) was higher in subjects treated with Cibinqo monotherapy 200 mg once daily (28% in Trial-AD-1 and 24% in Trial-AD-2) and 100 mg once daily (11% in both trials) compared to placebo (2% in both trials). A higher proportion of subjects in the Cibinqo monotherapy 100 mg or 200 mg once daily arm compared to placebo achieved improvement in itching at week 12.(1) The proportions of subjects achieving PP-NRS4 at week 2 was higher in subjects treated with Cibinqo 200 mg once daily (30%) and 100 mg once daily (14%) in combination with background medicated topical therapies compared to placebo

	(8%). Examination of age, gender, race, weight, and previous systemic AD therapy treatment did not identify differences in response to Cibinqo 100 mg or 200 mg once daily among these subgroups in Trial-AD-1, Trial- AD-2, and Trial-AD-3.(1)
Safety	Abrocitinib carries the following boxed warnings:(1) • Increased risk of serious bacterial, fungal, viral, and opportunistic infections leading to hospitalization or death, including tuberculosis (TB). Discontinue treatment with Cibinqo if serious or opportunistic infection occurs. Test for latent TB before and during therapy, and if positive, start treatment for TB prior to use. Monitor all patients for active TB during treatment, even if initial latent TB test is negative. • A higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients 50 years of age and older with at least one cardiovascular risk factor treated with a JAK inhibitor compared with a TNF blocker for RA. • Malignancies, including non-melanoma skin cancer (NMSC), have occurred in patients treated with Cibinqo. Lymphoma and other malignancies (excluding NMSC) have occurred at a higher rate in patients receiving JAK inhibitors used to treat inflammatory conditions compared to TNF blockers. Patients who are current or past smokers are at additional increased risk. • Major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke) have occurred in patients treated with Cibinqo. In patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of MACE was observed in patients treated with a JAK inhibitor compared with a TNF blocker for RA. Patients who are current or past smokers are at additional increased risk. Discontinue Cibinqo in patients that have experienced a myocardial infarction or stroke. • Deep venous thrombosis (DVT) and pulmonary embolism (PE) have occurred in patients treated with Cibinqo. In patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of thrombosis was observed when compared with TNF blockers. Avoid Cibinqo in patients at risk. If symptoms of thrombosis occur, discontinue Cibinqo and treat appropriately. Abrocitinib is contraindicated in patients taking antiplatelet therapies, except for low dose aspirin (less than or equal to 81 mg daily), during the first 3 months of treatment.(1)

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** All target agents are eligible for continuation of therapy 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. ONE of the following: A. The patient has a diagnosis of moderate-to-severe atopic dermatitis (AD) AND ALL of the following: 1. ONE of the following: A. The patient has at least 10% body surface area involvement **OR** B. The patient has involvement of body sites that are difficult to treat with prolonged topical corticosteroid therapy (e.g., hands, feet, face, neck, scalp, genitals/groin, skin folds) **OR** C. The patient has an Eczema Area and Severity Index (EASI) score greater than or equal to 16 **OR** D. The patient has an Investigator Global Assessment (IGA) score greater than or equal to 3 **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to at least a medium-potency topical

Module	Clinical Criteria for Approval
	corticosteroid used in the treatment of AD after at least a 4-week duration of therapy **OR** B. The patient has an intolerance or hypersensitivity to at least a medium-potency topical corticosteroid used in the treatment of AD **OR** C. The patient has an FDA labeled contraindication to ALL medium-, high-, and super-potency topical corticosteroids used in the treatment of AD **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response to a topical calcineurin inhibitor (e.g., Elidel/pimecrolimus, Protopic/tacrolimus) used in the treatment of AD after at least a 6-week duration of therapy **OR** B. The patient has an intolerance or hypersensitivity to a topical calcineurin inhibitor used in the treatment of AD **OR** C. The patient has an FDA labeled contraindication to ALL topical calcineurin inhibitors used in the treatment of AD **AND** 4. The prescriber has documented the patient's baseline (prior to therapy with the requested agent) pruritus and other symptom severity (e.g., erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and/or lichenification) **OR** B. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **OR** C. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has a diagnosis of moderate-to-severe atopic dermatitis (AD), then BOTH of the following: A. The patient is currently treated with topical emollients and practicing good skin care **AND**

Module	Clinical Criteria for Approval
	B. The patient will continue the use of topical emollients and good skin care practices in combination with the requested agent **AND** 3. The patient has been tested for latent tuberculosis (TB) AND if positive the patient has begun therapy for latent TB **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., dermatologist, allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. ONE of the following (please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (submitted copy of clinical trials, phase III studies, guidelines required) **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval**: 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. ONE of the following: A. The patient has a diagnosis of moderate-to-severe atopic dermatitis AND BOTH of the following: 1. The patient has had a reduction or stabilization from baseline (prior to therapy with the requested agent) of ONE of the following: A. Affected body surface area **OR**

Module	Clinical Criteria for Approval
	B. Flares **OR** C. Pruritus, erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and/or lichenification **OR** D. A decrease in the Eczema Area and Severity Index (EASI) score **OR** E. A decrease in the Investigator Global Assessment (IGA) score **AND** 2. The patient will continue standard maintenance therapies (e.g., topical emollients, good skin care practices) in combination with the requested agent **OR** B. The patient has a diagnosis other than moderate-to-severe atopic dermatitis AND has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., dermatologist, allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. ONE of the following (please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (submitted copy of clinical trials, phase III studies, guidelines required) **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed**: AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval**: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR**

Module	Clinical Criteria for Approval
	2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months

CONTRAINDICATION AGENTS

Contraindicated as Concomitant Therapy
Agents NOT to be used Concomitantly Abrilada (adalimumab-afzb) Actemra (tocilizumab) Adalimumab Adbry (tralokinumab-ldrm) Amjevita (adalimumab-atto) Arcalyst (rilonacept) Avsola (infliximab-axxq) Benlysta (belimumab) Bimzelx (bimekizumab-bkzx) Cibinqo (abrocitinib) Cimzia (certolizumab) Cinqair (reslizumab) Cosentyx (secukinumab) Cyltezo (adalimumab-adbm) Dupixent (dupilumab)

Contraindicated as Concomitant Therapy
Enbrel (etanercept)
Entyvio (vedolizumab)
Fasenra (benralizumab)
Hadlima (adalimumab-bwwd)
Hulio (adalimumab-fkjp)
Humira (adalimumab)
Hyrimoz (adalimumab-adaz)
Idacio (adalimumab-aacf)
Ilaris (canakinumab)
Ilumya (tildrakizumab-asmn)
Inflectra (infliximab-dyyb)
Infliximab
Kevzara (sarilumab)
Kineret (anakinra)
Leqselvi (deuruxolitinib)
Litfulo (ritlecitinib)
Nemluvio (nemolizumab-ilto)
Nucala (mepolizumab)
Olumiant (baricitinib)
Omvoh (mirikizumab-mrkz)
Opzelura (ruxolitinib)
Orencia (abatacept)
Otezla (apremilast)
Pyzchiva (ustekinumab-ttwe)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rinvoq (upadacitinib)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Saphnelo (anifrolumab-fnia)
Selarsdi (ustekinumab-aekn)
Siliq (brodalumab)
Simlandi (adalimumab-ryvk)
Simponi (golimumab)
Simponi ARIA (golimumab)
Skyrizi (risankizumab-rzaa)
Sotyktu (deucravacitinib)

Contraindicated as Concomitant Therapy
Spevigo (spesolimab-sbzo) subcutaneous injection
Stelara (ustekinumab)
Taltz (ixekizumab)
Tezspire (tezepelumab-ekko)
Tofidence (tocilizumab-bavi)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tyenne (tocilizumab-aazg)
Tysabri (natalizumab)
Velsipity (etrasimod)
Wezlana (ustekinumab-auub)
Xeljanz (tofacitinib)
Xeljanz XR (tofacitinib extended release)
Xolair (omalizumab)
Yuflyma (adalimumab-aaty)
Yusimry (adalimumab-aqvh)
Zeposia (ozanimod)
Zymfentra (infliximab-dyyb)

CMV Oral

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
LIVTENCITY® (maribavir) Tablets	Treatment of adults and pediatric patients (12 years of age and older and weighing at least 35 kg) with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet		2
PREVYMIS® (letermovir) Tablets	Prophylaxis of cytomegalovirus (CMV) infection and disease in adult CMV-seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT) Prophylaxis of CMV disease in adult kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-])		1

REFERENCES

Number	Reference
1	PREVYMIS prescribing information. Merck Sharp & Dohme LLC. August 2023.
2	LIVTENCITY prescribing information. Takeda Pharmaceuticals America, Inc. April 2023.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Livtencity	**Quantity limit for Livtencity** will be approved for an increased quantity when **ALL** of the following are met:

Module	Clinical Criteria for Approval
	1. The patient has a post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet **AND** 2. The patient will NOT be using the requested agent in combination with ganciclovir and/or valganciclovir for the requested indication **AND** 3. There is support for therapy with a higher dose and/or and increased quantity for the requested indication **Length of Approval:** up to 12 months
Prevymis	**Quantity limit for Prevymis** will be approved for an increased quantity and/or an extended duration when **BOTH** of the following are met: 1. ONE of the following: A. The patient has had an additional allogeneic hematopoietic stem cell transplant (HSCT) and requires initiation of PREVYMIS **OR** B. The patient has had an additional kidney transplant and is at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-]) and requires initiation of PREVYMIS **OR** C. There is support for therapy with a higher dose and/or a longer duration for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** Additional transplant: 200 tablets/365 days Higher quantity/longer duration: Approve quantity requested/365 days

Coagulation Factor VIIa

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
NovoSeven RT® (coagulation Factor VIIa [recombinant]) Lyophilized powder for solution, for intravenous use	• Treatment of bleeding episodes and perioperative management in adults and children with hemophilia A or B with inhibitors, congenital Factor VII (FVII) deficiency, and Glanzmann's thrombasthenia with refractoriness to platelet transfusions, with or without antibodies to platelets • Treatment of bleeding episodes and perioperative management in adults with acquired hemophilia		1
Sevenfact® (coagulation Factor VIIa [recombinant]-jncw) Lyophilized powder for solution, for intravenous use	• Treatment and control of bleeding episodes occurring in adults and adolescents (12 years of age and older) with Hemophilia A or B with inhibitors Limitation of Use: Sevenfact is not indicated for treatment of congenital factor VII deficiency		2

CLINICAL RATIONALE

Congenital hemophilia A and congenital hemophilia B	Congenital hemophilia A and congenital hemophilia B are genetic disorders caused by missing or defective Factor VIII (FVIII) (for hemophilia A) and Factor IX (FIX) (for hemophilia B), a clotting protein. Although it is passed down from parents to children, about 1/3 of cases found have no previous family history.(3-4) People with hemophilia A and hemophilia B bleed longer than other people. Bleeds can occur internally, into joints and muscles, or externally, from minor

	cuts, dental procedures, or injuries. How often a person bleeds and the severity of those bleeds depends on how much FVIII or FIX a person produces naturally.(3-4) Inhibitor development is the most severe complication of treatment for patients with inherited hemophilia A or B. Choice of product for treatment depends on multiple factors, including type of inhibitor (low- or high- responding), current titer of inhibitor, location of the bleed, previous response to a product, availability of clinical trial data supporting use of the products and concomitant medications (e.g., emicizumab). For high-titer inhibitors immune tolerance induction (ITI) is the best option for inhibitor eradication.(5)\ If left unchecked a persistent inhibitor will present a severe burden on patients and families as the ongoing physical, emotional, and in many cases financial toll continue to intensify. Healthcare providers will often attempt to proactively stamp out an inhibitor through ITI. ITI is an approach to inhibitor eradication where the body's immune system begins to tolerate a therapy after daily doses of factor are administered over time. The majority of people who undergo ITI therapy will see an improvement within 12 months, but more difficult cases can take two years or longer. There is a general consensus that failure of ITI is the inability to achieve successful tolerance within 2-3 years of initiation of an ITI regimen.(12) ITI can take several months to several years to be effective. The Hemophilia Federation of America recommends that if success has not occurred within 33 months of beginning ITI and there is a lack of a 20% decrease in the inhibitor titer over a 6 month period that it is considered a failure.(13) In the cases of high-responding inhibitors treatment is based on several components including the type of hemophilia and the nature of the bleed. During a life or limb-threatening bleeding episode physicians can remove antibodies from the body using plasmapheresis. This is only a temporary solution however as within a few days the body will produce large amounts of new antibodies. For the person with high responding inhibitors there are therapies that can effectively treat bleeds by circumventing the need to replace FVIII. These agents are commonly referred to as bypassing agents (BPAs) and include activated prothrombin complex concentrate (aPCC) and recombinant activated Factor VII concentrates (rFVIIa).(6) To date, the evidence for the benefits of secondary prophylaxis as compared to on-demand treatment of hemophilic patients with inhibitors is limited. In a randomized, double blind, prospective clinical trial secondary prophylaxis in

	patients with congenital hemophilia A and B with inhibitors was evaluated. The primary efficacy endpoint was number of bleeds per month during the prophylaxis period as compared to the pre-prophylaxis period. A bleed was defined as rebleeding if it occurred at the same site within 6 hours of treatment and episodes beginning 6 hours after treatment or occurring in another site were defined as a new episode. Secondary efficacy endpoints included the number of bleeds per month occurring in the post-prophylaxis period as compared to those observed in the observation and prophylaxis period, at specific bleeding sites (target joint, joint, muscle, soft-tissue bleeds), and cause of bleed (traumatic, spontaneous and other) over the entire trial period.(7) The observed benefits of rFVIIa prophylaxis in hemophilic patients with inhibitors were consistent with reports of secondary prophylactic treatment in patients without inhibitors. Bleeding frequency was reduced by 45-59% during prophylaxis with doses of 90 and 270 mcg/kg respectively (p less than 0.0001). Although all types of bleeds were similarly reduced, the effect was most pronounced for spontaneous joint bleeds.(7) Treatments for patients with inhibitors continue to be investigated. Sequential or concomitant therapy with rFVIIa and aPCC might be helpful in difficult to treat patients for whom monotherapy with either agent is ineffective. Clinical data is limited, and more substantial, well-controlled studies evaluating this approach are needed. Combined use of the two agents should only be carried out in the inpatient setting that has experience of this treatment, along with careful monitoring.(14) Another form of combination therapy involves the administration of FVIII with either rFVIIa or aPCC for prophylaxis. An invitro study using plasma from patients with high-titer inhibitors demonstrated that the addition of FVIII enhanced the hemostatic effect of both bypassing agents. FVIII combined with aPCC had a synergistic effect on thrombin formation, whereas FVIII combined with rFVIIa had an additive effect.(14)
Acquired hemophilia A	Under certain conditions individuals who were not born with hemophilia may develop antibodies or inhibitors that cause destruction of FVIII resulting in clinical bleeding due to very low levels of this clotting factor. Such inhibitors may be seen in patients with cancer, systemic lupus erythematosus, and other autoimmune disorders. Often no associated condition can be identified.(5) Although about 1/3 of patients do not require therapy to control bleeds, bleeding severity varies and more than 1/3 of patients had multiple bleeding episodes. Subcutaneous bleeding (ecchymoses) is the most common manifestation of

	acquired hemophilia followed by hematoma, melena, hematuria, and retroperitoneal. Intracranial hemorrhage is rare but can be fatal. In contrast to congenital hemophilia A, joint bleeding is infrequent.(8)
Congenital Factor VII deficiency	Factor VII (FVII), or proconvertin, deficiency was first recognized in 1951. Considered the most common of rare bleeding disorders its incidence is estimated at 1 per 300,000-500,000. It is inherited in an autosomal recessive fashion, and it affects men and women equally. FVII is a protein that, when bound to tissue factor, initiates the clotting cascade which leads to the formation of a blood clot.(9) Symptoms are usually linked to the level of FVII in the blood but not always. For instance, some people with low FVII levels may have mild symptoms. Babies are often diagnosed with FVII deficiency within the first 6 months of life, after sustaining a bleed in the central nervous system, such as an intracranial hemorrhage, or gastrointestinal tract. People with severe FVII deficiency experience joint and muscle bleeds, easy bruising, and bleeds after surgery. Bleeds can also occur in the skin, mouth, nose and genitourinary tract. Women often experience severe menorrhagia.(9) The main treatment for FVII deficiency is recombinant Factor VIIa (rFVIIa). Prothrombin complex concentrates (PCCs) can also be used, but the amount of Factor VII they contain can vary considerably. Fresh frozen plasma (FFP) is also an option.(9) Because of the very short half-life of FVII, prophylaxis in FVII deficiency is considered a difficult endeavor. The clinical efficacy and safety of prophylactic regimens, and indications for their use, were evaluated in FVII deficient patient in the Seven Treatment Evaluation Registry (STER). Information was recorded in the STER database from 34 patients with FVII deficiency receiving prophylaxis in 13 hemophilia centers (11 countries).(10) The reasons for initiating prophylaxis and the treatment regimens used varied among the patients analyzed. Overall prophylaxis yielded “excellent” results in 68% of the courses.(10)
Glanzmann's thrombasthenia	People with Glanzmann’s thrombasthenia (GT) have platelets that lack a protein (glycoprotein IIb/IIIa) that helps them stick together to form a clot. Laboratory tests are needed to diagnose GT. The symptoms of GT include bruising, petechiae, nosebleeds, and heavy menstrual bleeding. GT affects approximately 1 in a million people.(11)
Efficacy	NovoSeven RT is recombinant Factor VIIa and, when complexed with tissue factor can activate coagulation Factor X to Factor Xa, as well as coagulation

	Factor IX to Factor IXa. Factor Xa, in complex with other factors, then converts prothrombin to thrombin, which leads to the formation of a hemostatic plug by converting fibrinogen to fibrin and thereby inducing local hemostasis. This process may also occur on the surface of activated platelets.(1) The active ingredient in Sevenfact is a recombinant analog of human Factor VIIa, a vitamin K-dependent coagulation factor. In the presence of both calcium and phospholipids, Factor VIIa in a complex with tissue factor (TF) activates Factor X to Factor Xa, directly bypassing the reactions that require Factor VIII or Factor IX. Activation of Factor X to Factor Xa initiates the common pathway of the coagulation cascade in which prothrombin is activated to thrombin, which then converts fibrinogen to fibrin to form a hemostatic plug, thereby achieving clot formation at the site of hemorrhage.(2)

Safety	• **NovoSeven RT** has no known contraindications but does contain a boxed warning of:(1)
	
	  ○ Serious arterial and venous thrombotic events following administration of NovoSeven RT
	  ○ Discuss the risks and explain the sign and symptoms of thrombotic and thromboembolic events to patients who will receive NovoSeven RT
	  ○ Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis
	
	• **Sevenfact** is contraindicated in:(2)
	
	  ○ Known allergy to rabbits or rabbit proteins
	  ○ Severe hypersensitivity reaction to Sevenfact or any of its components
	
	• **Sevenfact** contains a boxed warning of:(2)
	
	  ○ Serious arterial and venous thrombotic events may occur following administration of Sevenfact
	  ○ Discuss the risk and explain the sign and symptoms of thrombotic and thromboembolic events to patients who will receive Sevenfact
	  ○ Monitor patients for signs or symptoms of activation of the coagulation system and for thrombosis

REFERENCES

Number	Reference
1	NovoSeven RT Prescribing Information. Novo Nordisk Inc. July 2020.
2	Sevenfact Prescribing Information. LFB S.A. November 2022.
3	National Hemophilia Foundation. Bleeding disorders A-Z/Types/Hemophilia A. Accessed at https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-a.
4	National Hemophilia Foundation. Bleeding Disorders A-Z/Types/Hemophilia B. Accessed at: https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-b.
5	Medical and Scientific Advisory Council (MASAC) MASAC recommendations concerning products licensed for the treatment of hemophilia and other bleeding disorders. Document #280. August 2023.
6	National Hemophilia Foundation Bleeding Disorders A-Z Overview Inhibitors Treatment for Inhibitors. Treatment for Inhibitors | National Hemophilia Foundation.
7	Konkle BA, Ebbesen LS, Erhardtsen E, et al. Randomized, prospective clinical trial of recombinant factor VIIa for secondary prophylaxis in hemophilia patients with inhibitors. J Thromb Haemost 2007; 5: 1904-13.
8	National Organization for Rare Disorders (NORD). Rare Disease Database. Acquired Hemophilia. Accessed at: https://rarediseases.org/rare-diseases/acquired-hemophilia/.
9	National Hemophilia Foundation. Bleeding Disorders A-Z/Types/Other Factor Deficiencies/Factor VII. Accessed at: https://www.hemophilia.org/bleeding-disorders-a-z/types/other-factor-deficiencies/factor-vii.
10	Napolitano M, Glanslly-Blalzot M, Dolce A, et al. Prophylaxis in congenital factor VII deficiency: indications, efficacy and safety. Results from the Seven Treatment Evaluation Registry (STER). Haematologica 2013 Apr; 98(4):538-44.
11	National Hemophilia Foundation. Bleeding Disorders A-Z/Types/Inherited Platelet Disorders. Accessed at: https://www.hemophilia.org/bleeding-disorders-a-z/types/inherited-platelet-disorders.
12	Srivastave A, Santagostino E, Dougall A, et al. World Federation of Hemophilia Guidelines for the Management of Hemophilia. 3rd edition. August 2020.

Number	Reference
13	Dimichele DM, Hoots WK, Pipe SW, et al. International workshop on immune tolerance induction: consensus recommendations. Haemophilia (2007), 13 (Suppl. 1), 1-22.
14	Ljung R, Auerswald G, Benson G, et al. Inhibitors in haemophilia A and B: Management of bleeds, inhibitor eradication and strategies for difficult-to-treat patients. Eur J Haematol. 2019;102:111-122.
15	Reference no longer used

ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
Sevenfact							
85100026402117	Sevenfact	Coagulation Factor VIIa (Recom)-jncw For Inj	1 MG	Dependent on patient weight and number of doses			
85100026402145	Sevenfact	Coagulation Factor VIIa (Recom)-jncw For Inj	5 MG	Dependent on patient weight and number of doses			
NovoSeven RT							
85100026202117	Novoseven rt	Coagulation Factor VIIa	1 MG	Dependent on patient weight and number of doses			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
		(Recomb) For Inj 1 MG (1000 MCG)					
85100026202126	Novoseven rt	Coagulation Factor VIIa (Recomb) For Inj 2 MG (2000 MCG)	2 MG	Dependent on patient weight and number of doses			
85100026202145	Novoseven rt	Coagulation Factor VIIa (Recomb) For Inj 5 MG (5000 MCG)	5 MG	Dependent on patient weight and number of doses			
85100026202160	Novoseven rt	Coagulation Factor VIIa (Recomb) For Inj 8 MG (8000 MCG)	8 MG	Dependent on patient weight and number of doses			

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
NovoSeven RT	**NovoSeven RT** will be approved when ALL of the following are met: 1. ONE of the following: A. BOTH of the following: 1. ONE of the following A. The patient has a diagnosis of hemophilia A AND BOTH of the following: 1. The patient has inhibitors to Factor VIII **AND** 2. The requested agent is being used for ONE of the following: A. On-demand use for bleeds AND ONE of the following: 1. The prescriber communicated with the patient (via any means) regarding the frequency and severity of the patient's bleeds and has verified that the patient does not have greater than 5 on-demand doses on hand **OR** 2. There is support for the patient having more than 5 on-demand doses on hand (supportive reasoning required) **OR** B. Prophylaxis AND ALL of the following: 1. ONE of the following: A. The patient has tried and had an inadequate response to Immune Tolerance Induction (ITI) [Immune Tolerance Therapy (ITT)] **OR** B. The patient has an inhibitor level greater than or equal to 200 BU (lab records required) **OR** C. The patient is not a candidate for ITI **AND** 2. The patient will NOT be using the requested agent in combination with Hemlibra **AND**

Module	Clinical Criteria for Approval
	3. The patient will NOT be using the requested agent in combination with Feiba [activated prothrombin complex (aPCC)] used for prophylaxis (on-demand use of aPCC is acceptable) **OR** C. Peri-operative management of bleeding **OR** D. As a component of Immune tolerance induction (ITI)/Immune tolerance therapy (ITT) AND ONE of the following: 1. The patient has NOT had more than 33 months of ITT/ITI therapy **OR** 2. There is support for the continued use of ITT/ITI therapy (i.e., the patient has had a greater than or equal to 20% decrease in inhibitor level over the last 6 months and needs further treatment to eradicate inhibitors) (medical records required) **OR** B. The patient has a diagnosis of hemophilia B AND BOTH of the following: 1. The patient has inhibitors to Factor IX **AND** 2. The requested agent is being used for ONE of the following: A. On-demand use for bleeds AND ONE of the following: 1. The prescriber communicated with the patient (via any means) regarding the frequency and severity of the patient's bleeds and has verified that the patient does not have greater than 5 on-demand doses on hand **OR** 2. There is support for the patient having more than 5 on-demand doses on hand (supportive reasoning required) **OR** B. Prophylaxis AND BOTH of the following: 1. ONE of the following: A. The patient has tried and had an inadequate response to Immune Tolerance Induction

Module	Clinical Criteria for Approval
	(ITI) [Immune Tolerance Therapy (ITT)] **OR** B. The patient has an inhibitor level greater than or equal to 200 BU (lab records required) **OR** C. The patient is not a candidate for ITI **AND** 2. The patient will NOT be using the requested agent in combination with Feiba [activated prothrombin complex (aPCC)] used for prophylaxis (on-demand use of aPCC is acceptable) **OR** C. Peri-operative management of bleeding **OR** D. As a component of Immune tolerance induction (ITI)/Immune tolerance therapy (ITT) AND ONE of the following: 1. The patient has NOT had more than 33 months of ITT/ITI therapy **OR** 2. There is support for the continued use of ITT/ITI therapy (i.e., the patient has had a greater than or equal to 20% decrease in inhibitor level over the last 6 months and needs further treatment to eradicate inhibitors) (medical records required) **OR** C. The patient has a diagnosis of congenital Factor VII deficiency AND the requested agent will be used for ONE of the following: 1. On-demand use for bleeds AND ONE of the following: A. The prescriber communicated with the patient (via any means) regarding the frequency and severity of the patient's bleeds and has verified that the patient does not have greater than 5 on-demand doses on hand **OR** B. There is support for the patient having more than 5 on-demand doses on hand (supportive reasoning required) **OR** 2. Prophylaxis **OR**

Module	Clinical Criteria for Approval
	3. Perioperative use **OR** D. The patient has a diagnosis of Glanzmann's thrombasthenia AND BOTH of the following: 1. The patient is refractory to platelet transfusions **AND** 2. The requested agent will be used for ONE of the following: A. On-demand use for bleeds AND ONE of the following: 1. The prescriber communicated with the patient (via any means) regarding the frequency and severity of the patient's bleeds and has verified that the patient does not have greater than 5 on-demand doses on hand **OR** 2. There is support for the patient having more than 5 on-demand doses on hand (supportive reasoning required) **OR** B. Perioperative use **OR** E. The patient has a diagnosis of acquired hemophilia AND the requested agent will be used for ONE of the following: 1. On-demand use for bleeds AND ONE of the following: A. The prescriber communicated with the patient (via any means) regarding the frequency and severity of the patient's bleeds and has verified that the patient does not have greater than 5 on-demand doses on hand **OR** B. There is support for the patient having more than 5 on-demand doses on hand (supportive reasoning required) **OR** 2. Perioperative use **OR** F. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **OR** B. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND**

Module	Clinical Criteria for Approval
	2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., prescriber working in a hemophilia treatment center [HTC], hematologist with hemophilia experience) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient will NOT be using the requested agent in combination with another Factor VIIa agent **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** Peri-operative dosing: 1 time per request On-demand: up to 3 months Prophylaxis: up to 12 months ITT/ITI: up to 6 months, or up to a total of 33 months of ITT/ITI therapy, or requested duration - whichever is shortest, all other indications: 3 months NOTE: If Quantity Limit applies please see Quantity Limit criteria
Sevenfact	**Sevenfact** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of hemophilia A AND BOTH of the following: 1. The patient has inhibitors to Factor VIII **AND** 2. The requested agent is being used for on-demand use for bleeds **OR** B. The patient has a diagnosis of hemophilia B AND BOTH of the following: 1. The patient has inhibitors to Factor IX **AND** 2. The requested agent is being used for on-demand use for bleeds **OR** C. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis [e.g., prescriber working in a hemophilia treatment center (HTC), hematologist with hemophilia experience] or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with another Factor VIIa agent **AND**

Module	Clinical Criteria for Approval
	5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. ONE of the following: A. The prescriber communicated with the patient (via any means) regarding the frequency and severity of the patient's bleeds and has verified that the patient does not have greater than 5 on-demand doses on hand **OR** B. There is support for the patient having more than 5 on-demand doses on hand (supportive reasoning required) **Length of Approval:** up to 3 months NOTE: If Quantity Limit applies, please see Quantity Limit Criteria

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
NovoSeven RT	**Quantity Limit for the requested agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit defined by BOTH of the following: A. The requested dose is within the FDA labeled dosing **AND** B. The requested quantity (number of doses) is appropriate based on intended use (e.g., on-demand, prophylaxis, perioperative) **OR** 2. There is support for exceeding the defined program quantity limit (dose and/or number of doses) (medical records required) **Length of Approval:** Peri-operative dosing: 1 time per request On-demand: up to 3 months Prophylaxis: up to 12 months ITT/ITI: up to 6 months, or up to a total of 33 months of ITT/ITI therapy, or requested duration, whichever is shortest up to 3 months for all other diagnoses
Sevenfact	**Quantity Limit for the Requested Agent(s)** will be approved when ONE of the following are met: 1. The requested quantity (dose) does NOT exceed the program quantity limit defined by BOTH of the following: A. The requested dose is within the FDA labeled dosing **AND**

Module	Clinical Criteria for Approval
	B. The requested quantity (number of doses) is appropriate based on intended use (e.g., on-demand) **OR** 2. There is support for exceeding the defined program quantity limit (dose and/or number of doses) (medical records required) **Length of Approval:** up to 3 months

Copay Waiver

ACA Prevention

CLINICAL RATIONALE

	The Affordable Care Act (ACA) requires a member-friendly mechanism for waiving the cost share for an alternative recommended product deemed medically necessary by the provider when a health care provider considers the $0 covered product is inappropriate for an individual. https://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs12.html https://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/Downloads/aca_implementation_faqs26.pdf

OBJECTIVE

Aspirin ACA Prevention:

The intent of the ACA Prevention Copay Waiver Criteria is to help ensure the copay waiver, when applicable based on the member's benefit, is applied to the appropriate population as described by the United States Preventative Services Task Force (USPSTF).

Bowel Prep:

The intent of the ACA Prevention Copay Waiver Criteria is to help ensure the copay waiver, when applicable based on the member's benefit, is applied to the appropriate population as described by the United States Preventative Services Task Force (USPSTF).

Breast Cancer:

The intent of the ACA Prevention Copay Waiver Criteria is to help ensure the copay waiver, when applicable based on the member's benefit, is applied to the appropriate population as described by the United States Preventative Services Task Force (USPSTF).

Contraceptives ACA Prevention:

The intent of the ACA Prevention Copay Waiver Criteria is to help ensure the copay waiver, when applicable based on the member's benefit, is applied to the appropriate population as described by Health Resources & Services Administration (HRSA) in support of Women's Preventive Care.

Fluoride Supplement:

The intent of the ACA Prevention Copay Waiver Criteria is to help ensure the copay waiver, when applicable based on the member's benefit, is applied to the appropriate population as described by the United States Preventative Services Task Force (USPSTF) and Bright Futures/Health Resources & Services Administration (HRSA).

Folic Acid:

The intent of the ACA Prevention Copay Waiver Criteria is to help ensure the copay waiver, when applicable based on the member's benefit, is applied to the appropriate population as described by the United States Preventative Services Task Force (USPSTF).

Human Immunodeficiency Virus (HIV) Infection: Pre-exposure Prophylaxis (PrEP):

The intent of the ACA Prevention Copay Waiver Criteria is to help ensure the copay waiver, when applicable based on the member's benefit, is applied to the appropriate population as described by the United States Preventative Services Task Force (USPSTF).

Infant Eye Ointment:

The intent of the ACA Prevention Copay Waiver Criteria is to help ensure the copay waiver, when applicable based on the member's benefit, is applied to the appropriate population as described by the United States Preventative Services Task Force (USPSTF).

Iron Supplements :

The intent of the ACA Prevention Copay Waiver Criteria is to help ensure the copay waiver, when applicable based on the member's benefit, is applied to the appropriate population as described by the Bright Futures/Health Resources & Services Administration (HRSA).

Statin:

The intent of the ACA Prevention Copay Waiver Criteria is to help ensure the copay waiver, when applicable based on the member's benefit, is applied to the appropriate population as described by the United States Preventative Services Task Force (USPSTF). The USPSTF recommendation requires the calculation of Atherosclerotic Cardiovascular Disease (ASCVD) risk. The calculation requires inputting the patient's sex, age, race, high density lipoprotein (HDL) cholesterol, total cholesterol, blood pressure, whether the patient has diabetes, whether the patient is under treatment for hypertension, and whether the patient is an active smoker.(1)

1. American College of Cardiology and American Heart Association's Atherosclerotic Cardiovascular Disease (ASCVD) calculator. Available at: https://tools.acc.org/ASCVD-Risk-Estimator/ Accessed on 7/27/23.

Tobacco:

The intent of the ACA Prevention Copay Waiver Criteria is to help ensure the copay waiver, when applicable based on the member's benefit, is applied to the appropriate population as described by the United States Preventative Services Task Force (USPSTF).

Vaccine:

The intent of the ACA Prevention Copay Waiver Criteria is to help ensure the copay waiver, when applicable based on the member's benefit, is applied to the appropriate population as described by the Advisory Committee on Immunization Practices (ACIP) and Centers for Disease Control (CDC) in support of routine immunizations for children, adolescents, and adults.

CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Aspirin ACA Prevention Copay Waiver Criteria	The requested aspirin will be approved when ALL of the following are met: 1. The requested aspirin agent is covered under the pharmacy benefit or has been approved through the coverage exception process **AND** 2. There is support that the requested aspirin agent is medically necessary **AND** 3. The requested agent is the 81 mg strength aspirin **AND** 4. The patient is pregnant, at high risk of preeclampsia, and using the requested agent after 12 weeks of gestation **Length of Approval:** 9 months
Bowel Prep Agents ACA Prevention Copay Waiver Criteria	The requested bowel prep agent will be approved when ALL of the following are met: 1. The requested bowel prep agent is covered under the pharmacy benefit or has been approved through the coverage exception process **AND** 2. There is support that the requested bowel prep agent is medically necessary **AND** 3. The requested agent will be used for the preparation of colorectal cancer screening using fecal occult blood testing, sigmoidoscopy, or colonoscopy **AND**

Module	Clinical Criteria for Approval
	4. The patient is 45 years of age or over **Length of Approval:** 12 months
Breast Cancer Primary Prevention Agent ACA Copay Waiver Criteria	The requested breast cancer primary prevention agent will be approved when ALL of the following are met: 1. The requested breast cancer primary prevention agent is covered under the pharmacy benefit or has been approved through the coverage exception process **AND** 2. There is support that the requested breast cancer primary prevention agent is medically necessary **AND** 3. The requested agent is tamoxifen, raloxifene, or an aromatase inhibitor (anastrozole, exemestane, letrozole) **AND** 4. The patient is 35 years of age or over **AND** 5. The agent is requested for the primary prevention of breast cancer **AND** 6. ONE of the following: A. The plan has not implemented a sex requirement **OR** B. The plan has implemented a sex requirement AND ONE of the following: 1. The patient's sex is female **OR** 2. The requested agent is medically appropriate for the patient's sex **Length of Approval:** 12 months
Contraceptives ACA Prevention Copay Waiver Criteria	The requested contraceptive agent will be approved when ALL of the following are met: 1. The requested contraceptive agent is covered under the pharmacy benefit or has been approved through the coverage exception process **AND** 2. The requested agent is being used for contraception **AND** 3. There is support that the requested contraceptive agent is medically necessary **Length of Approval:** 12 months
Fluoride supplement ACA Prevention Copay Waiver Criteria	The requested fluoride supplement agent will be approved when ALL of the following are met: 1. The requested fluoride supplement is covered under the pharmacy benefit or has been approved through the coverage exception process **AND**

Module	Clinical Criteria for Approval
	2. There is support that the requested fluoride supplement is medically necessary **AND** 3. The patient is 6 months to 16 years of age **Length of Approval:** 12 months
Folic Acid ACA Prevention Copay Waiver Criteria	The requested folic acid agent will be approved when ALL of the following are met: 1. The requested folic acid is covered under the pharmacy benefit or has been approved through the coverage exception process **AND** 2. There is support that the requested folic acid supplement is medically necessary **AND** 3. The requested folic acid supplement contains 0.4-0.8 mg of folic acid **AND** 4. The requested folic acid supplement is to be used in support of pregnancy **AND** 5. ONE of the following: A. The plan has not implemented a sex requirement **OR** B. The plan has implemented a sex requirement AND ONE of the following: 1. The patient's sex is female **OR** 2. The requested agent is medically appropriate for the patient's sex **Length of Approval:** 12 months
Human Immunodeficiency Virus (HIV) Infection: Pre-exposure Prophylaxis (PrEP) ACA Prevention Copay Waiver Criteria	The requested HIV infection pre-exposure prophylaxis (PrEP) agent will be approved when ALL of the following are met: 1. The requested PrEP agent is covered under the pharmacy benefit or has been approved through the coverage exception process **AND** 2. The requested agent is being used for PrEP **AND** 3. There is support that the requested PrEP agent is medically necessary**AND** 4. The requested PrEP agent is ONE of the following: A. Tenofovir disoproxil fumarate and emtricitabine combination ingredient agent **OR** B. Tenofovir alafenamide and emtricitabine combination ingredient agent **OR** C. Cabotegravir **AND**

Module	Clinical Criteria for Approval
	5. The patient has increased risk for HIV infection **AND** 6. The patient has recently tested negative for HIV **Length of Approval:** 12 months
Infant Eye Ointment ACA Prevention Copay Waiver Criteria	The requested infant eye ointment agent will be approved when ALL of the following are met: 1. The requested infant eye ointment is covered under the pharmacy benefit or has been approved through the coverage exception process **AND** 2. There is support that the requested infant eye ointment is medically necessary **AND** 3. The patient is 3 months of age or younger **AND** 4. The requested agent is requested for the prevention of gonococcal ophthalmia neonatorum **Length of Approval:** 3 months
Iron Supplements ACA Prevention Copay Waiver Criteria	The requested iron supplement will be approved when ALL of the following are met: 1. The requested iron supplement is covered under the pharmacy benefit or has been approved through the coverage exception process **AND** 2. There is support that the requested iron supplement is medically necessary **AND** 3. The patient is under 12 months of age **AND** 4. The patient is at increased risk for iron deficiency anemia **Length of Approval:** 12 months
Statin ACA Prevention Copay Waiver Criteria	The requested statin will be approved when ALL of the following are met: 1. The requested statin is covered under the pharmacy benefit or has been approved through the coverage exception process **AND** 2. There is support that the requested statin is medically necessary **AND** 3. The requested statin is for use in the primary prevention of cardiovascular disease (CVD) **AND** 4. The patient is 40-75 years of age (inclusive) **AND** 5. The patient has at least one of the following risk factors: A. Dyslipidemia B. Diabetes C. Hypertension

Module	Clinical Criteria for Approval
	D. Smoking **AND** 6. The patient has a calculated 10-year risk of a cardiovascular event of 10% or greater per the American College of Cardiology and American Heart Association's Atherosclerotic Cardiovascular Disease (ASCVD) calculator **Length of Approval:** 12 months
Tobacco Cessation ACA Prevention Copay Waiver Criteria	The requested tobacco cessation agent will be approved when ALL of the following are met: 1. The requested tobacco cessation agent is covered under the pharmacy benefit or has been approved through the coverage exception process **AND** 2. The patient is a non-pregnant adult **AND** 3. ONE of the following: A. The requested tobacco cessation agent is not covered on a $0 Affordable Care Act (ACA) list AND BOTH of the following: 1. There is support that the requested tobacco cessation agent is medically necessary **AND** 2. ONE of the following: A. The patient has received less than 180 day supply of the requested tobacco cessation agent type (e.g., NRT, bupropion, varenicline) in the past 365 days **OR** B. The patient has received 180 or more day supply of the requested tobacco cessation agent type (e.g., NRT, bupropion, varenicline) in the past 365 days AND ONE of the following: 1. The patient is currently being treated with the requested tobacco cessation agent type (e.g., NRT, bupropion, varenicline) and the patient is expected to be successful on this course of therapy [patient will be approved for remainder of up to a 24-week course] **OR** 2. There is support for the anticipated success of repeating therapy with the requested tobacco cessation agent type (e.g., NRT, bupropion, varenicline) [patient will be approved for an additional 24-week course of therapy] **OR**

Module	Clinical Criteria for Approval
	B. The requested tobacco cessation agent is covered on a $0 Affordable Care Act (ACA) list AND ONE of the following: 1. The patient has received more than 180 day supply of the requested tobacco cessation agent type (e.g., NRT, bupropion, varenicline) in the past 365 days AND ONE of the following: A. The patient is currently being treated with the requested tobacco cessation agent type (e.g., NRT, bupropion, varenicline) and is expected to be successful on this course of therapy [patient will be approved for remainder of a 24-week course] **OR** B. There is support for the anticipated success of repeating therapy with the requested tobacco cessation agent type (e.g., NRT, bupropion, varenicline) [patient will be approved for an additional 24-week course of therapy] **Length of Approval:** 12 months
Vaccine ACA Prevention Copay Waiver Criteria	The requested vaccine will be approved when ALL of the following are met: 1. The requested vaccine is covered under the pharmacy benefit or has been approved through the coverage exception process **AND** 2. There is support that the requested vaccine is medically necessary **AND** 3. The requested vaccine will be used per the recommendations of the Advisory Committee on Immunization Practices/CDC **Length of Approval:** 12 months

Corticotropin

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Acthar® Gel (repository corticotropin) Intramuscular injection Subcutaneous injection	Infantile Spasm (IS) in infants and children under 2 years of age NOTE: Acthar is FDA approved for numerous indications, however, the FDA has only evaluated clinical trials in infants under 2 years of age with infantile spasms(7,8) Indicated in the following disorders: • Acute exacerbations of multiple sclerosis (MS) in adults. Controlled clinical trials have shown Acthar Gel to be effective in speeding the resolution of acute exacerbations of multiple sclerosis. However, there is no evidence that it affects the ultimate outcome or natural history of the disease • Rheumatic disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), ankylosing spondylitis • Collagen diseases: during an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus and systemic dermatomyositis (polymyositis) • Dermatologic diseases: severe erythema multiforme and Stevens-Johnson syndrome • Allergic states: serum sickness		1

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Ophthalmic diseases: severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as keratitis, iritis, iridocyclitis, diffuse posterior uveitis and choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation • Respiratory diseases: Symptomatic sarcoidosis • Edematous states: To induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus		
Purified Cortrophin® Gel (repository corticotropin) Intramuscular injection Subcutaneous injection	Indicated in the following disorders: • Rheumatic disorders: As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy), ankylosing spondylitis, acute gouty arthritis • Collagen diseases: during an exacerbation or as maintenance therapy in selected cases of systemic lupus erythematosus and systemic dermatomyositis (polymyositis) • Dermatologic diseases: severe erythema multiforme (Stevens-Johnson syndrome) and severe psoriasis • Allergic states: atopic dermatitis and serum sickness • Ophthalmic diseases: severe acute and chronic allergic and inflammatory processes involving the eye and its adnexa such as allergic conjunctivitis, keratitis, iritis and iridocyclitis, diffuse posterior uveitis and		6

Agent(s)	FDA Indication(s)	Notes	Ref#
	choroiditis, optic neuritis, chorioretinitis, and anterior segment inflammation • Respiratory diseases: Symptomatic sarcoidosis • Edematous states: To induce a diuresis or a remission of proteinuria in the nephrotic syndrome without uremia of the idiopathic type or that due to lupus erythematosus • Nervous system: Acute exacerbations of multiple sclerosis		

CLINICAL RATIONALE

Infantile Spasms	Infantile spasm (IS), also referred to as West Syndrome, is a specific seizure syndrome that is characterized by clinical flexor or extensor spasms, often involving the extremities and head/neck; developmental regression (intellectual disability); and electroencephalography (EEG) finding of hypsarrhythmia (chaotic brain waves).(2,3) Neurological and/or developmental outcomes in patients with IS are usually poor. Children with symptomatic spasms more frequently exhibit neurological deficits and cognitive and developmental delays, while a higher percentage of patients with idiopathic/cryptogenic IS may have a normal or near-normal outcome if appropriate treatment is initiated in a timely fashion. Goals of therapy for IS includes complete cessation of clinical events and resolution of hypsarrhythmia or modified hypsarrhythmia on video EEG.(3) Guidelines recommend ACTH and vigabatrin for the treatment of infantile spasms. Both ACTH and vigabatrin may be useful for short-term treatment, but ACTH is preferred over vigabatrin, except in patients with tuberous sclerosis. Hormonal therapy (ACTH or prednisolone) has been shown to lead to better neurodevelopmental outcomes in patients with cryptogenic IS when compared to vigabatrin.(2,3) Guidelines recommend treating for 14 days and then tapering down, as response is typically seen within 14 days or sooner. Low dose ACTH is probably as effective as high-dose ACTH therapy and should be considered as an alternative to high dose therapy.(2) A 2010 U.S. consensus statement suggests initiating a taper of ACTH after two weeks of therapy at the maximum dose. No data is available to guide therapy in relapse in patients who responded to an

	initial treatment course. Typically, a second course (four to six weeks) of the agent that was previously effective in obtaining control is administered.(4) Acthar Gel was first approved in 1952 prior to the 1962 drug amendments requiring clinical trials proving safety and efficacy.(1,5) Repository corticotropin injection is available as Acthar Gel (Mallinckrodt Pharmaceuticals, Inc), formerly known as H.P. Acthar Gel (Questcor Pharmaceuticals), and Purified Cortrophin Gel (ANI Pharmaceuticals, Inc). Acthar Gel and Purified Cortrophin Gel are highly purified sterile preparations of the adrenocorticotropic hormone (ACTH) available in 16% gelatin (for Acthar Gel) or 15% gelatin (for Purified Cortrophin Gel) to provide a prolonged release after intramuscular or subcutaneous injection.(9) Repository corticotropin injection was originally approved by the U.S. Food and Drug Administration (FDA) in 1952 for a broad range of corticosteroid-responsive conditions including rheumatic, collagen, dermatologic, allergic states, ophthalmic, respiratory and edematous states. Current labeled indications include multiple sclerosis, rheumatic disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmologic diseases, respiratory diseases, and edematous states. In addition, the FDA approved the use of repository corticotropin injection (Acthar Gel only) for treatment of infantile spasms in infants and children under 2 years of age.(9) In August 2021, the U.S. FDA approved Purified Cortrophin Gel for virtually the same indications as Acthar Gel except for the infantile spasms indication. There are a lack of clinical studies comparing the effectiveness of ACTH gel to corticosteroids in corticosteroid-responsive conditions. In addition, there is no reliable evidence of the effectiveness of ACTH gel in persons who have failed to respond to corticosteroids.(9)
Efficacy	The effectiveness of Acthar Gel as a treatment for infantile spasms was demonstrated in a single blinded (video EEG interpreter blinded) clinical trial in which patients were randomized to receive either a 2 week course of treatment with Acthar Gel (75 U/m^2 intramuscular twice daily) or prednisone (1 mg/kg by mouth twice daily). The primary outcome was a comparison of the number of patients in each group who were treatment responders, defined as a patient having complete suppression of both clinical spasms and hypsarrhythmia on a full sleep cycle video EEG performed 2 weeks following treatment initiation, rated by an investigator blinded to treatment. Thirteen of 15 patients (86.7%) responded to Acthar Gel as compared to 4 of 14 patients (28.6%) given prednisone ($p<0.002$). The 2-week treatment was followed by a 2-week period of taper. Non-responders to the prednisone treatment were eligible to receive

	Acthar Gel treatment. Seven of 8 patients (87.5%) responded to Acthar Gel after not responding to prednisone. Similarly, the 2 non-responder patients from the Acthar Gel treatment were eligible to receive treatment with prednisone. One of the 2 patients (50%) responded to the prednisone treatment after not responding to Acthar Gel.(1) A supportive single-blind, randomized clinical trial comparing high-dose, long-duration treatment (150 U/m^2 once daily for 3 weeks, n=30) of Acthar Gel with low-dose, short duration treatment (20 U once daily for 2 weeks, n=29) for the treatment of infantile spasms was also evaluated in infants and children less than 2 years of age. Non-responders (defined as in the previously described study) in the low-dose group received a dose escalation at 2 weeks to 30 U once daily. Nominal statistical superiority of the high dose treatment, as compared to the low dose treatment, was observed for cessation of spasms but not for the resolution of hypsarrhythmia.(1) There is no clinical data for the FDA indication for Cortrophin Gel. No additional clinical trials for Cortrophin were completed to show efficacy for the approved indications.(6)
Safety	Acthar Gel is contraindicated in the following:(1) • Intravenous administration • Suspicion of congenital infections in infants under 2 years of age • In patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency or hyperfunction, or sensitivity to porcine proteins • Concomitant administration of live or live attenuated vaccines in patients receiving immunosuppressive doses of Acthar Gel Purified Cortrophin gel is contraindicated in the following:(6) • Intravenous administration • In patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of or the presence of a peptic ulcer, congestive heart failure, uncontrolled hypertension, primary adrenocortical insufficiency or hyperfunction, or sensitivity to porcine proteins

REFERENCES

Number	Reference
1	Acthar Gel prescribing information. Mallinckrodt ARD, Inc. February 2024.
2	Go, CY, Mackay MT, Weiss SK, Weiss SK, et al. Evidence-based guideline update: Medical treatment of infantile spasms: American Academy of Neurology. *Neurology* 2012;78;1974-1980
3	Nelson, Gary Rex. Management of Infantile Spasms. *Transl Pedatr*. 2015;4(4):260-270.
4	Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. Epilepsia 2010; 51:2175.
5	White Junod, S. (2008). FDA and Clinical Drug Trials: A Short History. Washington. https://www.fda.gov/media/110437/download.
6	Purified Cortrophin Gel prescribing information. ANI Pharmaceuticals, Inc. October 2023.
7	U.S. Food and Drug Administration. Center for Drug Evaluation and Research. (2010). Application 022432Orig1s000 Internal Consult on draft labeling (Package Insert) for H.P. Acthar Gel. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022432Orig1s000OtherR.pdf
8	U.S. Food and Drug Administration. Center for Drug Evaluation and Research. (2010). Application 022432Orig1s000 Action Memo for NDA 22-432, for the use of H.P. Acthar Gel (repository corticotrophin injection) in the treatment of Infantile Spasms (IS). https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022432Orig1s0900SumR.pdf
9	U.S. Food and Drug Administration. Center for Drug Evaluation and Research. (2022). Application: 008975Orig1s008. Approval Package for Purified Cortrophin Gel. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/008975Orig1s008.pdf.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	

Preferred Target Agent(s)	Non-Preferred Target Agent(s)
Acthar Gel (repository corticotropin)	Purified Cortrophin Gel (repository corticotropin)

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has a diagnosis of infantile spasms **AND**
2. The patient is less than 24 months of age **AND**
3. If the client has preferred agent(s), then ONE of the following:
   A. The requested agent is a preferred agent **OR**
   B. The patient has tried and had an inadequate response to the preferred agent(s) **OR**
   C. The patient has an intolerance or hypersensitivity to the preferred agent(s) that is NOT expected to occur with the requested agent **OR**
   D. The patient has and FDA labeled contraindication to the preferred agent(s) that is NOT expected to occur with the requested agent **AND**
4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND**
5. The requested quantity (dose) is within FDA labeled dosing for the requested indication

Length of Approval: 6 months

Target Agent(s) will NOT be approved and are NOT medically necessary for all other indications including but not limited to:

1. Multiple Sclerosis
2. Rheumatic Disorders
3. Collagen diseases
4. Dermatologic diseases
5. Allergic states
6. Ophthalmic diseases
7. Respiratory diseases
8. Edematous states

The effectiveness of repository corticotropin has not been demonstrated as clinically superior to conventional corticosteroids and/or immunosuppressive therapy for uses other than infantile spasms.

Daybue (trofinetide)

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Daybue™ (trofinetide) Oral solution	Treatment of Rett syndrome in adults and pediatric patients 2 years of age and older		1

CLINICAL RATIONALE

Rett Syndrome	Rett syndrome (RTT) is a rare X-linked neurodevelopmental disorder characterized by loss of speech and purposeful hand use, with the development of distinctive hand movements and gait abnormalities. Until methyl-CpG-binding protein 2 (MECP2) was identified as the causative gene, diagnosis had been based only on consensus clinical criteria which had key clinical elements that identify classic/typical RTT, but also variant/atypical forms. Because the MECP2 mutation is the most commonly observed cause of RTT, the disease caused by the MECP2 mutation is called classic/typical RTT. Mutation screening identifies MECP2 gene alterations in 95–97% of patients with classical/typical RTT, though MLPA testing may be needed to detect deletions otherwise missed by genetic sequencing.(2,7,8) Whereas MECP2 mutation is the classic/typical RTT, the similar clinical manifestations involving other genes is historically called the atypical RTT (e.g., CDKL5 mutation, FOXG1 mutation). Mutations in CDKL5 and FOXG1 have resulted in unique diseases that are distinguishable from RTT, since the specific symptoms of the disease vary depending on the causative gene involved. For example, mutations in CDKL5 cause early life epilepsy, while those in FOXG1 are known to cause characteristic stereotypic movements and severe microcephaly. The diseases caused by CDKL5 and FOXG1 mutations are referred to as CDD (CDKL5 deficiency disorder) and FOXG1 syndrome, respectively. Because an effective treatment for these diseases is yet to be found, elucidation

	of the molecular signaling pathways controlled by the driver genes is an important prerequisite for the development of viable therapies.(3,4,5) Symptoms of RTT include loss of purposeful hand skills, loss of spoken language, gait abnormalities, abnormal hand movements, breathing distubances, impaired sleep, growth retardation, abnormal muscle tone, and seizures.(7,8)
Efficacy	The mechanism by which trofinetide exerts therapeutics effects in patients with Rett syndrome is unknown.(1) Trofinetide is a novel synthetic analog of glycine-proline-glutamate (GPE), the N-terminal tripeptide of insulin-like growth factor 1 (IGF-1).(6) There is evidence that the level of IGF-1 is decreased in the cerebrospinal fluid of RTT patients. Supplementing with IGF-1 can improve motor function, respiration, anxiety, and other behaviors, as well as prolong the life span of RTT mice. In clinical trials, recombinant human IGF-1 can improve abnormal respiratory movement, cognitive ability, irritability, and anxiety in RTT patients.(10) The efficacy of Daybue for the treatment of Rett syndrome was established in a 12-week randomized, double-blind, placebo-controlled study in patients with Rett syndrome 5 to 20 years of age (Study 1; NCT04181723). Patients (N=187) had a diagnosis of typical Rett syndrome according to the Rett Syndrome Diagnostic Criteria with a documented disease-causing mutation in the MECP2 gene. Patients were randomized to receive Daybue (N=93) or matching placebo (N=94) for 12 weeks. The Daybue dosage was based on patient weight to achieve similar exposure in all patients.(1) The co-primary efficacy measures were change from baseline after 12 weeks of treatment in the total score of the Rett Syndrome Behaviour Questionnaire (RSBQ) and the Clinical Global Impression-Improvement (CGI-I) score. The RSBQ is a 45-item rating scale completed by the caregiver that assesses a range of symptoms of Rett syndrome (breathing, hand movements or stereotypies, repetitive behaviors, night-time behaviors, vocalizations, facial expressions, eye gaze, and mood). The Clinical Global Impression scale (CGI) is a clinician-rated scale used to rate patients' global functioning before and after treatment in trials, assessing whether a patient has improved or worsened.(1,9) Treatment with Daybue demonstrated a statistically significant difference in favor of Daybue as compared to placebo on the co-primary efficacy endpoints, the change from baseline in RSBQ total score and the CGI-I score at week 12.(1)
Safety	Daybue has no FDA labeled contraindications.(1)

REFERENCES

Number	Reference
1	Daybue prescribing information. Acadia Pharmaceuticals Inc. March 2023.
2	Guerrini R, Parrini E. Epilepsy in Rett Syndrome, and CDKL5- and FOXG1-Gene-Related Encephalopathies. Epilepsia. 2012 Sep;53(12):2067-2078.
3	Percy AK, Neul JL, Peters S, et al. Current Status of Developmental Encephalopathies: Rett Syndrome, MECP2 Duplication Disorder, CDKL5 Deficiency Disorder, and FOXG1 Disorder. Transl Sci Rare Dis. 2023 Jan;1-28.
4	Akol I, Gather F, Vogel T. Paving Therapeutic Avenues for FOXG1 Syndrome: Untangling Genotypes and Phenotypes from a Molecular Perspective. Int J Mol Sci. 2022 Jan;23(2):954.
5	Ma M, Adams HR, Seltzer LE, et al. Phenotype Differentiation of FOXG1 and MEPC2 Disorders: A New Method for Characterization of Developmental Encephalopathies. J Pediatr. 2016 Nov;178:233-240.
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7	International Rett Syndrome Foundation. Rett Syndrome: Primary Care Guidelines. Available at: https://www.rettsyndrome.org/wp-content/uploads/IRSF_PrimaryCareGdlns_REV2021.pdf
8	Fu C, Armstrong D, Marsh E, et al. Consensus Guidelines on Managing Rett Syndrome Across the Lifespan. BMJ Paediatr Open. 2020 Sep;4(1).
9	Singh J, Fiori F, Law ML, et al. Development and Psychometric Properties of the Multi-System Profile of Symptoms Scale in Patients with Rett Syndrome. J Clin Med. 2022;11:1-19.
10	Yuan ZF, Mao SS, Shen J, et al. Insulin-Like Growth Factor-1 Down-Regulates the Phosphorylation of FXYD1 and Rescues Behavioral Deficits in a Mouse Model of Rett Syndrome. Neurosci. 2020 Jan;14.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** Daybue 1. Information has been provided that indicates the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. The patient has a diagnosis of classic/typical Rett syndrome (RTT) **AND** 2. The patient has a disease-causing mutation in the MECP2 gene **AND** 2. If the patient has an FDA approved indication, then ONE of the following**:** A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 3. The patient's weight is 9 kg or greater **AND** 4. The prescriber has assessed baseline status (prior to therapy with the requested agent) of the patient's RTT symptoms (e.g., speech patterns, hand movements, gait, growth, muscle tone, seizures, breathing patterns, quality of sleep) **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., geneticist, neurologist, pediatrician) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 3 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Clinical Criteria for Approval
	Renewal Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient has had clinical benefit with the requested agent (e.g., speech patterns, hand movements, gait, growth, muscle tone, seizures, breathing patterns, quality of sleep) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., geneticist, neurologist, pediatrician) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. The prescriber has provided information in support of therapy with a higher dose for the requested indication **Length of Approval:** Initial: 3 months; Renewal: 12 months

Dojolvi

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Dojolvi® (triheptanoin) Oral liquid	A source of calories and fatty acids for the treatment of pediatric and adult patients with molecularly confirmed long-chain fatty acid oxidation disorders (LC-FAOD)		1

CLINICAL RATIONALE

Long Chain Fatty Acid Oxidation Disorders	Long-chain fatty acid oxidation disorders (LC-FAODs) are rare, life-threatening, autosomal recessive genetic disorders characterized by acute crises of energy production and chronic energy deficiency. Patients may present with rhabdomyolysis induced by exercise; fasting or illness; hepatic dysfunction, including severe hypoglycemia and hyperammonemia; and cardiomyopathy. These clinical manifestations can lead to frequent hospitalizations and premature death. LC-FAODs are caused by mutations in nuclear genes encoding mitochondrial enzymes involved in the conversion of dietary long-chain fatty acids (LCFAs) into energy during times of fasting and physiologic stress.(2) Fatty acid oxidation disorders are often captured as part of newborn screenings. A plasma acylcarnitine profile is necessary for diagnosis following an abnormal NBS. DNA testing is considered standard for confirmation and can be helpful in genotype/phenotype correlations. DNA sequencing may reveal variants of uncertain significance, so further investigation of enzyme activity through fibroblast or lymphocyte testing may provide additional information of functional significance.(3,4,5) Current management options leave many patients continuing to experience major clinical events, and mortality rates remain elevated. The current standard therapy for LC-FAODs is avoidance of fasting as well as supplementation of medium-chain triglyceride oil which does not require the typical steps of LC-FAOD for metabolism. Despite this therapy, patients with LC-FAODs continue to

	experience recurring hospitalizations, and high morbidity and mortality rates. In recent years, the use of medium, odd-chain fatty acids, such as triheptanoin, have been studied as a treatment of LC-FAODs due to its anaplerotic (replenishment of metabolic pathway intermediates) properties. Due to favorable safety and efficacy data from clinical trials, this novel agent has the potential to transform the treatment of LC-FAODs and improve patient outcomes in this patient population.(2,3)
Efficacy	The efficacy of triheptanoin as a source of calories and fatty acids was evaluated in Study 3 (NCT01379625), a 4-month double-blind randomized controlled study comparing triheptanoin (7-carbon chain fatty acid) with trioctanoin (8-carbon chain fatty acid). The study enrolled 32 adult and pediatric patients with a confirmed diagnosis of LC-FAOD and evidence of at least one significant episode of rhabdomyolysis and at least two of the following diagnostic criteria: disease specific elevation of acylcarnitines on a newborn blood spot or in plasma, low enzyme activity in cultured fibroblasts, or one or more known pathogenic mutations in CPT2, ACADVL, HADHA, or HADHB. The dosage of study drug was titrated to a protocol-specified target of 20% DCI (actual mean daily dose achieved was 16% for triheptanoin and 14% for trioctanoin). The recommended target dosage of Dojolvi is up to 35% of DCI. After 4 months, patients in both groups had similar mean changes from baseline in left ventricular ejection fraction and wall mass on resting echocardiogram and similar maximal heart rates on treadmill ergometry.(1)
Safety	Triheptanoin carries no contraindications nor boxed warnings.(1)

REFERENCES

Number	Reference
1	Dojolvi prescribing information. Ultragenyx Pharmaceutical Inc. October 2023.
2	Vockley J. Long-Chain Fatty Acid Oxidation Disorders and Current Management Strategies. Am J Manag Care. 2020 Aug;26(7 Suppl):S147-S154.
3	Baker JJ, Burton BK. Diagnosis and Clinical Management of Long-chain Fatty-acid Oxidation Disorders: A Review. TouchREV Endocrinol. 2021 Nov;17(2):108-111.

Number	Reference
4	Knottnerus SJG, Bleeker JC, Wust RCI, et al. Disorders of Mitochondrial Long-Chain Fatty Acid Oxidation and the Carnitine Shuttle. Rev Endocr Metab Disord. 2018;19(1):93-106.
5	Merritt JL, Norris M, Kanungo S. Fatty Acid Oxidation Disorders. Ann Transl Med. 2018;6(24):473.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent** will be approved when ALL of the following are met: 1. The patient has ONE of the following: A. The patient has a diagnosis of long-chain fatty acid oxidation disorder (LCFAOD) AND ALL of the following: 1. The diagnosis has been confirmed by at least TWO of the following: A. Disease-specific elevations of acylcarnitines on a newborn blood spot or in plasma B. Enzyme activity assay (in cultured fibroblasts or lymphocytes) demonstrating deficiency of an enzyme associated with LCFAODs C. Genetic testing demonstrating pathogenic mutation in a gene associated with LCFAODs **AND** 2. The patient had symptomatic LCFAOD prior to therapy with the requested agent **AND** 3. The patient will not be concurrently using another medium chain triglyceride product **AND** 4. The patient will not be using the requested agent for more than 35% of the patient's total prescribed daily caloric intake **OR** B. The patient has another FDA labeled indication for the requested agent and route of administration **OR** C. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent

Module	Clinical Criteria for Approval
	Length of Approval: 12 months **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Renewal Evaluation** **Target Agent** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. If the patient has a diagnosis of LCFAOD, BOTH of the following: A. The patient will not be concurrently using another medium chain triglyceride product **AND** B. The patient will not be using the requested agent for more than 35% of the patient's total prescribed daily caloric intake **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months

DPP-4 Inhibitors and Combinations

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Janumet® (sitagliptin/metformin) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes. • Has not been studied in patients with a history of pancreatitis		5
Janumet® XR (sitagliptin-metformin HCl Tab ER) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes. • Has not been studied in patients with a history of pancreatitis		6
Januvia® (sitagliptin) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes.		1

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Has not been studied in patients with a history of pancreatitis.		
Jentadueto® (linagliptin/metformin) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes • Has not been studied in patients with a history of pancreatitis		7
Jentadueto XR® (linagliptin/metformin ER) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes • Has not been studied in patients with a history of pancreatitis		8
Kazano®, Alogliptin/metformin Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes mellitus		10
Kombiglyze™ XR (saxagliptin/metformin)* Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment	*- generic available	9

Agent(s)	FDA Indication(s)	Notes	Ref#
	with both saxagliptin and metformin is appropriate Limitations of use: • Not indicated for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis		
Nesina®, Alogliptin Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes mellitus		2
Onglyza® (saxagliptin)* Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Not used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis	*-generic available	3
Oseni®, Alogliptin/pioglitazone Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes		11

Agent(s)	FDA Indication(s)	Notes	Ref#
Tradjenta® (linagliptin) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Should not be used in patients with type 1 diabetes, as it would not be effective in these settings • Has not been studied in patients with a history of pancreatitis		4
Zituvimet™ (sitagliptin free base/metformin) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Limitations of Use: • Zituvimet is not recommended in patients with type 1 diabetes mellitus • Zituvimet has not been studied in patients with a history of pancreatitis		15
Zituvimet XR™ (sitagliptin free base/metformin) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Limitations of Use: • Zituvimet is not recommended in patients with type 1 diabetes mellitus • Zituvimet has not been studied in patients with a history of pancreatitis		16

Agent(s)	FDA Indication(s)	Notes	Ref#
Zituvio™ (sitagliptin) Tablet	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of Use: • Zituvio is not recommended in patients with type 1 diabetes mellitus • Zituvio has not been studied in patients with a history of pancreatitis		14

CLINICAL RATIONALE

Diabetes	The American Diabetes Association (ADA) states that first-line therapy depends on comorbidities, patient-centered treatment factors, and management needs and generally includes metformin and comprehensive lifestyle modification. Because type 2 diabetes is a progressive disease in many patients, maintenance of glycemic targets with monotherapy is often possible for only a few years, after which combination therapy is necessary. Traditional recommendations have been to use stepwise addition of medications to metformin to maintain A1C at target.(12,13) Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death. Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release form that can be given once daily. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, weight, and cardiovascular mortality.(13)
Safety	Janumet, Jentadueto, Jentadueto XR, Kazano, Kombiglyze XR, Zituvimet, and Zituvimet XR carry a black box warning for lactic acidosis:(7-10,15) • Post-marketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. The onset of metformin associated lactic acidosis is often subtle, accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, somnolence, and abdominal pain.

	Metformin associated lactic acidosis was characterized by elevated blood lactate levels (greater than 5 mmol/Liter), anion gap acidosis (without evidence of ketonuria or ketonemia), an increased lactate/pyruvate ratio; and metformin plasma levels generally greater than 5 mcg/ml • Risk factors for metformin-associated lactic acidosis include renal impairment, concomitant use of certain drugs (e.g., carbonic anhydrase inhibitors such as topiramate), age 65 years old or greater, having a radiological study with contrast, surgery and other procedures, hypoxic states (e.g., acute congestive heart failure), excessive alcohol intake, and hepatic impairment. • Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high-risk groups are provided in the full prescribing information • If metformin-associated lactic acidosis is suspected, immediately discontinue the medication and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. Oseni carries a black box warning for congestive heart failure:(11) • Thiazolidinediones, including pioglitazone, cause or exacerbate congestive heart failure in some patients. • After initiation of Oseni and after dose increases, monitor patients carefully for signs and symptoms of heart failure (e.g., excessive, rapid weight gain, dyspnea and/or edema). If heart failure develops, it should be managed according to current standards of care and discontinuation or dose reduction of pioglitazone in Oseni must be considered. • Oseni is not recommended in patients with symptomatic heart failure. Initiation of Oseni in patients with established New York Heart Association (NYHA) Class III or IV heart failure is contraindicated. Janumet, Janumet XR, Kombiglyze XR, Zituvimet, and Zituvimet XR have the following contraindications:(5,6,9,15) • Severe renal impairment: (eGFR below 30 mL/min/1.73 m^2). • Metabolic acidosis, including diabetic ketoacidosis. • History of a serious hypersensitivity reaction (e.g., anaphylaxis, angioedema, exfoliative skin conditions) to the active ingredients, metformin, or any excipients.

	Jentadueto, Jentadueto XR, and Kazano have the following contraindications:(7,8,10) • Severe renal impairment (eGFR below 30 mL/min/1.73 m^2). • Metabolic acidosis, including diabetic ketoacidosis. • Hypersensitivity to the active ingredients or any of the excipients. Januvia, Nesina, Onglyza, and Tradjenta have the following contraindication:(1-4) • History of serious hypersensitivity to the active ingredient or any of the excipients. Oseni has the following contraindication:(11) • Serious hypersensitivity reaction to alogliptin or pioglitazone, components of Oseni, or any of the excipients. • Do not initiate Oseni in patients with established NYHA Class III or IV heart failure. Zituvio has the following contraindication:(14) • History of a serious hypersensitivity reaction to sitagliptin or any of the excipients in Zituvio, such as anaphylaxis or angioedema.

REFERENCES

Number	Reference
1	Januvia prescribing information. Merck & Co., Inc. July 2022.
2	Nesina prescribing information. Takeda Pharmaceuticals America, Inc. July 2023.
3	Onglyza prescribing information. Astra Zeneca. October 2019.
4	Tradjenta prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. June 2023.
5	Janumet prescribing information. Merck & Co., Inc. July 2022.
6	Janumet XR prescribing information. Merck & Co., Inc. July 2022.

Number	Reference
7	Jentadueto prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. June 2023.
8	Jentadueto XR prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. June 2023.
9	Kombiglyze XR prescribing information. Bristol-Meyers Squibb Company/AstraZeneca Pharmaceuticals LP. October 2019.
10	Kazano prescribing information. Takeda Pharmaceuticals America, Inc. July 2023.
11	Oseni prescribing information. Takeda Pharmaceuticals America, Inc. March 2022.
12	American Diabetes Association. Standards of Medical Care in Diabetes-2022. Available at https://diabetesjournals.org/care/issue/45/Supplement_1.
13	Nuha A. ElSayed, et. al, American Diabetes Association, 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2023. Diabetes Care 1 January 2023; 46 (Supplement_1): S140–S157. https://doi.org/10.2337/dc23-S009.
14	Zituvio prescribing information. Zydus Pharmaceuticals (USA) Inc. October 2023.
15	Zituvimet prescribing information. Zydus Pharmaceuticals (USA) Inc. July 2024.
16	Zituvimet XR prescribing information. Zydus Pharmaceuticals (USA) Inc. July 2024.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR**

Module	Clinical Criteria for Approval
	B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Dry Eye Disease

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Cequa® (cyclosporine) Ophthalmic solution	Increase tear production in patients with keratoconjunctivitis sicca (dry eye)		1
Eysuvis® (loteprednol etabonate) Ophthalmic suspension	Short-term (up to two weeks) treatment for the signs and symptoms of dry eye disease		11
Miebo® (perfluorohexyloctane) Ophthalmic solution	Treatment of the signs and symptoms of dry eye disease		10
Restasis® (cyclosporine)* Ophthalmic emulsion	Indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.	*generic available	2
Tyrvaya® (varenicline) Nasal spray	Treatment of the signs and symptoms of dry eye disease		12

Agent(s)	FDA Indication(s)	Notes	Ref#
Vevye® (cyclosporine) Ophthalmic solution	Treatment of the signs and symptoms of dry eye disease		13
Xiidra® (lifitegrast) Ophthalmic solution	Treatment of the signs and symptoms of dry eye disease		3

CLINICAL RATIONALE

Dry Eye Disease	Dry eye disease (also known as dry eye syndrome) is a multifactorial disease of the ocular surface with loss of homeostasis of the tear film. It is accompanied by ocular symptoms where tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.(6) The tear film secreting glands and ocular surface function as an integrated system. Disease or dysfunction of this system results in unstable and poorly maintained tear film that causes symptoms of ocular irritation and possible damage to the ocular surface. Dry eye disease may be exacerbated by systemic medications (e.g., diuretics, antihistamines, anticholinergics, systemic retinoids, antidepressants) and rosacea.(4) Dry eye disease is often associated with Sjogren syndrome, an autoimmune multisystem disorder that most often affects the tear and salivary glands. Tear deficiency may occur in other systemic diseases, such as lymphoma, sarcoidosis, hemochromatosis, and amyloidosis. Dry eye disease may also develop due to systemic viral infections, such as retroviruses, Epstein-Barr virus, and HIV.(4) The American Academy of Ophthalmology and the Tear Film and Ocular Surface Society (TFOS) categorized dry eye into three severity levels based on both symptoms and signs. Due to the nature of the disease, this classification is imprecise because the characteristics overlap at each level of severity.(4,6,7)

	• Mild dry eye: symptoms of irritation, itching, soreness, ocular discomfort, burning or intermittent blurred vision • Moderate dry eye: increased discomfort and frequency of symptoms, and negative effect on visual function may become more consistent • Severe dry eye: increasing frequency of visual symptoms that may become constant as well as potentially disabling The American Academy of Ophthalmology recommend treating mild dry eye with the following:(4,8) • Education and environmental modifications • Elimination of offending topical or systemic medications • Aqueous enhancement using artificial tear substitutes, gels, or ointment • Eyelid therapy (warm compresses and eyelid scrubs) • Treatment of contributing ocular factors such as blepharitis or meibomianitis • Correction of eyelid abnormality For treatment of moderate dry eye, the following are recommended in addition to mild dry eye treatment options:(4,8) • Topical anti-inflammatory agents (topical cyclosporine and corticosteroids), systemic omega 3 fatty acids supplements • Punctal plugs • Spectacle side shields and moisture chambers For treatment of severe dry eye, the following are recommended in addition to mild and moderate dry eye treatment options:(4,8) • Systemic cholinergic agonists • Mucolytic agents • Autologous serum tears • Therapeutic contact lenses • Surgical punctal occlusion • Tarsorrhaphy Because of the inconsistent correlation between reported symptoms and clinical signs as well as the relatively poor specificity and/or sensitivity of clinical tests,

	patients with suggestive symptoms without signs should be placed on trial treatments with artificial tears when other potential causes of ocular irritation have been eliminated. As the severity of the dry eyes increases, aqueous enhancement of the eye using topical agents is appropriate. Emulsions, gels, and ointments can be used. The use of artificial tears may be increased, but the practicality of frequent tear instillation depends on the lifestyle or manual dexterity of the patient. Non-preserved tear substitutes are generally preferable; however, tears with preservatives may be sufficient for patients with mild dry eye and an otherwise healthy ocular surface. When tear substitutes are used frequently and chronically (e.g., more than 4 times a day), non-preserved tears are generally recommended. It is imperative to treat any causative factors that are amenable to treatment.(4) Anti-inflammatory therapies may be considered in addition to aqueous enhancement therapies. However, since dry eye symptoms tend to wax and wane over long periods of time, the lack of long-term data on the effectiveness of cyclosporine and the costs of longer-term (e.g., annual, lifetime) treatment should be weighed.(4) Pre-treatment with topical ophthalmic corticosteroids either before or during initiation with a non-glucocorticoid anti-inflammatory agent may provide more rapid improvement in symptoms of dry eye disease and decrease the incidence of severe stinging associated with a topical immunomodulator agent compared to a topical immunomodulator alone.(8) The AAO also notes that topical corticosteroid use for dry eye disease is controversial, but use for induction therapy prior to initiating non-glucocorticoid anti-inflammatory agents as maintenance. Once the patient is in a successful maintenance phase, steroids are used for acute flare-ups triggered by travel, allergies, respiratory infections, or exposures to environmental irritants with maintenance therapy.(9) The Sjogren's Syndrome Foundation's Clinical Practice Guidelines on Ocular Management in Sjögren's Patients states the following.(5) • Management depends upon the nature of the dry and the severity of symptoms. • In early disease, tear replacement with topically applied artificial tear or lubricant solutions may be sufficient, but progressive or more severe inflammation of the lacrimal gland and ocular surface occur both as an inciting event in many cases and as a secondary effect as the dry eye disease worsens, called keratoconjunctivitis sicca (KCS), requires the use of dietary supplements (omega 3 essential fatty acids), anti-

	inflammatory measures (e.g., topical corticosteroids or cyclosporine), or oral secretagogues. • Plugging of the lacrimal puncta can be done once the inflammatory component of dry eye is controlled. Control of lid margin (meibomian gland) disease may require topical antibiotic or systemic doxycycline therapy. The most severe cases of dry eye, particularly those unresponsive to more standard therapy, may require use of topical autologous serum or partial closure of the interpalpebral fissure to reduce surface exposure. Scleral contact lenses may be needed to control severe ocular surface damage.
Drops per bottle	Miebo manufacturer notes a smaller than average drop size of 11 uL compared to other aqueous formulations containing water estimated to be approximately 30-50 uL/drop.(14)
Safety	Cequa (cyclosporine), Miebo (perfluorohexyloctane), Tyrvaya (varenicline), and Vevye (cyclosporine) have no FDA labeled contraindications for use.(1,10,12,13) Eysuvis (loteprednol etabonate) is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.(11) Restasis (cyclosporine) is contraindicated in patients with hypersensitivity to any of the ingredients in the formulation.(2) Xiidra (lifitegrast) is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.(3)

REFERENCES

Number	Reference
1	Cequa prescribing information. Sun Pharma Global. December 2022.
2	Restasis prescribing information. Allergan, Inc. July 2017.

Number	Reference
3	Xiidra prescribing information. Shire US, Inc. June 2020.
4	Akpek EK, Amescua G, Farid M, et al. Dry Eye Syndrome Preferred Practice Pattern®. *Ophthalmology*. 2019;126(1):P286-P334. doi:10.1016/j.ophtha.2018.10.023
5	Foulks GN, Forstot SL, Donshik PC, et al. *The Sjögren's Foundation Clinical Practice Guidelines for Ocular Management in Sjögren's*.; 2015. https://sjogrens.org/sites/default/files/inline-files/SF_CPG-Ocular_2022_0.pdf
6	Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. *The Ocular Surface*. 2017;15(3):276-283. doi:10.1016/j.jtos.2017.05.008
7	Wolffsohn JS, Arita R, Chalmers RL, et al. TFOS DEWS II Diagnostic Methodology report. *The Ocular Surface*. 2017;15(3):539-574. doi:10.1016/j.jtos.2017.05.001
8	Jones L, Downie LE, Korb DR, et al. TFOS DEWS II Management and Therapy Report. *The Ocular Surface*. 2017;15(3):575-628. doi:10.1016/j.jtos.2017.05.006
9	Savvy steroid use. American Academy of Ophthalmology. Published May 5, 2016. https://www.aao.org/eyenet/article/savvy-steroid-use
10	Miebo prescribing information. Bausch & Lomb Inc. January 2024.
11	Eysuvis prescribing information. Alcon Laboratories, Inc. November 2023.
12	Tyrvaya prescribing information. Oyster Point Pharma, Inc. February 2024.
13	Vevye prescribing information. Novaliq GmbH. May 2023.
14	The MIEBO experience MIEBO™ (perfluorohexyloctane ophthalmic solution) | Official HCP Site. https://www.miebo-ecp.com/the-miebo-experience/

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Cequa (cyclosporine), Miebo (perfluorohexyloctane), Tyrvaya (varenicline), Vevye (cyclosporine), and Xiidra (lifitegrast)** will be approved when ALL of the following are met: 1. ONE of the following: A. BOTH of the following: 1. The patient has a diagnosis of dry eye disease (i.e., dry eye syndrome, keratoconjunctivitis sicca [e.g., Sjögren's Syndrome]) **AND** 2. ONE of the following: A. The patient has previously tried or is currently using aqueous enhancements (e.g., artificial tears, gels, ointments [target agents not included]) **OR** B. The patient has an intolerance or hypersensitivity to aqueous enhancements **OR** C. The patient has an FDA labeled contraindication to ALL aqueous enhancements **OR** B. The patient has another FDA labeled indication for the requested agent **OR** C. The patient has an indication that is supported in compendia for the requested agent and route of administration **AND** 2. The patient will NOT be using the requested agent in combination with Verkazia (cyclosporine) or another target agent in this program (e.g., Cequa, Eysuvis, Miebo, Restasis, Tyrvaya, Vevye, Xiidra) **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence **Length of Approval:** Miebo (perfluorohexyloctane) and Tyrvaya (varenicline) - 2 months; Cequa (cyclosporine), Vevye (cyclosporine), Xiidra (lifitegrast) - 3 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Initial Evaluation** **Eysuvis (loteprednol etabonate)** will be approved when ALL of the following are met: 1. ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient has a diagnosis of dry eye disease (i.e., dry eye syndrome, keratoconjunctivitis sicca [e.g., Sjögren's Syndrome]) AND ONE of the following: 1. The patient has NOT been previously treated with the requested agent AND ONE of the following: A. The patient has tried and had an inadequate response to at least ONE generic ophthalmic corticosteroid **OR** B. The patient has an intolerance or hypersensitivity to therapy with generic ophthalmic corticosteroids that is not expected to occur with the requested agent **OR** C. The patient has an FDA labeled contraindication to ALL generic ophthalmic corticosteroids that is not expected to occur with the requested agent **OR** 2. The patient has been previously treated with the requested agent AND ALL of the following: A. ONE of the following: 1. The patient has tried and had an inadequate response to at least ONE generic ophthalmic corticosteroid **OR** 2. The patient has an intolerance or hypersensitivity to therapy with generic ophthalmic corticosteroids that is not expected to occur with the requested agent **OR** 3. The patient has an FDA labeled contraindication to ALL generic ophthalmic corticosteroids that is not expected to occur with the requested agent **AND** B. The patient has had clinical benefit with the requested agent **AND** C. The patient's eyes have been examined under magnification (e.g., slit lamp), and the intraocular pressure has been evaluated **OR** B. The patient has another FDA labeled indication for the requested agent **OR** C. The patient has an indication that is supported in compendia for the requested agent and route of administration **AND** 2. The patient will NOT be using the requested agent in combination with Verkazia (cyclosporine) or another target agent in this program (e.g., Cequa, Eysuvis, Miebo, Restasis, Tyrvaya, Vevye, Xiidra) **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence **Length of Approval:** 3 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Clinical Criteria for Approval
	Initial Evaluation **Restasis (cyclosporine ophthalmic emulsion)** will be approved when ALL of the following are met: 1. ONE of the following: A. ALL of the following: 1. The patient has a diagnosis of dry eye disease (i.e., dry eye syndrome, keratoconjunctivitis sicca [e.g., Sjögren's Syndrome]) **AND** 2. The patient will NOT be using the requested agent in combination with punctal plug(s) **AND** 3. ONE of the following: A. The patient has previously tried or is currently using aqueous enhancements (e.g., artificial tears, gels, ointments [target agents not included]) **OR** B. The patient has an intolerance or hypersensitivity to aqueous enhancements **OR** C. The patient has an FDA labeled contraindication to ALL aqueous enhancements **OR** B. The patient has another FDA labeled indication for the requested agent **OR** C. The patient has an indication that is supported in compendia for the requested agent and route of administration **AND** 2. The patient will NOT be using the requested agent in combination with Verkazia (cyclosporine) or another target agent in this program (e.g., Cequa, Eysuvis, Miebo, Restasis, Tyrvaya, Vevye, Xiidra) **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence **Length of Approval:** 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met:

Module	Clinical Criteria for Approval
	1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The patient will NOT be using the requested agent in combination with Verkazia (cyclosporine) or another target agent in this program (e.g., Cequa, Eysuvis, Miebo, Restasis, Tyrvaya, Vevye, Xiidra) **AND** 4. If the requested agent is Eysuvis (loteprednol etabonate), the patient's eyes have been examined under magnification (e.g., slit lamp), and the intraocular pressure has been evaluated **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** Eysuvis (loteprednol etabonate) - 3 months, all other agents - 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Erectile Dysfunction - Phosphodiesterase Type 5 Inhibitors, Topical Prostaglandin

Quantity Limit

ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
40304090107230		Vardenafil HCl Orally Disintegrating Tab 10 MG	10 MG	Quantity of 30 tablets per month is cumulative for Cialis/tadalafil 2.5 mg and 5 mg. All agents (except for Cialis/tadalafil 2.5 mg and 5 mg) are limited to 6 doses per month. The quantity of 6 doses per month is cumulative.			
40304090100310		Vardenafil HCl Tab 2.5 MG	2.5 MG	Quantity of 30 tablets per month is cumulative for Cialis/tadalafil 2.5 mg and 5 mg. All agents (except for Cialis/tadalafil 2.5 mg and 5 mg) are limited to 6 doses per month. The quantity of 6 doses per month is cumulative.			
40304090100320		Vardenafil HCl Tab 5 MG	5 MG	Quantity of 30 tablets per month is cumulative for Cialis/tadalafil 2.5 mg and 5 mg. All agents (except for Cialis/tadalafil 2.5 mg and 5 mg) are limited to 6 doses per month.			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
				The quantity of 6 doses per month is cumulative.			
40304080000310	Cialis	Tadalafil Tab 10 MG	10 MG	Quantity of 30 tablets per month is cumulative for Cialis/tadalafil 2.5 mg and 5 mg. All agents (except for Cialis/tadalafil 2.5 mg and 5 mg) are limited to 6 doses per month. The quantity of 6 doses per month is cumulative.			
40304080000302	Cialis	Tadalafil Tab 2.5 MG	2.5 MG	Quantity of 30 tablets per month is cumulative for Cialis/tadalafil 2.5 mg and 5 mg. All agents (except for Cialis/tadalafil 2.5 mg and 5 mg) are limited to 6 doses per month. The quantity of 6 doses per month is cumulative.			
40304080000320	Cialis	Tadalafil Tab 20 MG	20 MG	Quantity of 30 tablets per month is cumulative for Cialis/tadalafil 2.5 mg and 5 mg. All agents (except for Cialis/tadalafil 2.5 mg and 5 mg) are limited to 6 doses per month. The quantity of 6 doses per month is cumulative.			
40304080000305	Cialis	Tadalafil Tab 5 MG	5 MG	Quantity of 30 tablets per month is cumulative for Cialis/tadalafil 2.5 mg and 5 mg. All agents (except for Cialis/tadalafil 2.5 mg and 5 mg) are limited to 6 doses per month.			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
				The quantity of 6 doses per month is cumulative.			
40304090100330	Levitra	Vardenafil HCl Tab 10 MG	10 MG	Quantity of 30 tablets per month is cumulative for Cialis/tadalafil 2.5 mg and 5 mg. All agents (except for Cialis/tadalafil 2.5 mg and 5 mg) are limited to 6 doses per month. The quantity of 6 doses per month is cumulative.			
40304090100340	Levitra	Vardenafil HCl Tab 20 MG	20 MG	Quantity of 30 tablets per month is cumulative for Cialis/tadalafil 2.5 mg and 5 mg. All agents (except for Cialis/tadalafil 2.5 mg and 5 mg) are limited to 6 doses per month. The quantity of 6 doses per month is cumulative.			
40304070100330	Viagra	Sildenafil Citrate Tab 100 MG	100 MG	Quantity of 30 tablets per month is cumulative for Cialis/tadalafil 2.5 mg and 5 mg. All agents (except for Cialis/tadalafil 2.5 mg and 5 mg) are limited to 6 doses per month. The quantity of 6 doses per month is cumulative.			
40304070100310	Viagra	Sildenafil Citrate Tab 25 MG	25 MG	Quantity of 30 tablets per month is cumulative for Cialis/tadalafil 2.5 mg and 5 mg. All agents (except for Cialis/tadalafil 2.5 mg and 5 mg) are limited to 6 doses per month.			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
				The quantity of 6 doses per month is cumulative.			
40304070100320	Viagra	Sildenafil Citrate Tab 50 MG	50 MG	Quantity of 30 tablets per month is cumulative for Cialis/tadalafil 2.5 mg and 5 mg. All agents (except for Cialis/tadalafil 2.5 mg and 5 mg) are limited to 6 doses per month. The quantity of 6 doses per month is cumulative.			

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL	**Quantity Limit for the Target Agent(s)** will be approved when ALL of the following are met: 1. The patient will NOT be using the requested agent in combination with another phosphodiesterase type 5 (PDE5) inhibitor for the requested indication **AND** 2. The requested agent has been prescribed for preservation of erectile function following radical retropubic prostatectomy **AND** 3. The quantity requested is less than or equal to 30 tablets per month **Length of Approval:** Preservation of erectile function following a radical retropubic prostatectomy: 30 tablets per month for 12 months

Egrifta (tesamorelin)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Egrifta SV® (tesamorelin) Subcutaneous injection	Reduction of excess abdominal fat in HIV-infected adult patients with lipodystrophy Limitations of Use: • Long-term cardiovascular safety of EGRIFTA SV has not been established. Consider risk/benefit of continuation of treatment in patients who have not had a reduction in visceral adipose tissue. • EGRIFTA SV is not indicated for weight loss management as it has a weight neutral effect. • There are no data to support improved compliance with anti-retroviral therapies in HIV-positive patients taking EGRIFTA SV.		1

CLINICAL RATIONALE

Overview	Patients with human immunodeficiency virus infection (HIV) treated with antiretroviral therapy (ART) often demonstrate lipodystrophy, abnormal fat distribution. These patients commonly have accumulation of fat in the abdomen and an increase in visceral adipose tissue (VAT).(3,6,7) Multiple classes of ART have been associated with VAT accumulation, with clinically visible changes showing at least 1-2 years after initiation, and HIV infection may intrinsically promote adipose tissue inflammation despite virologic suppression.(5,7) An increase in VAT has been associated with cardiovascular disease, dyslipidemia, insulin resistance, neurocognitive dysfunction, metabolic syndrome, and inflammatory consequences.(3,5,6,7) Due to the efficacy of modern ART, persons living with human immunodeficiency virus infection (PLWH) are living longer and non-AIDS events are the leading cause of morbidity and mortality.(5,7) Increased waist circumference (WC) secondary to VAT accumulation can have a negative impact on body image, ART adherence, and

	quality of life.(3,6,7) Lifestyle changes (i.e., exercise, diet) may be helpful in the management of lipohypertrophy, with exercise reducing abdominal obesity in most studies of PLWH, as well as growth hormone axis therapy. An association exists between an increase in VAT and a decrease in growth hormone (GH) secretion, which can be attributed to the lipolytic effects of GH.(7)
Efficacy	Tesamorelin is a growth hormone-releasing factor (GHRF) analog that acts on the anterior pituitary gland to increase endogenous GH release.(5,7) At an End of Phase 2 (EOP2) meeting on March 30, 2005, the FDA agreed that a decrease in VAT of 8-10% would be an acceptable endpoint for the phase III clinical trials for tesamorelin due to the clinically meaningful improvement in body self image it could provide, and did not require evidence of CV risk reduction associated with VAT changes. Egrifta was eventually approved by the FDA in November 2010 with testimonials from the patient and medical community as well as the absence of an approved therapy for this condition weighing in on the decision.(2) The clinical evidence for the efficacy of tesamorelin was derived from 2 randomized, double-blind, placebo-controlled studies conducted in HIV-infected patients with lipodystrophy and excess abdominal fat (abdominal lipohypertrophy). Both studies (Study 1 and Study 2) consisted of a 26-week Main Phase and a 26-week Extension Phase. Main inclusion criteria were age 18 to 65 years, a waist circumference greater than or equal to 95 cm (37.4 inches) and a waist-to-hip ratio greater than or equal to 0.94 for men and greater than or equal to 94 cm (37.0 inches) and greater than or equal to 0.88 for women, respectively. Patients were on a stable anti-retroviral regimen for at least 8 weeks prior to randomization. Patients meeting the inclusion/exclusion criteria were randomized in a 2:1 ratio to receive a 2 mg dose of Egrifta (1 mg/vial formulation) or placebo subcutaneously daily for 26 weeks. The primary efficacy assessment for each of these studies was the percent change from baseline to Week 26 in visceral adipose tissue (VAT). Secondary endpoints included changes from baseline in triglycerides, ratio of total cholesterol to HDL cholesterol, IGF-1 levels, patient-reported outcomes related to body image, and safety parameters. Other endpoints included changes from baseline in waist circumference, abdominal subcutaneous tissue (SAT), trunk fat, and lean body mass. In both studies, Egrifta-treated patients completing the 26-week treatment period were re-randomized to blinded therapy with either daily placebo or a 2 mg dose of Egrifta for an additional 26-week treatment period (Extension Phase) in order to assess maintenance of VAT reduction and to gather long-term safety data.(1) Study 1 randomized 412 HIV-infected patients with lipodystrophy and excess abdominal fat to receive either tesamorelin (n = 273) or placebo (n = 137). At baseline for the two groups combined, mean waist circumference was 104 cm

	and mean VAT was 176 cm^2. The twenty-six week completion rate in Study 1 was 80%. The percent change from baseline to week 26 in VAT was significantly greater in the tesamorelin group, which had a decrease of 27cm^2 (-18% mean change), as compared with an increase of 4 cm^2 (2% mean change) in the placebo group. The percent change from week 26 to week 52 in VAT was significantly greater in the tesamorelin treated group, which had an increase of 3 cm^2 (0%), as compared with an increase of 25 cm^2 (22%) in the placebo group. Waist circumference in the treatment group decreased 3 cm from baseline to week 26 versus a 1 cm decrease in the placebo group. From weeks 26 to 52, the treatment group waist circumference decreased 0.2 cm while increasing 2.4 cm in the placebo group.(1) Patients treated with tesamorelin during the main and extension phase maintained VAT loss over the 52-week treatment period (-18.1%, p less than 0.001 versus baseline). Patients who were randomized to the placebo group for the extension phase regained VAT lost at week 26 (-1.6%, p = 0.19 versus baseline) and gained back most of the VAT lost by week 39 of treatment.(6) Study 2 randomized 404 HIV-infected patients with lipodystrophy and excess abdominal fat to receive either tesamorelin (n = 270) or placebo (n = 126). At baseline for the two groups combined, mean waist circumference was 105 cm and mean VAT was 189 cm^2. The twenty-six week completion rate in Study 2 was 74%. The percent change from baseline to week 26 in VAT was significantly greater in the tesamorelin group, which had a decrease of 21 cm^2 (-14% mean change), as compared with a decrease of 0 cm^2 (-2% mean change) in the placebo group. In the extension phase, the percent change from week 26 to week 52 in VAT was significantly greater in the tesamorelin group, which had a decrease of 11 cm^2 (-5% mean change), as compared with an increase of 24 cm^2 (16% mean change) in the placebo group. Waist circumference in the treatment group decreased 2 cm from baseline to week 26 versus a 1 cm decrease in in the placebo group. From weeks 26 to 52, the treatment group waist circumference decreased 1.1 cm while increasing 0.2 cm in placebo group.(1) Patients treated with tesamorelin during the main and extension phase maintained VAT loss over the 52-week treatment period (-17.5%, p less than 0.001 versus baseline). Patients who were randomized to the placebo group for the extension phase regained VAT lost at week 26 (-1.3%, p = 0.432 versus baseline), indicating improvement in VAT in this group was not sustained after treatment discontinuation.(3) A post hoc analysis of the two studies compared tesamorelin non-responders to responders (defined as those with greater than or equal to 8% reduction in VAT) for reduction in triglyceride levels and glucose homeostasis. The study reported that compared to non-responders, HIV-infected patients who responded to

	tesamorelin have significantly improved triglyceride levels, adiponectin levels, and preservation of glucose homeostasis over 52 weeks. This suggests reducing VAT is associated with metabolic benefits in this patient population.(4) A 2017 consensus opinion on the treatment of excess adiposity in adults with treated HIV infection recommends measuring waist circumference (WC) after 6 months of treatment as a VAT surrogate. Any reduction in waist circumference may represent a meaningful reduction in VAT when interpreted alongside other patient specific factors (e.g., patient well-being, quality of abdominal fat, and change in glucose and lipid parameters). Patients who do not achieve WC reduction after 6 months of treatment should consider discontinuation.(7)
Safety	Tesamorelin is contraindicated in the following:(1) • Patients with disruption of the hypothalamic-pituitary axis due to hypophysectomy, hypopituitarism, pituitary tumor/surgery, head irradiation, or head trauma • Patients with active malignancy (either newly diagnosed or recurrent) • Patients with a known hypersensitivity to tesamorelin or any of the agent's excipients • Pregnant women

REFERENCES

Number	Reference
1	Egrifta SV prescribing information. Theratechnologies Inc. February 2024.
2	Egrifta FDA Review. Center for Drug Evaluation and Research. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022505Orig1s000SumR.pdf
3	Falutz J, Potvin D, Mamputu JC, et al. Effects of Tesamorelin, a Growth Hormone–Releasing Factor, in HIV-Infected Patients With Abdominal Fat Accumulation: A Randomized Placebo-Controlled Trial With a Safety Extension. *J Acquir Immune Defic Syndr*. 2010;53(3):311-322. doi:10.1097/qai.0b013e3181cbdaff
4	Stanley T, Falutz J, Marsolais C, et al. Reduction in visceral adiposity is associated with an improved metabolic profile in HIV-Infected patients receiving tesamorelin. *Clinical Infectious Diseases*. 2012;54(11):1642-1651. Doi:10.1093/cid/cis251

Number	Reference
5	Adrian S, Scherzinger A, Sanyal A, et al. The Growth Hormone Releasing Hormone Analogue, Tesamorelin, Decreases Muscle Fat and Increases Muscle Area in Adults with HIV. *J Frailty Aging*. 2019;8(3):154-159. doi:10.14283/jfa.2018.45
6	Falutz J, Allas S, Mamputu JC, et al. Long-term safety and effects of tesamorelin, a growth hormone-releasing factor analogue, in HIV patients with abdominal fat accumulation. AIDS. 2008;22(14):1719-1728. doi:10.1097/qad.0b013e32830a5058
7	Lake JE, Stanley T, Apovian CM, et al. Practical review of recognition and management of obesity and lipohypertrophy in human immunodeficiency virus infection. *Clinical Infectious Diseases*. 2017;64(10):1422-1429. Doi:10.1093/cid/cix178

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of human immunodeficiency virus (HIV) infection **AND** 2. The requested agent is being prescribed to reduce excess abdominal fat in HIV-associated lipodystrophy **AND** 3. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 4. The prescriber has measured and recorded baseline (prior to therapy with the requested agent) visceral adipose tissue (VAT) and waist circumference **AND** 5. The patient is currently being treated with antiretroviral therapy (ART) **AND** 6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., infectious disease, HIV specialist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent

Module	Clinical Criteria for Approval
	Length of Approval: 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient is currently being treated with antiretroviral therapy (ART) **AND** 3. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following: A. The patient has achieved or maintained an 8% decrease in visceral adipose tissue (VAT) from baseline (prior to therapy with the requested agent) **OR** B. The patient has maintained or had a decrease in their waist circumference from baseline (prior to therapy with the requested agent) **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., infectious disease, HIV specialist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months

Elagolix/Relugolix

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Myfembree® (relugolix, estradiol hemihydrate, norethindrone acetate) Tablet	Management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal patients Management of moderate to severe pain associated with endometriosis in premenopausal patients Limitations of Use: Use of Myfembree should be limited to 24 months due to the risk of continued bone loss which may not be reversible.		3
Oriahnn® (elagolix, estradiol, norethindrone acetate) Capsule	Management of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) in premenopausal patients Limitations of Use: Use of Oriahnn should be limited to 24 months due to the risk of continued bone loss, which may not be reversible.		2
Orilissa® (elagolix) Tablet	Management of moderate to severe pain associated with endometriosis Limitations of Use: Limit the duration of use based on the dose and coexisting condition (refer to labeling for additional details).		1

CLINICAL RATIONALE

Endometriosis	Endometriosis is an estrogen-dependent, benign, inflammatory disease that affects patients during their premenarcheal, reproductive, and postmenopausal hormonal stages. While endometriosis is a common and nonmalignant process, ectopic endometrial tissue and resultant inflammation can cause dysmenorrhea, dyspareunia, chronic pain, and infertility. Symptoms can range from minimal to severely debilitating. While definitive diagnosis of endometriosis requires tissue

	biopsy and histologic confirmation, the combination of symptoms, signs, and imaging findings can be used to make a presumptive, nonsurgical diagnosis of endometriosis.(4,5) The first line option for the treatment of mild and moderate pain associated with endometriosis is hormonal contraceptives as combined (oral, vaginal ring or transdermal), oral progestin-only, levonorgestrel-releasing intrauterine system, or an etonogestrel-releasing subdermal implant as this therapy has low risk with few side effects and provides symptom relief for many patients. For those who have severe pain or continue to experience symptoms on hormonal contraceptive therapy, the use of gonadotropin-releasing hormone (GnRH) antagonists is recommended as second-line (e.g., if hormonal contraceptives or progestins have been ineffective). Patients who do not respond to medical treatment may move on to laparoscopy or hysterectomy for treatment.(5,12)
Uterine Leiomyomas	Uterine Leiomyomas, also known as myomata or fibroids, are the most common gynecologic benign tumors. Uterine leiomyomas are classified based on their location in the uterine wall and are referred to as submucous, intramural, and subserosal. Uterine leiomyomas are monoclonal tumors that arise from the muscular layer of the uterus and consist of large amounts of collagen, fibronectin, and proteoglycan. Leiomyomas can become enlarged causing significant distortion of the uterine surface or cavity.(6,7) Many patients with uterine leiomyomas are asymptomatic, but symptomatic patients may experience significant symptoms that interfere with daily living. The clinical characteristics can be broken down into three categories:(6) • Heavy or abnormal uterine bleeding (the most common symptom) • Pelvic pressure and pain • Reproductive dysfunction (i.e., infertility, miscarriages, preterm labor) Uterine leiomyomas are generally diagnosed via pelvic examination and pelvic ultrasound. Other imagining, such as saline-infused sonogram, MRI, and hysteroscopy, are used if further evaluation of the leiomyomas is needed.(8,9) Hysterectomy is the only definitive treatment and eliminates the possibility of recurrence for patients who do not desire future childbearing or do not wish to retain their uterus. The American College of Gynecology and Obstetrics indicates the following are alternative options to hysterectomy:(9) • Hormonal contraceptives (combined hormonal contraceptive pills, progestin-only pills, levonorgestrel releasing IUDs) are widely used for control of abnormal menstruation and are often first line therapy,

	however, they only offer short term relief and direct data to support their effectiveness is limited • Tranexamic acid, an antifibrinolytic medication that prevents fibrin degradation, is an effective treatment for heavy menstrual bleeding, but limited data is associated with a statistically significant decrease in abnormal uterine bleeding • Gonadotropin releasing hormone antagonists, with hormonal add-back therapy, are recommended for treatment of heavy menstrual bleeding associated with uterine leiomyomas for up to two years • Gonadotropin releasing hormone agonists, with or without hormonal add-back therapy are recommended for the short-term treatment of abnormal uterine bleeding and uterine enlargement associated with leiomyomas and as a bridge to other treatment strategies • Uterine artery embolization, laparoscopic radiofrequency ablation, or myomectomy are alternatives for patients who desire uterine preservation and are counseled about the limited available data on reproductive outcomes
Efficacy	**Myfembree(3)** The efficacy and safety of Myfembree in patients with heavy menstrual bleeding associated with uterine fibroids were evaluated in two replicate, 24-week, multinational, randomized, double-blind, placebo-controlled studies in a total of 768 premenopausal patients with heavy menstrual bleeding associated with uterine fibroids in Study L1 (NCT03049735) and Study L2 (NCT03103087). For study inclusion, patients had to have uterine fibroids confirmed by ultrasound examination, and menstrual blood loss (MBL) volume of greater than or equal to 80 mL per cycle for two menstrual cycles or greater than or equal to 160 mL during one cycle to be included in the studies. Patients with hemoglobin less than 8.0 g/dL were excluded from the study. Iron therapy was required for patients with hemoglobin greater than or equal to 8 g/dL and less than or equal to 10 g/dL. Patients were allowed, but not required, to take calcium and vitamin D during the study. Treatment was initiated within the first seven days after the onset of menses. The primary endpoint of both studies was the proportion of patients in the Myfembree group compared with patients in the placebo group, who achieved menstrual blood loss volume of less than 80 mL and at least a 50% reduction from baseline MBL volume over the last 35 days of treatment. Key secondary endpoints were related to amenorrhea, MBL volume, and change in hemoglobin. In both Study L1 and Study L2, a statistically higher proportion of patients treated

	with Myfembree achieved the primary endpoint of both an MBL volume of less than 80 mL and at least a 50% reduction from baseline in MBL volume over the last 35 days of treatment compared with placebo. In Studies L1 and L2, 50.0% and 50.4% of patients treated with Myfembree, respectively, achieved amenorrhea compared to 6.2% and 3.1% treated with placebo, respectively, over the last 35 days of treatment. The mean MBL volumes in Studies L1 and L2 at baseline were 243.8 mL and 246.7 mL in the Myfembree group and 223.2 mL and 211.8 mL in the placebo group, respectively. The mean reduction in MBL volume from baseline to Week 24 in the Myfembree group was 82.0% in Study L1 and 84.3% in Study L2, compared with placebo which was 19.1% and 15.1%, respectively. A hemoglobin response was defined as a hemoglobin increase greater than 2 g/dL from baseline to Week 24 in the subgroup of patients with anemia at baseline (hemoglobin less than or equal to 10.5 g/dL). A statistically higher proportion treated with Myfembree compared with placebo had greater than 2 g/dL improvement in hemoglobin levels. The efficacy of Myfembree in premenopausal patients with moderate to severe pain associated with endometriosis was assessed in two 24-week, multinational, randomized, double-blind, placebo-controlled studies; Study S1 (NCT03204318) and Study S2 (NCT03204331). Study S1 included at total of 424 patients and Study S2 a total of 405. For study inclusion, patients had to have endometriosis confirmed by direct visualization during surgery and/or histology in addition to pain associated with endometriosis during a placebo run-in period. Dysmenorrhea (DYS) and non-menstrual pelvic pain (NMPP) were assessed daily using an 11-point numerical rating scale (NRS) ranging from 0 ("no pain") to 10 ("pain as bad as you can imagine"). The co-primary endpoints of studies S1 and S2 were dysmenorrhea and non-menstrual pelvic pain response. Participants in Study S1 showed a 47.6% difference from placebo in dysmenorrhea response and a 18.9% difference in non-menstrual pelvic pain response at week 24, and Study S2 showed differences of 44.6% and 23.4%, respectively. **Orilissa(1,11)** The efficacy of Orilissa 150 mg once daily and 200 mg twice daily for the management of moderate to severe pain associated with endometriosis was demonstrated in two multinational double-blind, placebo-controlled trials in 1686 premenopausal patients (Study EM-1 [NCT01620528] and Study EM-2 [NCT01931670]). Each placebo-controlled trial assessed the reduction in moderate to severe endometriosis-associated pain over 6 months of treatment. Each element is scored from 0 (absent) to 3 (severe) for a maximum total score of 15. Subjects were required to have non-menstrual pelvic pain for at least four days in the preceding 35 days, a bone mineral density (BMD) greater then -1.5,

	and the diagnosis of endometriosis was surgically confirmed. Patients were excluded if they had clinically significant gynecologic conditions (e.g., persistent or complex ovarian cyst(s), cancer, pelvic inflammatory disease), a history of osteoporosis, or other metabolic bone disease. The co-primary efficacy endpoints were (1) the proportion of subjects whose dysmenorrhea responded to treatment at Month 3 and (2) the proportion of subjects whose pelvic pain not related to menses (also known as non-menstrual pelvic pain) responded to treatment at Month 3. A higher proportion of patients treated with Orilissa 150 mg once daily or 200 mg twice daily were responders for dysmenorrhea and non-menstrual pelvic pain compared to placebo in a dose-dependent manner at Month 3. Patients in these studies also provided a daily self-assessment of their endometriosis pain using a numeric rating scale (NRS) that asked subjects to rate their endometriosis pain at its worst over the last 24 hours on a scale from 0 (no pain) to 10 (worst pain ever). In Study EM-1, baseline NRS scores were 5.7 for Orilissa 150 mg once daily, 5.5 for Orilissa 200 mg twice daily and 5.6 for placebo. In Study EM-2, baseline NRS scores were 5.7 for Orilissa 150 mg once daily, 5.3 for Orilissa 200 mg twice daily and 5.6 for placebo. Patients taking Orilissa 150 mg once daily and 200 mg twice daily reported a statistically ($p<0.001$) significant reduction from baseline in NRS scores compared to placebo at Month 3 in both Studies EM-1 and EM-2 (Study EM-1: 0.7 points for Orilissa 150 mg once daily and 1.3 points for Orilissa 200 mg twice daily; Study EM-2: 0.6 points for Orilissa 150 mg once daily and 1.2 points for Orilissa 200 mg twice daily). In addition, both Orilissa treatment groups showed statistically significantly greater mean decreases from baseline compared to placebo in dysmenorrhea and non-menstrual pelvic pain scores at Month 6. **Oriahnn(2,10)** The efficacy of Oriahnn in the management of heavy menstrual bleeding (HMB) associated with uterine fibroids was demonstrated in two randomized, double-blind, placebo-controlled studies (Study UF-1 [NCT02654054] and Study UF-2 [NCT02691494]) in which 790 premenopausal patients with heavy menstrual bleeding received Oriahnn (elagolix 300 mg, estradiol 1 mg, and norethindrone acetate 0.5 mg in the morning and elagolix 300 mg in the evening) or placebo for 6 months. Patients were eligible if they were premenopausal females, had ultrasound confirmed diagnosis of uterine fibroids with heavy bleeding. Heavy menstrual bleeding at baseline was defined as having at least two menstrual cycles with greater than 80 mL of menstrual blood loss (MBL) as assessed by alkaline hematin (AH) method (an objective, validated measure to quantify MBL

volume on sanitary products). Eligible patients were required to complete a washout period if previously treated with hormonal/antihormonal therapies. Patients were excluded if they had persistent or complex ovarian cyst(s), cancer, pelvic inflammatory disease, history of osteoporosis, or a bone mineral density (BMD) T score of -1.5 or less.

The primary endpoint in both studies was the proportion of responders, defined as patients who achieved both 1) MBL volume less than 80 mL at the Final Month and 2) 50% or greater reduction in MBL volume from baseline to the final month. A higher proportion of Oriahnn-treated patients were responders compared to placebo-treated patients.

	Study UF-1		Study UF-2	
	Oriahnn N=206	Placebo N=102	Oriahnn N=189	Placebo N=94
Patients with MBL volume less than 80 mL and greater than or equal to 50% reduction in MBL volume from Baseline to the Final Month	68.5%	8.7%	76.5%	10.5%
Difference from placebo % 95% CI P-value	59.8% (51.1, 68.5) less than 0.001		66.0% (57.1, 75.0) less than 0.001	

In Study UF-1, mean baseline MBL was 238 mL for Oriahnn and 255 mL for placebo. In Study UF-2, mean baseline MBL was 228 mL for Oriahnn and 254 mL for placebo. Patients taking Oriahnn had a mean reduction of MBL volume from Baseline to Final Month in both Studies UF-1 and UF-2 compared to patients taking placebo (Study UF-1: -177 mL for Oriahnn and 1 mL for placebo; Study UF-

	2: -169 mL for Oriahnn and -4 mL for placebo). In Studies UF-1 and UF-2, a greater proportion (57% and 61%, respectively) of patients receiving Oriahnn experienced suppression of bleeding, defined as no bleeding (but spotting allowed), at Final Month, compared to 4% and 5%, respectively, of patients receiving placebo. In Studies UF-1 and UF-2, a greater proportion of Oriahnn-treated patients who were anemic with baseline Hgb less than or equal to 0.5 g/dL achieved an increase greater than 2 g/dL in Hgb from Baseline to Month 6 compared to placebo-treated patients. Over 90% of patients with baseline Hgb less than or equal to 10.5 g/dL took supplemental iron.

Safety	Myfembree has the following boxed warnings:(3)
	
	• Estrogen and progestin combinations, including Myfembree, increase the risk of thrombotic or thromboembolic disorders including pulmonary embolism (PE), deep vein thrombosis (DVT), stroke and myocardial infarction (MI), especially in patients at increased risk for these events.
	• Myfembree is contraindicated in patients with current or a history of thrombotic or thromboembolic disorders and in patients at increased risk for these events, including patients over 35 years of age who smoke or patients with uncontrolled hypertension.
	
	Myfembree is contraindicated in patients:(3)
	
	• With a high risk of arterial, venous thrombotic, or thromboembolic disorders. Examples include patients over 35 years of age who smoke, and patients who are known to have:
	  ○ current or history of deep vein thrombosis or pulmonary embolism
	  ○ vascular disease (e.g., cerebrovascular disease, coronary artery disease, peripheral vascular disease)
	  ○ thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation)
	  ○ inherited or acquired hypercoagulopathies
	  ○ uncontrolled hypertension
	  ○ headaches with focal neurological symptoms or migraine headaches with aura if over 35 years of age
	
	• Who are pregnant. Exposure to Myfembree early in pregnancy may increase the risk of early pregnancy loss
	• With known osteoporosis, because of the risk of further bone loss

	• With current or history of breast cancer or other hormone-sensitive malignancies, and with increased risk for hormone-sensitive malignancies
	• With known hepatic impairment or disease
	• With undiagnosed abnormal uterine bleeding
	• With known anaphylactic reaction, angioedema, or hypersensitivity to Myfembree or any of its components. Anaphylactoid reactions have been reported.
	
	Orilissa has the following contraindications:(1)
	
	• Pregnancy
	• Known osteoporosis
	• Severe hepatic impairment
	• Organic anion transporting polypeptide (OATP) 1B1 that significantly increase elagolix plasma concentrations
	• Hypersensitivity reactions
	
	Oriahnn has the following boxed warnings:(2)
	
	• Estrogen and progestin combinations, including Oriahnn, increase the risk of thrombotic or thromboembolic disorders including pulmonary embolism, deep vein thrombosis, stroke and myocardial infarction, especially in patients at increased risk for these events.
	• Oriahnn is contraindicated in patients with current or a history of thrombotic or thromboembolic disorders and in patients at increased risk for these events, including patients over 35 years of age who smoke and patients with uncontrolled hypertension.
	
	Oriahnn is contraindicated in patients:(2)
	
	• With a high risk of arterial, venous thrombotic, or thromboembolic disorders. Examples include patients over 35 years of age who smoke, and patients who are known to have:
	  ○ current or history of deep vein thrombosis or pulmonary embolism
	  ○ vascular disease (e.g., cerebrovascular disease, coronary artery disease, peripheral vascular disease)
	  ○ thrombogenic valvular or thrombogenic rhythm diseases of the heart (for example, subacute bacterial endocarditis with valvular disease, or atrial fibrillation)
	  ○ inherited or acquired hypercoagulopathies

	○ uncontrolled hypertension ○ headaches with focal neurological symptoms or have migraine headaches with aura if over age 35 • Who are pregnant. Exposure to Oriahnn early in pregnancy may increase the risk of early pregnancy loss • With known osteoporosis because of the risk of further bone loss • With current or history of breast cancer or other hormonally-sensitive malignancies, and with increased risk for hormonally-sensitive malignancies • With known hepatic impairment or disease • With undiagnosed abnormal uterine bleeding • With known anaphylactic reaction, angioedema, or hypersensitivity to Oriahnn or any of its components • Taking inhibitors of organic anion transporting polypeptide (OATP)1B1 (a hepatic uptake transporter) that are known or expected to significantly increase elagolix plasma concentrations Elagolix causes a dose-dependent decrease in bone mineral density (BMD). BMD is greater with increasing duration of use and may not be completely reversible after stopping treatment. The impact of these BMD decreases on long-term bone health and future fracture risk are unknown. Consider assessment of BMD in patients with a history of a low-trauma fracture or other risk factors for osteoporosis or bone loss, and do not use in patients with known osteoporosis.(1)

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Number	Reference
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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Myfembree	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient has a diagnosis of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) and BOTH of the following: 1. The patient's diagnosis of uterine fibroids was confirmed via imaging (e.g., ultrasound) **AND** 2. The patient has NOT had a hysterectomy **OR** B. The patient has a diagnosis of moderate to severe pain associated with endometriosis **AND** 2. The patient is premenopausal (e.g., less than 12 months since last menstrual period) **AND** 3. The patient's bone health has been assessed AND allows for initiating therapy with the requested agent **AND** 4. ONE of the following: A. The patient has tried and had an inadequate response to at least ONE hormonal contraceptive used in the treatment of the requested indication **OR** B. The patient has an intolerance or hypersensitivity to at least ONE hormonal contraceptive used in the treatment of the requested indication **OR** C. The patient has an FDA labeled contraindication to ALL hormonal contraceptive therapies (i.e., oral, topical patches, implants, injections, IUD) used in the treatment of the requested indication **AND** 5. The patient will NOT be using the requested agent in combination with another GnRH antagonist agent targeted in this program (e.g., elagolix, relugolix) for the requested indication **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 7. ONE of the following: A. The patient is initiating therapy with the requested agent **OR** B. The patient is not initiating therapy with the requested agent and BOTH of the following: 1. There is support confirming the number of months the patient has been on therapy **AND** 2. The total duration of treatment with the requested agent has NOT exceeded 24 months per lifetime **Length of Approval:** up to 6 months, with a lifetime maximum of 24 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met:

Module	Clinical Criteria for Approval
	1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient is premenopausal (e.g., less than 12 months since last menstrual period) **AND** 3. The patient has had clinical benefit with the requested agent **AND** 4. The patient's bone health has been assessed AND allows for continued therapy with the requested agent **AND** 5. The patient has NOT had a fragility fracture since starting therapy with the requested agent **AND** 6. The patient will NOT be using the requested agent in combination with another GnRH antagonist agent targeted in this program (e.g., elagolix, relugolix) for the requested indication **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 8. BOTH of the following: A. There is support confirming the number of months the patient has been on therapy **AND** B. The total duration of treatment with the requested agent has NOT exceeded 24 months per lifetime **Length of Approval:** up to 6 months, with a lifetime maximum of 24 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
Oriahnn	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of heavy menstrual bleeding associated with uterine leiomyomas (fibroids) **AND** 2. The patient's diagnosis of uterine fibroids was confirmed via imaging (e.g., ultrasound) **AND** 3. The patient has NOT had a hysterectomy **AND** 4. The patient is premenopausal (e.g., less than 12 months since last menstrual period) **AND** 5. The patient's bone health has been assessed AND allows for initiating therapy with the requested agent **AND** 6. ONE of the following: A. The patient has tried and had an inadequate response to at least ONE hormonal contraceptive used in the treatment of the requested indication **OR** B. The patient has an intolerance or hypersensitivity to at least ONE hormonal contraceptive used in the treatment of the requested indication **OR**

Module	Clinical Criteria for Approval
	C. The patient has an FDA labeled contraindication to ALL hormonal contraceptive therapies (i.e., oral, topical patches, implants, injections, IUD) **AND** 7. The patient will NOT be using the requested agent in combination with another GnRH antagonist agent targeted in this program (e.g., elagolix, relugolix) for the requested indication **AND** 8. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 9. ONE of the following: A. The patient is initiating therapy with the requested agent **OR** B. The patient is not initiating therapy with the requested agent and BOTH of the following: 1. There is support confirming the number of months the patient has been on therapy **AND** 2. The total duration of treatment with the requested agent has NOT exceeded 24 months per lifetime **Length of Approval:** up to 6 months, with a lifetime maximum of 24 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient is premenopausal (e.g., less than 12 months since last menstrual period) **AND** 3. The patient has had clinical benefit with the requested agent **AND** 4. The patient's bone health has been assessed AND allows for continued therapy with the requested agent **AND** 5. The patient has NOT had a fragility fracture since starting therapy with the requested agent **AND** 6. The patient will NOT be using the requested agent in combination with another GnRH antagonist agent targeted in this program (e.g., elagolix, relugolix) for the requested indication **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 8. BOTH of the following: A. There is support confirming the number of months the patient has been on therapy **AND**

Module	Clinical Criteria for Approval
	B. The total duration of treatment with the requested agent has NOT exceeded 24 months per lifetime **Length of Approval:** up to 6 months, with a lifetime maximum of 24 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
Orilissa	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of moderate to severe pain associated with endometriosis **AND** 2. The patient is premenopausal (e.g., less than 12 months since last menstrual period) **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response to at least ONE hormonal contraceptive therapy used in the treatment of the requested indication **OR** B. The patient has an intolerance or hypersensitivity to at least ONE hormonal contraceptive therapy used in the treatment of the requested indication **OR** C. The patient has an FDA labeled contraindication to ALL hormonal contraceptive therapies (i.e., oral, topical patches, implants, injections, IUD) used in the treatment of the requested indication **AND** 4. The patient's bone health has been assessed AND allows for initiating therapy with the requested agent **AND** 5. The patient will NOT be using the requested agent in combination with another GnRH antagonist agent targeted in this program (e.g., elagolix, relugolix) for the requested indication **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 7. ONE of the following: A. The patient does NOT have coexisting moderate hepatic impairment (Child-Pugh [CP]/ Child-Turcotte-Pugh [CTP] Class B) AND ONE of the following: 1. The patient is initiating therapy with the requested agent and strength **OR** 2. The patient is not initiating therapy with the requested agent and strength and BOTH of the following: A. There is support confirming the number of months the patient has been on therapy **AND** B. ONE of the following: 1. The requested strength is 150 mg AND the total duration of treatment with the requested strength has NOT exceeded 24 months per lifetime **OR**

Module	Clinical Criteria for Approval
	2. The requested strength is 200 mg AND the total duration of treatment with the requested strength has NOT exceeded 6 months per lifetime **OR** B. The patient does have coexisting moderate hepatic impairment (Child-Pugh [CP]/ Child-Turcotte-Pugh [CTP] Class B) AND BOTH of the following: 1. The requested strength is 150 mg **AND** 2. ONE of the following: A. The patient is initiating therapy with the requested agent and strength **OR** B. The patient is not initiating therapy with the requested agent and strength and BOTH of the following: 1. There is support confirming the number of months the patient has been on therapy **AND** 2. The total duration of treatment with the requested strength has NOT exceeded 6 months per lifetime **Length of Approval:** up to 6 months with a lifetime maximum of 24 months with the 150 mg without coexisting moderate hepatic impairment, a lifetime maximum of 6 months with the 150 mg with coexisting moderate hepatic impairment, or a lifetime maximum of 6 months with the 200 mg NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process (*please note requests for 200 mg strength should always be reviewed under initial criteria) [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient is premenopausal (e.g., less than 12 months since last menstrual period) **AND** 3. The patient has had clinical benefit with the requested agent **AND** 4. The patient's bone health has been assessed AND allows for continued therapy with the requested agent **AND** 5. The patient has NOT had a fragility fracture since starting therapy with the requested agent **AND** 6. The patient will NOT be using the requested agent in combination with another GnRH antagonist agent targeted in this program (e.g., elagolix, relugolix) for the requested indication **AND**

Module	Clinical Criteria for Approval
	7. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 8. BOTH of the following: A. There is support confirming the number of months the patient has been on therapy with the requested agent and strength **AND** B. ONE of the following: 1. The patient does NOT have coexisting moderate hepatic impairment (Child-Pugh [CP]/ Child-Turcotte-Pugh [CTP] Class B) AND the total duration of treatment with the requested strength has NOT exceeded 24 months per lifetime **OR** 2. The patient does have coexisting moderate hepatic impairment (Child-Pugh [CP]/ Child-Turcotte-Pugh [CTP] Class B) AND the total duration of treatment with the requested strength has NOT exceeded 6 months per lifetime **Length of Approval:** up to 6 months with a lifetime maximum of 24 months with the 150 mg without coexisting moderate hepatic impairment OR a lifetime maximum of 6 months with the 150 mg with coexisting moderate hepatic impairment NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity limit for the Target Agent(s)** will be approved when the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **Length of Approval:** Myfembree and Oriahnn: up to 6 months with a lifetime maximum of 24 months. Orilissa: up to 6 months with a lifetime maximum of 24 months with the 150 mg without coexisting moderate hepatic impairment, a lifetime maximum of 6 months with the 150 mg with coexisting moderate hepatic impairment, and a lifetime maximum of 6 months with the 200 mg

Empaveli (pegcetacoplan)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
EMPAVELI® (pegcetacoplan) Injection for subcutaneous use	Treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH)		1

CLINICAL RATIONALE

Paroxysmal Nocturnal Hemoglobinuria	Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic, progressive, life-threatening, rare, multi-systemic disease developing as a result of a somatic mutation of hematopoietic stem cells, and characterized by clonal, complement-mediated intravascular hemolysis. PNH is mainly a disease of adults with a median age of onset in the thirties. High Precision Flow Cytometry is the most useful and accepted diagnostic test to confirm the diagnosis of PNH. Flow cytometry is performed by incubating the patient's peripheral blood cells with fluorescently-labeled monoclonal antibodies that bind to glycosylphosphatidylinositol (GPI) anchored proteins, which are reduced or absent on blood cells in PNH. Since different blood cell lineages display different combinations of GPI-linked proteins, and some proteins bind to cell surfaces via both GPI-linked and GPI-independent mechanisms, it is recommended that at least two independent flow cytometry reagents be used on at least two cell lineages (e.g., red blood cells [RBCs] and white blood cells [WBCs]) to establish a diagnosis of PNH.(2) The lack of the complement inhibitor CD59 on RBCs surface is mostly responsible for the clinical manifestations in PNH. These patients manifest with chronic intravascular hemolysis, paroxysmal flares of hemolysis, and a propensity for thrombosis. Intravascular hemolysis leads to release of free hemoglobin (Hb) into the blood. Free Hb, in turn, can cause various toxic effects,

	including hypercoagulability, changes in vascular tone from reduction of circulating nitric oxide, and renal damage.(3) Extravascular hemolysis also occurs in patients with PNH because C3 fragments that are not destroyed by the membrane attack complex (MAC) intravascularly can accumulate on the GPI-negative red blood cell (lacking CD55) surface and these fragments opsonize the RBCs, causing reticuloendothelial destruction in the liver and spleen.(3) The main clinical situations or diseases that should be considered in the differential diagnosis of PNH are:(3) • Coombs-negative hemolytic anemia (e.g., hemoglobinopathies, hereditary spherocytosis), microangiopathic hemolytic anemias, drug- or toxin-induced hemolysis/anemias, disseminated intravascular coagulation, and autoimmune hemolysis • Venous thrombosis in atypical sites, including myeloproliferative disorders; solid tumors associated with hypercoagulability; extrinsic compression of vessels, and; inherited/acquired thrombophilias • Anemia and/or other cytopenias related to bone marrow failure syndrome (e.g., aplastic anemia, myelodysplastic syndrome [MDS]) PNH is classified into three different categories:(3) • Classic PNH (PNH with clinical and laboratory findings of intravascular hemolysis [IVH] without any evidence of bone marrow deficiency) • PNH in the setting of another specified bone marrow disorder (evidence of hemolysis, as well as another specified bone marrow disorder [e.g., aplastic anemia, MDS]) • Subclinical PNH (patients with a small population of PNH cells and no clinical or laboratory evidence of hemolysis or thrombosis) Historically, patients with PNH had a median survival of ten years after diagnosis, however since the development of complement inhibitors survival rates have improved to approximately 75%(4). The approach to therapy depends on the severity of symptoms and the degree of hemolysis. The treatment options for PNH are supportive care, allogenic hematopoietic stem cell transplantation (HSCT), and a complement blockade.(2-3)
Efficacy	EMPAVELI binds to complement protein C3 and its activation fragment C3b, thereby regulating the cleavage of C3 and the generation of downstream effectors of complement activation. In PNH extravascular hemolysis (EVH) is facilitated by C3b opsonization while IVH is mediated by the downstream MAC.

	Pegcetacoplan acts proximally in the complement cascade controlling both C3b-mediated EVH and terminal complement-mediated IVH.(1) The efficacy and safety of EMPAVELI in patients with PNH were assessed in a randomized, open-label, active comparator-controlled, 16-week Phase 3 study (Study APL2-302; NCT03500549). The study enrolled patients with PNH who had been treated with a stable dose of eculizumab for at least the previous 3 months and with Hb levels less than 10.5 g/dL.(1) Eligible patients entered a 4-week run-in period during which they received EMPAVELI 1,080 mg subcutaneously twice weekly in addition to their current dose of eculizumab. Patients were then randomized in a 1:1 ratio to receive either 1,080 mg of EMPAVELI twice weekly or their current dose of eculizumab through the duration of the 16-week randomized controlled period. If required due to a lactate dehydrogenase (LDH) greater than 2 X the upper limit of normal (ULN), the dose of EMPAVELI could be adjusted to 1,080 mg every three days.(1) The efficacy of EMPAVELI was based on change from baseline to Week 16 (during randomized controlled period) in Hb level. Baseline was defined as the average of measurements recorded prior to taking the first dose of EMPAVELI. Supportive efficacy data included transfusion avoidance, defined as the proportion of patients who did not require a transfusion during the randomized controlled period, and change from baseline to Week 16 in absolute reticulocyte count (ARC).(1) EMPAVELI was superior to eculizumab for the change from baseline in Hb level at Week 16 (P<0.0001). The adjusted mean change from baseline in Hb level was 2.37 g/dL in the group treated with EMPAVELI versus -1.47 g/dL in the eculizumab group, demonstrating an adjusted mean increase of 3.84 g/dL with EMPAVELI compared to eculizumab at week 16 (95% CI, 2.33-5.34).(1) Non-inferiority was demonstrated in the endpoints of transfusion avoidance and change from baseline in ARC.(1) Study APL2-308 enrolled patients with PNH who had not been treated with any complement inhibitor within 3 months prior to enrollment and with Hb levels less than the lower limit of normal. Eligible patients were randomized in a 2:1 ration to receive EMPAVELI or supportive care (control arm) (excluding complement inhibitors [e.g., transfusions, corticosteroids, supplements such as iron, folate, and vitamin B12]) through the duration of the 26-week treatment period. The efficacy of EMPAVELI was based on the percentage of patients achieving Hb stabilization, defined as avoidance of a > 1 g/dL decrease in Hb levels from

<table>
<tr>
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<td>baseline in the absence of transfusion, and the change from baseline in LDH level. Supportive efficacy data included change from baseline in ARC, change from baseline in Hb, and transfusion avoidance, defined as the proportion of patients who did not require a transfusion through Week 26. Baseline was defined as the average of measurements recorded prior to taking the first dose of EMPAVELI or prior to randomization to the control arm treatment group. Efficacy results are shown below.(1)
<table>
<tr><th></th><th>EMPAVELI</th><th>Control Arm</th><th>Difference (95% CI)
p-value</th></tr>
<tr><td>Hb Stabilization (n, %)</td><td>30 (85.7%)</td><td>0 (0%)</td><td>73% (57%,89%)
p<0.0001</td></tr>
<tr><td>Change from Baseline in LDH (Least Square [LS] Mean CFB, Standard Error [SE])</td><td>-1870 (101.0)</td><td>-400 (313.3)</td><td>-1470 (-2113.4,-827.3)
p<0.0001</td></tr>
<tr><td>Change from baseline in ARC (LS, Mean CFB, SE)</td><td>-123 (9.2)</td><td>-19 (25.2)</td><td>-103 (-158.9, -48.7)
p=0.0002)</td></tr>
<tr><td>Change from baseline in Hb (LS, Mean CFB, SE)</td><td>2.9 (0.38)</td><td>0.3 (0.76)</td><td>2.7 (0.99, 4.35)
p=0.0019</td></tr>
<tr><td>Transfusion Avoidance (n, %)</td><td>32 (91%)</td><td>1 (6%)</td><td>72% (56%, 80%)
p<0.0001</td></tr>
</table>
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<tr>
<td>Safety</td>
<td>EMPAVELI contains the following boxed warnings:(1)

• EMPAVELI increases the risk of serious infections, especially those caused by encapsulated bacteria, such as Streptococcus</td>
</tr>
</table>

	pneumoniae, *Neisseria meningitidis*, and *Haemophilus influenzae* type B. Life-threatening and fatal infections have occurred and these infections may become rapidly life-threatening or fatal if not recognized and treated early. ○ Vaccinate patients against encapsulated bacteria as recommended at least 2 weeks prior to administering the first dose of EMPAVELI unless risks of delaying EMPAVELI therapy outweigh the risks of developing a serious infection ○ Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria ○ Patients receiving EMPAVELI are at increased risk for invasive disease caused by encapsulated bacteria, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious infections and evaluate immediately if infection is suspected EMPAVELI is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the EMPAVELI REMS.(1) EMPAVELI is contraindicated in the following:(1) • Patients with a hypersensitivity to pegcetacoplan or any of the excipients • Initiation in patients with unresolved serious infection caused by encapsulated bacteria including *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* type B

REFERENCES

Number	Reference
1	Empaveli prescribing information. Apellis Pharmaceuticals, Inc. February 2024.
2	Sahin F, Akay OM, Ayer M, et al. Pesg PNH diagnosis, follow-up and treatment guidelines. PubMed Central (PMC). Published 2016. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4981648/

Number	Reference
3	Cançado RD, Da Silva Araújo A, Sandes AF, et al. Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria. Hematology, Transfusion and Cell Therapy. 2021;43(3):341-348. doi:10.1016/j.htct.2020.06.006
4	Shah N, Bhatt H. Paroxysmal nocturnal hemoglobinuria. StatPearls - NCBI Bookshelf. Published July 31, 2023. https://www.ncbi.nlm.nih.gov/books/NBK562292/

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH) as confirmed by flow cytometry with at least 2 independent flow cytometry reagents on at least 2 cell lineages (e.g., RBCs and WBCs) demonstrating that the patient's peripheral blood cells are deficient in glycosylphosphatidylinositol (GPI) – linked proteins (lab tests required) **OR** B. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with Soliris (eculizumab) for the requested indication (NOTE: if the patient is switching from Soliris, Soliris should be continued for the first 4 weeks after starting the requested agent and then Soliris should be discontinued) **AND** 5. The patient will NOT be using the requested agent in combination with Fabhalta (iptacopan), Ultomiris (ravulizumab-cwvz), or Piasky (crovalimab-akkz) for the requested indication **AND**

Module	Clinical Criteria for Approval
	6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had improvements or stabilization with the requested agent (e.g., decreased requirement of RBC transfusions, stabilization/improvement of hemoglobin, reduction of lactate dehydrogenase (LDH), stabilization/improvement of symptoms) (medical records required) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with Fabhalta (iptacopan), Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), or Piasky (crovalimab-akkz) for the requested indication **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. BOTH of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. ONE of the following: 1. The patient has a lactate dehydrogenase (LDH) level greater than 2X the upper limit of normal (lab test required) **OR** 2. ALL of the following: (medical records required) A. The patient had a prior LDH greater than 2X the upper limit of normal and required a dose increase **AND** B. The patient is currently using the requested quantity (dose) **AND** C. The requested quantity (dose) does NOT exceed 1,080 mg every three days **Length of Approval:** up to 12 months NOTE: If approving for every three days dosing approve a quantity of 10 vials/30 days for 12 months

Endari

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Endari® (L-glutamine) Oral powder*	To reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older	*generic available	

CLINICAL RATIONALE

Sickle Cell Disease	Sickle cell disease (SCD) is the name given to a group of lifelong inherited conditions that affect hemoglobin. People with SCD have atypical hemoglobin molecules called hemoglobin S, which can distort red blood cells into a sickle or crescent shape.(2) Signs and symptoms of SCD usually begin in early childhood. Characteristic features of SCD include anemia, repeated infections, and periodic episodes of pain. The severity of symptoms varies from person to person and can range from mild to requiring frequent hospitalizations.(2) SCD affects nearly every system in the body. SCD has both acute and chronic complications. An episode of severe pain [acute vaso-occlusive crisis (VOC)] is the most common acute complication of SCD. In addition to VOCs, other common acute complications of SCD include fever related to infection, acute kidney injury (AKI), hepatobiliary complications, acute anemia, splenic sequestration, acute chest syndrome (ACS), and acute stroke. Chronic complications of SCD can affect almost any organ, and certain acute complications often evolve into chronic phases. The most common chronic complications of SCD include chronic pain, chronic anemia, avascular necrosis, leg ulcers, pulmonary hypertension, renal complications, stuttering/recurrent priapism, and ophthalmologic complications.(2) Pain is the most common complication of SCD for both acute and chronic complications. Pain can be acute, chronic, or an acute episode superimposed on

	chronic pain. In SCD, pain is considered chronic if it lasts more than 3 months. People with SCD experience both nociceptive and neuropathic pain.(2) Recurrent and unpredictable episodes of vaso-occlusion are the hallmark of sickle cell disease. Discoveries over the past 2 decades have highlighted the important contributions of various cellular and soluble participants in the vaso-occlusive cascade. Although the molecular basis of SCD is well characterized, the complex mechanisms underlying VOC have not been fully elucidated. Based on direct observations in SCD mice, adhesive interactions of SS-RBCs and leukocytes to the endothelium play important roles in the initiation of VOC. It is thought that the activated adherent leukocytes, which are rigid and larger than sickle cell-red blood cells (SS-RBC), likely drive VOC in collecting venules, whereas the SS-RBCs may contribute in smaller vessels or in situations where there is no potent inflammatory trigger.(4) Triggers for VOC vary and can include inflammation, stress, increased viscosity, decreased flow, hemolysis, or a combination of the following factors:(4) • Endothelial activation by SS-RBCs and other inflammatory mediators • Recruitment of adherent leukocytes • Activation of recruited neutrophils and of other leukocytes (e.g., monocytes or iNKT cells) • Interactions of sickle erythrocytes with adherent neutrophils • Vascular clogging by heterotypic cell-cell aggregates composed of SS-RBCs, adherent leukocytes and possibly platelets • Increased transit time to greater than the delay time for deoxygenation-induced hemoglobin polymerization, propagating retrograde VOC • Ischemia as a result of the obstruction that creates a feedback loop of worsening endothelial activation Sickle hemoglobin can cause damage to the RBC membrane from deformation by polymer formation. In addition, the mutated globin can undergo autooxidation and precipitate on the inner surface of the RBC membrane, causing membrane damage via iron-mediated generation of oxidants. Both endothelial selectins, P-selectin and E-selectin, have been suggested to participate in VOC.(4) Nearly all people with SCD have chronic anemia, but individual baseline hemoglobin values vary widely depending upon hemoglobin genotype (HbSS, HbSC, HbSβ^+-thalassemia, HbSβ^0-thalassemia). It is important for the patient and the primary care provider to know the baseline or “steady state” hemoglobin

	value to inform ongoing monitoring and management during acute complications.(2) Hydroxyurea, a ribonucleotide reductase inhibitor, was identified as an option to increase fetal hemoglobin (HbF) levels in people with SCD. The initial clinical trial of hydroxyurea for the treatment of sickle cell anemia (SCA) involved two people. The results of this study showed favorable outcomes which lead to two extended studies with larger cohorts of people. Although HbF induction is the most powerful effect of hydroxyurea and provides the biggest direct benefit for people who have SCD, additional mechanisms of actions and benefits exist. Hydroxyurea lowers the number of circulating leukocytes and reticulocytes and alters the expression of adhesion molecules, all of which contribute to vaso-occlusion. Hydroxyurea also raises RBC volume [higher mean corpuscular volume (MCV)] and improves cellular deformability and rheology, which increases blood flow and reduces vaso-occlusion.(3) An expert panel report of evidence-based management of sickle cell disease supports the use of hydroxyurea with strong recommendations in the following:(3) • In adults with SCA who have three or more sickle cell-associated moderate to severe pain crises in a 12 month period • In adults with SCA who have sickle cell-associated pain that interferes with daily activity and quality of life • In adults with SCA who have a history of severe and/or recurrent acute coronary syndrome (ACS) • In adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life • In infants 9 months of age and older, children, and adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce SCD-related complications (e.g., pain, dactylitis, ACS, anemia) A clinical response to treatment with hydroxyurea may take 3-6 months. Therefore, the expert panel report of evidence-based management of sickle cell disease recommends a 6 month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy.(3) While hydroxyurea remains the first-line therapy for SCD, L-glutamine, crizanlizumab, and voxelotor have been approved as adjunctive or second-line treatments, and hematopoietic stem cell transplant with a matched sibling donor

	is now standard care for severe disease. The emergence of gene therapies for SCD now bring the potential for curative therapy without a matched donor.(5)
Efficacy	The mechanism of action of the amino acid L-glutamine in treating sickle cell disease (SCD) is not fully understood. Oxidative stress phenomena are involved in the pathophysiology of SCD. Sickle red blood cells (RBCs) are more susceptible to oxidative damage than normal RBCs, which may contribute to the chronic hemolysis and vaso-occlusive events associated with SCD. The pyridine nucleotides, NAD+ (oxidized nicotinamide adenine dinucleotide) and its reduced form NADH (nicotinamide adenine dinucleotide + hydrogen), play roles in regulating and preventing oxidative damage in RBCs. L-glutamine may improve the NAD redox potential in sickle RBCs through increasing the availability of reduced glutathione.(1) The efficacy of L-glutamine was evaluated in a randomized, double-blind, placebo controlled, multi-center clinical trial. The trial evaluated 230 patients with SCD who had 2 or more painful crises within the 12 months prior to enrollment. Eligible patients stabilized on hydroxyurea for at least 3 months continued their therapy throughout the study. Efficacy was demonstrated by a reduction in the number of sickle cell crises through Week 48 and prior to the start of tapering among patients that received L-glutamine compared to patients who received placebo. The recurrent crisis event time analysis yielded an intensity rate ratio (IRR) value of 0.75 with 95% CI= (0.62, 0.90) and (0.55, 1.01) based on unstratified models using the Andersen-Gill and Lin, Wei, Yang and Ying methods, respectively in favor of L-glutamine, suggesting that over the entire 48-week period, the average cumulative crisis count was reduced by 25% from the L-glutamine group over the placebo group.(1)
Safety	Endari (L-glutamine) has no FDA labeled contraindications for use.(1)

REFERENCES

Number	Reference
1	Endari prescribing information. Emmaus Medical, Inc. October 2020.
2	U.S. National Library of Medicine. Genetics Home Reference. Sickle cell disease. November 2019.
3	U.S. Department of Health and Human Services. National Institute of Health. Evidence-Based Management of Sickle Cell Disease. Expert Panel Report, 2014.

Number	Reference
4	Manwani D, Frenette PS, Vaso-occlusion in sickle cell disease: pathophysiology and novel targeted therapies. Blood. 2013 Dec 5; 122(24): 3892-3898.
5	Brandow AM, Liem RI. Advances in the diagnosis and treatment of sickle cell disease. Journal of Hematology & Oncology. 2022;15(1). doi:10.1186/s13045-022-01237-z.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of sickle cell disease **AND** 2. The patient is using the requested agent to reduce the acute complications of sickle cell disease **AND** 3. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 4. ONE of the following A. The patient has tried and had an inadequate response after at least 6 months duration of therapy with maximally tolerated hydroxyurea **OR** B. The patient has an intolerance or hypersensitivity to hydroxyurea **OR** C. The patient has an FDA labeled contraindication to hydroxyurea **AND** 5. ONE of the following: A. The patient will NOT be using the requested agent in combination with Adakveo (crizanlizumab-tmca) OR Oxbryta (voxelotor) for the requested indication **OR** B. There is support for use of the requested agent in combination with Adakveo (crizanlizumab-tmca) or Oxbryta (voxelotor) for the requested indication **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 7. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication

Module	Clinical Criteria for Approval
	Length of Approval: 12 months **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent (i.e., reduction in acute complications of sickle cell disease since initiating therapy with the requested agent) **AND** 3. ONE of the following: A. The patient will NOT be using the requested agent in combination with Adakveo (crizanlizumab-tmca) OR Oxbryta (voxelotor) for the requested indication **OR** B. There is support for use of the requested agent in combination with Adakevo (crizanlizumab-tmca) or Oxbryta (voxelotor) for the requested indication **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **Length of Approval:** 12 months

Enspryng (satralizumab-mwge)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Enspryng® (satralizumab-mwge) Injection for subcutaneous use	Treatment of adult patients with neuromyelitis optica spectrum disorder (NMOSD) who are anti-aquaporin-4 (AQP4) antibody positive		1

CLINICAL RATIONALE

Neuromyelitis Optica Spectrum Disorder	Neuromyelitis optica spectrum disorder (NMOSD), formerly known as Devic's disease, is a chronic disorder of the brain and spinal cord dominated by inflammation of the optic nerves (optic neuritis) and inflammation of the spinal cord (myelitis). Initially, it was thought to be a monophasic illness, consisting of episodes of inflammation of one or both optic nerves and the spinal cord over a short period of time (days or weeks) but, after the initial episode, no recurrence. It is now recognized that most patients satisfying current criteria for NMOSD experience repeated attacks separated by periods of remission. The interval between attacks may be weeks, months, or years.(2) Early in the course of the disease, it may be difficult to distinguish between NMOSD and multiple sclerosis (MS) because both may cause optic neuritis and myelitis. However, the optic neuritis and myelitis tend to be more severe in NMOSD; the brain MRI is more commonly normal, and the spinal fluid analysis does not usually show oligoclonal bands in NMOSD, which are features that help distinguish it from MS.(2) NMOSD can be AQP4 antibody positive or negative. The diagnostic criteria for NMOSD with AQP4 positive diagnosis are: at least 1 core clinical characteristic, a positive test for AQP4-IgG, and exclusion of alternative diagnoses. The core clinical characteristics are:(4) 1. Optic neuritis

	2. Acute myelitis 3. Area postrema syndrome (episodes of otherwise unexplained hiccups or nausea and vomiting) 4. Acute brainstem syndrome 5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions 6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions An international consensus panel reached several conclusions in addition to the above criteria to establish an NMOSD diagnosis. First, at least 1 discrete clinical attack of CNS symptoms must occur to establish a diagnosis of NMOSD. Although asymptomatic AQP4-IgG seropositive status may exist for years before clinical NMOSD presentation, the natural history of asymptomatic seropositivity is poorly understood. Second, NMOSD diagnosis is not warranted in asymptomatic patients with NMOSD-compatible MRI lesions because the expected clinical course in such individuals is unknown. Third, no clinical characteristic is pathognomonic of NMOSD. Accordingly, a single clinical manifestation is not diagnostic when AQP4-IgG is not detected. Finally, no single characteristic is exclusionary, but some are considered red flags that signal the possibility of alternative diagnoses. The main clinical red flags concern the temporal course of the syndrome rather than the actual manifestations. Most notably, a gradually progressive course of neurologic worsening over months to years is very uncommon (1%–2%) in NMOSD. However, after thorough investigation for potential competing disorders, the weight of evidence may justify NMOSD diagnosis despite presence of 1 or more red flags.(4) Treatment strategies for attack prevention in NMOSD and multiple sclerosis (MS) differ. Some MS immunotherapies appear to aggravate NMOSD, indicating an imperative for early, accurate diagnosis. Patients with NMOSD who are AQP4-IgG seropositive should be assumed to be at risk for relapse indefinitely and preventative treatment should be considered.(4) Azathioprine and mycophenolate mofetil have been used off label to prevent NMOSD attacks for decades. Their efficacy in NMOSD has been demonstrated in several retrospective studies and case series. In recent years, their use in NMOSD has declined in favor of rituximab owing to their comparative lower efficacy as demonstrated in multiple retrospective studies.(3) Rituximab is a commonly used off-label preventative therapy in NMOSD. Rituximab is a monoclonal antibody (MAB) against CD20-positive B-Cells which include pre B-cell, immature B-cell, and memory B-cell lineage but not plasmablasts or plasma cells. Its exact mechanism of action in NMOSD is unknown, but it is hypothesized to involve reduction of pathogenic antibody

	production, dampening of pro-inflammatory cytokines, and decreasing B-cell dependent antigen presentation to T-cells.(3) There are currently 4 FDA labeled therapies for AQP4 antibody positive NMOSD; Soliris, Ultomiris, Uplizna, and Enspryng.(3) Disability in NMOSD is a direct consequence of the relapse. Spontaneous gradual progression of disability like in MS is very rare in NMOSD. Thus, NMOSD relapses are a clinically relevant measure. Amongst secondary end points, disability is very important. The main categories are spinal cord/brainstem related, motor (weakness, spasticity), sensory (numbness and pain), bladder, bowel, sexual function, and vision. The expanded disability and status scale (EDSS) is suitable and well validated in MS research, but cerebellar and cerebral functional scales are not really applicable in NMOSD, as cognitive and cerebellar dysfunction is limited in NMOSD. The optic spinal impairment scale is derived and modified from EDSS. There are no formal psychometrics supporting the scale and it is not widely used. There are numerous vision specific scales, but none are specific for optic neuritis. Despite the use of the EDSS in NMOSD clinical trials, current literature does not support its use as a measure of NMOSD disease severity.(7)
Efficacy	The safety and efficacy of Enspryng for the treatment of adults with NMOSD were established in two studies.(1) Study 1 enrolled 95 adult subjects with NMOSD who were not on concurrent immunosuppressive therapy and randomized them in a 2:1 manner to Enspryng therapy or placebo; of those enrolled, 67% were AQP4 positive. Study 2 enrolled 76 adult subjects with NMOSD who were on concurrent immunosuppressive therapy (most commonly oral corticosteroids [52%] or azathioprine [42%]) and randomized them in a 1:1 manner to Enspryng therapy or placebo; of those enrolled, 68% were AQP4 positive. In both studies, subjects were required to have clinical evidence of relapse in the preceding 12 months and have an expanded disability status scale (EDSS) score between 0 and 6.5 to meet eligibility criteria.(1) The primary efficacy endpoint for both studies was the time to first confirmed relapse, as determined by a blinded committee that performed the adjudication of relapses.(1) In both studies the time to first confirmed relapse was significantly longer for those treated with Enspryng versus placebo; a 55% risk reduction was observed in Study 1 (hazard ratio 0.45; *p* equal to 0.0184) and a 62% risk reduction was observed in Study 2 (hazard ratio 0.38; *p* equal to 0.0184). AQP4 positive patients had a 74% risk reduction compared to placebo (hazard ratio 0.26; *p* =0.0014) and a 78% risk reduction compared to placebo (hazard ratio 0.22; *p* equal to 0.0143) in Study 1 and Study 2, respectively. Neither study demonstrated benefit in AQP4 negative patients. Among those who were

	AQP4 positive in Study 1, 76.5% (95% CI: 59.2-87.2) of Enspryng treated patients were relapse free at week 96 compared to 41.1% (95% CI: 20.8-60.4) of those treated with placebo. Among the same subjects in Study 2, 91.1% (95% CI: 68.4-97.7) of Enspryng treated patients were relapse free at week 96 compared to 56.8% (95% CI: 32.1-75.4) of those treated with placebo.(1)
Safety	Enspryng is contraindicated in patients with the following:(1) • A known hypersensitivity to satralizumab or any of the inactive ingredients • Active Hepatitis B infection • Active or untreated latent tuberculosis

REFERENCES

Number	Reference
1	Enspryng prescribing information. Genentech, Inc. July 2023.
2	National organization for rare disorders (NORD). Rare Disease Database. Neuromyelitis Optica Spectrum Disorder. - Symptoms, causes, treatment. NORD. National Organization for Rare Disorders. https://rarediseases.org/rare-diseases/neuromyelitis-optica/
3	Kümpfel T, Giglhuber K, Aktas O, et al. Update on the diagnosis and treatment of neuromyelitis optica spectrum disorders (NMOSD) - revised recommendations of the Neuromyelitis Optica Study Group (NEMOS). Part II: Attack therapy and long-term management. J Neurol. 2024 Jun;271(6):3702-3707. doi:10.1007/s00415-024-12288-2
4	Wingerchuk DM, Banwell B, Bennett JL, et al. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015;85(2):177-189. doi:10.1212/wnl.0000000000001729
5	Reference no longer used.
6	Reference no longer used.
7	Regulatory Workshop on Clinical Trials Designs in Neuromyelitis Optica Spectrum Disorders (NMOSD).; 2015:1-29. https://www.ema.europa.eu/en/documents/report/report-regulatory-workshop

Number	Reference
	on -clinical -trials -designs in -neuromyelitis -optica -spectrum -disorders (NMOSD). 16 June 2015-. en.pdf
8	Reference no longer used.

ALLOWED EXCEPTIONS QUANTITY LIMIT

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Allowed Exceptions	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
994050704 0E520	Enspryng	Satralizumab-mwge Subcutaneous Soln Pref Syringe	120 MG/ ML	* NOTE: Loading dose of 3 syringes for the first month is approvable			

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of neuromyelitis optica spectrum disorder (NMOSD) **AND** 2. The patient is anti-aquaporin-4 (AQP4) antibody positive (lab test required) **AND** 3. The diagnosis was confirmed by at least ONE of the following: A. Optic neuritis **OR** B. Acute myelitis **OR**

Module	Clinical Criteria for Approval
	C. Area postrema syndrome (episode of otherwise unexplained hiccups or nausea and vomiting) **OR** D. Acute brainstem syndrome **OR** E. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions **OR** F. Symptomatic cerebral syndrome with NMOSD-typical brain lesions **AND** 4. The patient has had at least 1 discrete clinical attack of CNS symptoms **AND** 5. Alternative diagnoses (e.g., multiple sclerosis, ischemic optic neuropathy) have been ruled out **AND** 6. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 7. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 8. The prescriber has screened the patient for hepatitis B viral (HBV) infection AND BOTH of the following: A. The patient does NOT have an active HBV infection **AND** B. If the patient has had a previous HBV infection or is a carrier for HBV infection the prescriber has consulted with a gastroenterologist or a hepatologist before initiating and during treatment with the requested agent **AND** 9. The patient does NOT have active or untreated latent tuberculosis **AND** 10. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 11. The patient will not be using the requested agent in combination with rituximab, Soliris, Uplizna, or Ultomiris for the requested indication **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND**

Module	Clinical Criteria for Approval
	2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. BOTH of the following: A. The patient does not have active hepatitis B infection **AND** B. If the patient has had a previous HBV infection or is a carrier for HBV infection the prescriber continues to consult with a gastroenterologist or a hepatologist during treatment with the requested agent **AND** 5. The patient does NOT have active or untreated latent tuberculosis **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 7. The patient will NOT be using the requested agent in combination with rituximab, Soliris, Uplizna, or Ultomiris for the requested indication **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: 1. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** 2. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months

Eohilia

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Eohilia™ (budesonide) Oral suspension	Treatment of eosinophilic esophagitis (EoE) for 12 weeks in adult and pediatric patients aged 11 years and older Limitations of use: • Eohilia has not been shown to be safe and effective for the treatment of EoE for longer than 12 weeks		1

CLINICAL RATIONALE

Eosinophilic Esophagitis	Eosinophilic Esophagitis (EoE) is an allergen/immune-mediated disease characterized by symptoms of esophageal dysfunction and marked eosinophilic inflammation of the esophageal mucosa in the absence of secondary causes. EoE has dramatically increased in prevalence over the years. EoE is characterized by symptoms related to esophageal dysfunction and histologically with eosinophil-predominant inflammation (a peak count of greater than or equal to 15 eosinophils per high-power field on esophageal biopsy). Atopic and allergic inflammatory conditions commonly occur concomitantly with EoE.(2) The symptoms of EoE are age dependent. Young children may refuse to eat, have decreased appetite, recurring abdominal pain, trouble swallowing, and vomiting. Young adults and adults have the same symptoms, but often struggle to swallow dry or dense, solid foods due to inflammation. Food impaction is a common cause for emergency room visits in patients with EoE. Patients may also have concurrent gastroesophageal reflux disease (GERD). EoE is a progressive disease if left untreated. The chronic inflammation can lead to tissue fibrosis and strictures in the esophagus that require esophageal dilation.(3) The diagnosis of EoE is suspected on the basis of chronic symptoms such as dysphagia, food impaction, food refusal, failure to progress with food introduction, heartburn, regurgitation, vomiting, chest pain, odynophagia,

	abdominal pain, and malnutrition. Due to the wide range of chronic symptoms, the diagnosis should be highly considered in the presence of concomitant atopic conditions and if there are endoscopic findings. Endoscopic findings associated with EoE include esophageal rings, longitudinal furrows, exudates, edema, strictures, or narrow caliber esophagus. Assessment of non-EoE disorders and esophageal biopsy are required to confirm the diagnosis of EoE, with at least 15 eosinophils (eos)/ high-power field (hpf) present on esophageal biopsy.(4) Nonpharmacological treatment of EoE includes dilation and diet. Dilation is only conditionally recommended for patients with dysphagia associated with strictures due to EoE, noting that the dilation does not address the underlying inflammation.(5) Both elemental and elimination diets have been shown to be effective, however, barriers of adherence and cost make this treatment modality feasible only for select patients.(5,6) Proton pump inhibitors (PPIs) are a first line treatment option for patients with EoE, and PPI monotherapy is widely used in practice. PPIs have a longstanding safety profile and have shown to be effective based on symptom response and histological remission. The 2020 American Gastroenterological Association (AGA) and the Joint Task Force on Allergy-Immunology Practice Parameters (JTF) guidelines conditionally recommend their use while the 2022 British Society of Gastroenterology (BSG) and British Society of Pediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) guidelines strongly recommend their use.(5,6) The AGA/JTF and BSG/BSPGHAN both strongly recommend the use of topical glucocorticoids for the treatment of EoE. Studies showed that topical (swallowed) budesonide or topical fluticasone induced histological remission significantly better than placebo and had similar adverse events to placebo. Due to the chronic nature of the disease and the risk of progression, topical corticosteroids may be continued as maintenance therapy after remission with short term use. A clinical review of the patient should guide this decision based on preference to avoid long term adverse effects of topical steroids, or to prevent undesirable outcomes of the disease itself.(5,6)
Efficacy	The efficacy and safety of Eohilia 2 mg twice daily were evaluated in two multicenter, randomized, double-blind, parallel-group, placebo-controlled 12-week studies (Study 1 [NCT02605837] and Study 2 [NCT01642212]). Eligible subjects in both studies had esophageal inflammation defined as greater than or equal to 15 eosinophils/high-power field (hpf) from at least 2 levels of the esophagus at baseline following a treatment course of a proton pump inhibitor (PPI) either prior to or during screening and at least 4 days of dysphagia as measured by the

Dysphagia Symptom Questionnaire (DSQ) over a 2-week period prior to randomization. Concomitant use of stable doses of inhaled or intranasal steroids (for conditions other than EoE), PPIs, H2-receptor antagonists, antacids, antihistamines or anti-leukotrienes, and maintenance immunotherapy was allowed. In Study 1, subjects were enrolled after maintaining a stable diet for at least 3 months prior to screening and were instructed to maintain a stable diet throughout the study. Subjects were excluded if they were on a full liquid or 6-food elimination diet. In Study 2, subjects were instructed to maintain a stable diet throughout the study. In both studies, subjects were instructed to not eat or drink for 30 minutes after taking the drug and then to rinse their mouth with water and spit out the contents without swallowing prior to resuming normal oral intake.(1)

A total of 318 subjects (277 adults and 41 pediatric subjects) were randomized and received at least one dose of study drug (Eohilia or placebo) in Study 1. The mean age of the study population was 34 years (range 11 to 56 years). Over 80% of the subjects were on concomitant PPI. The mean (SD) DSQ combined scores at baseline were 30.3 (13.9) and 30.4 (13.1) in the EOHILIA and placebo groups, respectively.(1)

A total of 92 subjects (58 adults and 34 pediatric subjects) were randomized and received at least one dose of study drug (Eohilia or placebo) in Study 2. The mean age of the study population was 22 years (range 11 to 42 years). Over 65% of the subjects were on concomitant PPI. The mean (SD) DSQ combined scores at baseline were 30.7 (16.0) and 29.0 (13.5) in the EOHILIA and placebo groups, respectively.(1)

Efficacy endpoints for both studies were the proportion of patients with a histologic response (defined as a peak eosinophil count of less than or equal to 6/hpf across all available esophageal levels) and the absolute change from baseline in subject-reported DSQ combined score after 12 weeks of treatment. Results are shown in the table below:(1)

	Study 1			**Study 2**		
Efficacy Endpoints	**Eohilia 2mg twice daily (n=213)**	**Placebo (n=105)**	**Treatment difference and 95% CI**	**Eohilia 2mg twice daily (n=50)**	**Placebo (n=42)**	**Treatment difference and 95% CI**

<table>
<tr><td></td><td>
<table>
<tr><td>Proportion of subjects achieving histological remission (peak esophageal intraepithelial eosinophil count ≤6 eos/hpf)</td><td>53.1%</td><td>1.0%</td><td>52.4% (43.3,59.1)</td><td>38.0%</td><td>2.4%</td><td>35.8% (17.2,50.0)</td></tr>
<tr><td>Absolute change from baseline in DSQ combined score (0-84*), LS mean (SE)</td><td>-10.2 (1.5)</td><td>-6.5 (1.8)</td><td>-3.7 (-6.8,-0.6)</td><td>-14.5 (1.8)</td><td>-5.9 (2.1)</td><td>-8.6 (-13.7,-3.5)</td></tr>
</table>
*Total biweekly DSQ scores range from 0 to 84, higher scores indicate greater frequency and severity of dysphagia

In both studies, during the last 2 weeks of the 12-week treatment periods, a greater proportion of subjects randomized to Eohilia experienced no dysphagia or only experienced dysphagia that “got better or cleared up on its own” compared to placebo, as measured by the subject-reported DSQ.(1)

In Study 1, 48 subjects from the Eohilia treatment arm entered a double-blind randomized withdrawal extension study and either received Eohilia 2mg twice daily or placebo for up to an additional 36 weeks. No statistically significant difference was demonstrated between the two groups based on eosinophil count and/or clinical symptoms measured by the DSQ at Week 36.(1)
</td></tr>
<tr><td>Safety</td><td>Eohilia is contraindicated in patients with hypersensitivity to budesonide. Serious hypersensitivity reactions, including anaphylaxis, have occurred with oral budesonide products.(1)</td></tr>
</table>

REFERENCES

Number	Reference
1	Eohilia prescribing information. Takeda Pharmaceuticals America, Inc. February 2024.
2	O'Shea K, Aceves SS, Dellon ES, et al. Pathophysiology of Eosinophilic Esophagitis. *Gastroenterology*. 2018;154(2):333-345. doi:10.1053/j.gastro.2017.06.065
3	The American Academy of Allergy, Asthma & Immunology. Eosinophilic Esophagitis: Symptoms, Diagnosis & Treatment. https://www.aaaai.org/conditions-treatments/related-conditions/eosinophilic-esophagitis. Last revised May 1, 2023.
4	Dellon ES, Liacouras CA, Molina-Infante J, et al. Updated International Consensus Diagnostic Criteria for Eosinophilic Esophagitis: Proceedings of the AGREE Conference. *Gastroenterology*. 2018;155(4):1022-1033.e10. doi:10.1053/j.gastro.2018.07.009
5	Hirano I, Chan ES, Rank MA, et al. AGA Institute and the Joint Task Force on Allergy-Immunology Practice Parameters Clinical Guidelines for the Management of Eosinophilic Esophagitis. Gastroenterology. 2020;158(6):1776-1786. doi:10.1053/j.gastro.2020.02.038
6	Dhar A, Haboubi H, Attwood S, et al. British Society of Gastroenterology (BSG) and British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) joint consensus guidelines on the diagnosis and management of eosinophilic oesophagitis in children and adults. *Gut*. May 2022:gutjnl-327326. doi:10.1136/gutjnl-2022-327326

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of eosinophilic esophagitis (EoE) AND the patient's diagnosis was confirmed by ALL of the following: A. Chronic symptoms of esophageal dysfunction **AND** B. Greater than or equal to 15 eosinophils per high-power field on esophageal biopsy **AND** C. Other causes that may be responsible for or contributing to symptoms and esophageal eosinophilia have been ruled out **AND**

Module	Clinical Criteria for Approval
	2. ONE of the following: A. The patient has tried and had an inadequate response to ONE standard corticosteroid therapy (i.e., swallowed budesonide nebulizer suspension, swallowed fluticasone MDI) used in the treatment of EoE **OR** B. The patient has an intolerance or hypersensitivity to standard corticosteroid therapy used in the treatment of EoE that is not expected to occur with the requested agent **OR** C. The patient has an FDA labeled contraindication to ALL standard corticosteroid therapies used in the treatment of EoE that is not expected to occur with the requested agent **OR** D. The patient has tried and had an inadequate response to ONE proton pump inhibitor (PPI) used in the treatment of EoE **OR** E. The patient has an intolerance or hypersensitivity to PPI therapy used in the treatment of EoE **OR** F. The patient has an FDA labeled contraindication to ALL PPI therapies used in the treatment of EoE **AND** 3. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. ONE of the following: A. The patient has not previously been treated with a course of therapy (12 weeks) with the requested agent **OR** B. The patient has previously been treated with a course of therapy with the requested agent, AND there is support for an additional course of therapy with the requested agent **Length of Approval:** 3 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 3 months

Ergotamine

Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Cafergot® (ergotamine tartrate/caffeine)* Tablet	Therapy to abort or prevent vascular headache, e.g., migraine, migraine variants, or so-called "histaminic cephalalgia"	*generic available	1
D.H.E. 45® (dihydroergotamine mesylate)* Injection	Acute treatment of migraine headaches with or without aura Acute treatment of cluster headache episodes	*generic available	2
Ergomar® (ergotamine tartrate) Sublingual tablet	Therapy to abort or prevent vascular headache, e.g., migraine, migraine variants, or so-called "histaminic cephalalgia"		3
Migergot® (ergotamine tartrate/caffeine) Suppository	Therapy to abort or prevent vascular headache, e.g., migraine, migraine variants, or so-called "histaminic cephalalgia"		4

CLINICAL RATIONALE

Acute Migraine	The American Headache Society 2015 guideline for The Acute Treatment of Migraine in Adults state that specific medications- triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan [oral, nasal spray, injectable, transcutaneous patch], zolmitriptan [oral and nasal spray]) and dihydroergotamine are effective (Level A) and ergotamine and other forms of dihydroergotamine are probably effective (Level B). Triptans are considered first-line treatments for moderate to severe migraine while dihydroergotamine is recommended for use as second- or third-line therapy for select patients or for those with refractory migraine. Intranasal dihydroergotamine has strong evidence of effectiveness but more adverse effects than triptans because of its

	decreased receptor specificity.(6) The evidence base for medication efficacy should be considered along with potential medication side effects and potential adverse events.(5) Pharmacologic properties, adverse effects, cost, route of administration vary, allowing treatment to be individualized based on symptoms, preferences, adverse effects, and cost.(6) Ergotamine has been used in clinical practice for the acute treatment of migraine for over 50 years with little agreement on its place in clinical practice. In a review of pre-clinical and clinical data on ergotamine as it relates to the treatment of migraine, specific suggestions for the patient groups and appropriate use of ergotamine have been agreed upon. In essence, ergotamine, from a medical perspective, is the drug of choice in a limited number of migraine sufferers who have infrequent or long duration headaches and are likely to comply with dosing restrictions. For most migraine sufferers requiring a specific anti-migraine treatment, a triptan is generally a better option from both an efficacy and side-effect perspective.(7)
Safety	D.H.E. 45 carries the following boxed warning:(2) Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of dihydroergotamine with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of dihydroergotamine, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated. D.H.E. 45 is contraindicated in the following:(2) • Patients with ischemic heart disease (e.g., angina pectoris, history of myocardial infarction, or documented silent ischemia) or patients who have clinical symptoms or findings consistent with coronary artery vasospasm including Prinzmetal's variant angina • Patients with uncontrolled hypertension • Use within 24 hours of 5-HT1 agonists (e.g., sumatriptan), ergotamine-containing or ergot-type medications, or methysergide • Patients with hemiplegic or basilar migraine • Patients with known peripheral arterial disease, sepsis, following vascular surgery, and severely impaired hepatic or renal function • Pregnant women • Patients who have previously shown hypersensitivity to ergot alkaloids • Nursing mothers

	• Use with peripheral and central vasoconstrictors because the combination may result in additive or synergistic elevation of blood pressure Ergotamine agents carry the following boxed warning:(1) • Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of ergotamine tartrate and ergotamine tartrate/caffeine with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of ergotamine tartrate and ergotamine tartrate/caffeine, the risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Hence, concomitant use of these medications is contraindicated. Ergotamine agents are contraindicated in the following:(1,3,4) • Coadministration of ergotamine with potent CYP 3A4 inhibitors (ritonavir, nelfinavir, indinavir, erythromycin, clarithromycin and troleandomycin) has been associated with acute ergot toxicity (ergotism) characterized by vasospasm and ischemia of the extremities, with some cases resulting in amputation. There have been rare reports of cerebral ischemia in patients on protease inhibitor therapy when ergotamine was coadministered, at least one resulting in death. Because of the increased risk for ergotism and other serious vasospastic adverse events, ergotamine use is contraindicated with these drugs and other potent inhibitors of CYP 3A4 (e.g., ketoconazole, itraconazole) • Ergotamine may cause fetal harm when administered to pregnant women. Ergotamine is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy or if the patient becomes pregnant while taking this product, the patient should be apprised of the potential hazard to the fetus. • Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function and sepsis • Hypersensitivity to any of the components

REFERENCES

Number	Reference
1	Cafergot prescribing information. Sandoz Inc. December 2019.
2	D.H.E. 45 prescribing information. Bausch Health U.S. LLC. April 2022.
3	Ergomar prescribing information. TerSera Therapeutics LLC. February 2020.
4	Migergot prescribing information. Cosette Pharmaceuticals, Inc. November 2022.
5	Marmura M, Silberstein SD, Schwedt TJ. The Acute Treatment of Migraine in Adults: The American Headache Society Evidence Assessment of Migraine Pharmacotherapies. *Headache.* 2015;55:3–20. https://doi.org/10.1111/head.12499
6	Mayans L, Walling A. Acute Migraine Headache: Treatment Strategies. *Am Fam Physician*. 2018;97(4):243-251.
7	Tfelt-Hansen P, Saxena PR, Dahlöf C, Pascual J, et al. Ergotamine in the acute treatment of migraine: A review and European consensus, *Brain*. 2000;123(1):9-18. https://doi.org/10.1093/brain/123.1.9

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Erythropoietins

Prior Authorization

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#

Aranesp®
 	
(darbepoetin alfa)
 	
Injection for intravenous or subcutaneous use
	• Anemia due to chronic kidney disease (CKD), including patients on dialysis and patients not on dialysis
	• Anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy
	
	Limitations of Use:
	
	• Aranesp has not been shown to improve quality of life, fatigue, or patient well-being
	• Aranesp is not indicated for use
	  ○ In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy
	  ○ In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure
	  ○ In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion
			1

Agent(s)	FDA Indication(s)	Notes	Ref#
	○ As a substitute for red blood cell transfusions in patients who require immediate correction of anemia		
Epogen® (epoetin alfa) Injection for intravenous or subcutaneous use	• Anemia due to Chronic Kidney Disease (CKD), in patients on dialysis and those not on dialysis to decrease the need for red blood cell (RBC) transfusion • Treatment of anemia due to zidovudine administered at less than or equal to 4200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of less than or equal to 500 mUnits/mL • Anemia in patients with non-myeloid malignancies, where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of 2 additional months of planned chemotherapy • Reduce the need of allogeneic RBC transfusions among patients with perioperative hemoglobin greater than 10 to less than or equal to 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery Limitations of Use: • Epogen has not been shown to improve quality of life, fatigue, or patient well-being Epogen is not indicated for use:		2

Agent(s)	FDA Indication(s)	Notes	Ref#
	• In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy • In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure • In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion • In patients scheduled for surgery who are willing to donate autologous blood • In patients undergoing cardiac or vascular surgery • As a substitute for RBC transfusions in patients who require immediate correction of anemia		
Mircera® (methoxypolyethylene glycol-epoetin beta) Injection for intravenous or subcutaneous use	• Anemia associated with chronic kidney disease (CKD) in adult patients on dialysis and not on dialysis • Anemia associated with chronic kidney disease in pediatric patients 5 to 17 years of age on hemodialysis who are converting from another erythropoiesis-stimulating agent (ESA) after their hemoglobin level was stabilized with an ESA Limitations of Use: • Mircera has not been shown to improve symptoms, physical functioning, or health-related quality of life		3

Agent(s)	FDA Indication(s)	Notes	Ref#
	Mircera is not indicated and is not recommended for use: • In the treatment of anemia due to cancer chemotherapy • As a substitute for RBC transfusions in patients who require immediate correction of anemia		
Procrit® (epoetin alfa) Injection for intravenous or subcutaneous use	• Anemia due to chronic kidney disease (CKD), in patients on dialysis and those not on dialysis to decrease the need for red blood cell (RBC) transfusion • Treatment of anemia due to zidovudine administered at less than or equal to 4200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of less than or equal to 500 mUnits/mL • Anemia in patients with non-myeloid malignancies, where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of 2 additional months of planned chemotherapy • Reduce the need of allogeneic RBC transfusions among patients with perioperative hemoglobin greater than 10 to less than or equal to 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery Limitations of Use:		4

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Procrit has not been shown to improve quality of life, fatigue, or patient well-being Procrit is not indicated for use: • In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy • In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure • In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion • In patients scheduled for surgery who are willing to donate autologous blood • In patients undergoing cardiac or vascular surgery • As a substitute for RBC transfusions in patients who require immediate correction of anemia		
Retacrit® (epoetin alfa-epbx) Injection for intravenous or subcutaneous use	• Anemia due to Chronic Kidney Disease (CKD), in patients on dialysis and those not on dialysis to decrease the need for red blood cell (RBC) transfusion • Treatment of anemia due to zidovudine administered at less than or equal to 4200 mg/week in HIV-infected patients with endogenous serum erythropoietin levels of less than or equal to 500 mUnits/mL • Anemia in patients with non-myeloid malignancies, where anemia is due to the effect of concomitant		5

Agent(s)	FDA Indication(s)	Notes	Ref#
	myelosuppressive chemotherapy, and upon initiation, there is a minimum of 2 additional months of planned chemotherapy • Reduce the need of allogeneic RBC transfusions among patients with perioperative hemoglobin greater than 10 to less than or equal to 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery Limitations of Use: • Retacrit has not been shown to improve quality of life, fatigue, or patient well-being Retacrit is not indicated for use: • In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy • In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure • In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion • In patients scheduled for surgery who are willing to donate autologous blood • In patients undergoing cardiac or vascular surgery • As a substitute for RBC transfusions in patients who require immediate correction of anemia		

CLINICAL RATIONALE

Anemia

The pathophysiologic origins of anemia can be grouped into three categories 1) decreased production of functional red blood cells (RBCs); 2) increased destruction of RBCs; and 3) blood loss. Anemia is characterized by a decrease in hemoglobin (Hb) concentration, RBC count, and/or hematocrit (Hct) to subnormal levels.(9) Treatment of anemia depends on disease severity and etiology. Treatment options include vitamins and/or mineral supplementation, treatment with erythropoietin therapy, and blood transfusion.(10)

The National Cancer Institute categorizes anemia into 4 active grades:(9)

Grade	**Scale** (hemoglobin level in g/dL)
1 (mild)	10 - less than lower limit of normal
2 (moderate)	8 - less than 10
3 (severe)	Less than 8
4 (life threatening)	Life-threatening consequences; urgent intervention indicated

Erythropoietin has the same biological effects as endogenous erythropoietin, and, therefore, stimulates RBC production in the bone marrow.(2,4)

Darbepoetin differs from epoetin alfa only in two additional N-glycosylation sites which results in an increased half-life.(1) When given in equipotent dosing, efficacy between epoetin and darbepoetin is considered similar. A report by the Agency for Healthcare Research and Quality (AHRQ) comparing effectiveness of the two agents when used to manage anemia in patients undergoing cancer treatment concluded there were no clinically significant differences in hemoglobin response, transfusion reduction, or thromboembolic events.(6) The American Society of Clinical Oncology/American Society of Hematology (ASCO/ASH) clinical practice guideline considers epoetin beta and alfa, darbepoetin, and biosimilar epoetin alfa to be equivalent with respect to both efficacy and safety.(16) The National Comprehensive Cancer Network (NCCN) guidelines for Cancer- and Chemotherapy - induced anemia note that either darbepoetin or epoetin alfa can be used in erythropoietin stimulating agents (ESA) therapy.(10)

NCCN notes that a biosimilar is a biological product that is highly similar to the FDA-approved originator product with the exception of minor differences in clinically inactive components and no differences regarding efficacy, safety, and purity. Biosimilars have the same amino acid sequence; however, they may differ at the protein level due to the nature and complexity of biologic products. If overall safety and efficacy remain unaffected, biosimilars may be approved for the same indications and can be substituted for the originator product.(9)

Although the equipotent doses have not been conclusively determined, the prescribing information for darbepoetin provides the following conversion chart from epoetin alfa to darbepoetin.(1)

Previous Weekly Epoetin alfa Dose (Units/week)	**Weekly darbepoetin dose (mcg/week)**	
	Adult	**Pediatric**
Less than 1500	6.25	The available data are insufficient to determine a darbepoetin dose
1500 to 2499	6.25	6.25
2500 to 4999	12.5	10
5000 to 10999	25	20
11000 to 17999	40	40
18000 to 33999	60	60
34000 to 89999	100	100
Greater than or equal to 90000	200	200

The Mircera prescribing information provides the following conversion chart from epoetin alfa or darbepoetin alfa to Mircera in patients with CKD.(3)

Previous Weekly Epoetin alfa Dose (units/week)	**Previous Weekly Darbepoetin alfa Dose (mcg/week)**	**Mircera Dose**	
		Once Monthly (mcg/month)	**Once Every Two Weeks (mcg/every two weeks)**

	<table><tr><td>Less than 8000</td><td>Less than 40</td><td>120</td><td>60</td></tr><tr><td>8000-16000</td><td>40-80</td><td>200</td><td>100</td></tr><tr><td>Greater than 16000</td><td>Greater than 80</td><td>360</td><td>180</td></tr></table>
Anemia associated with Chronic Kidney Disease (CKD)	Anemia in patients with CKD occurs due the kidneys inability to produce sufficient amounts of erythropoietins. KDIGO (Kidney Disease Improving Global Outcomes) Clinical Practice guidelines recommend the following as it pertains to use of ESAs:(12) • For CKD patients NOT on dialysis (ND) and a Hb of greater than or equal to 10.0 g/dl, the agency does not recommend ESA therapy be initiated • For CKD ND patients with Hb less than 10.0 g/dl, the decision to use ESA should be patient specific and based on a risk/benefit ratio • For CKD patients in stage 5D, ESA use is recommended to prevent Hb falling below 9.0 g/dl. The agency recommends starting therapy when the hemoglobin is between 9.0 and 10.0 g/dl • In general, ESAs should not be used to maintain Hb greater than 11.5 g/dl in adults with CKD. • For pediatric patients, the recommendation to use ESA therapy should be patient specific and based on a risk/benefit ratio • For all pediatric CKD patients on ESA therapy, Hb concentration should be maintained in the range of 11.0-12.0 g/dl The KIDIGO guidelines suggest that for adult CKD non-dialysis patients with a hemoglobin concentration less than 10 g/dL, the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia. ESA therapy should be used to avoid having the hemoglobin concentration fall below 9 g/dL by starting ESA therapy when the hemoglobin is between 9.0-10.0 g/dL. These guidelines state that in dialysis and non-dialysis patients with CKD receiving ESA therapy, the selected Hb target should generally be in the range of 10.0 to 12.0 g/dL.(12)
Chemotherapy Induced Anemia	Causes of anemia in patients with cancer are often multifactorial. Anemia may be attributed to underlying comorbidities such as bleeding, hemolysis, nutritional deficiencies, hereditary disease, renal insufficiency, hormone dysfunction, or a

	combination of these factors. The malignancy itself can also lead to or exacerbate anemia in several ways.(9) There is a wide variation in Hb levels among healthy subjects and a universal “normal" level is difficult to define. According to the NCCN panel, an Hb level less than or equal to 11 g/dL should prompt an evaluation of anemia in a patient with cancer. A drop of 2 g/dL or more below baseline is also cause for concern and assessment. Any other cause of anemia that may be found independent of cancer therapy should be treated as indicated. When no such etiology is identified, the effects of cancer-related inflammation and/or myelosuppressive chemotherapy (if applicable) should be considered the cause of anemia.(9) The decision regarding the best treatment option is dependent on many factors. While packed red blood cell transfusion is best for symptomatic patients requiring an immediate boost in Hb levels, consideration of ESA therapy and/or iron supplementation may be warranted for the long-term management of anemia in high-risk patients or in asymptomatic patients with comorbidities.(9) Special categories in considering ESA use from The National Comprehensive Cancer Network (NCCN) are:(9) ▪ Patients with cancer and CKD (moderate to severe): Consider treatment with ESAs by FDA dosing/dosing adjustments ▪ Patient undergoing palliative treatment: consider treatment with ESAs by FDA dosing/dosing adjustments, RBC transfusion, or clinical trial based on patient preferences ▪ Patients with cancer not receiving therapy, receiving non-myelosuppressive chemotherapy, or myelosuppressive chemotherapy with curative intent (e.g. early-stage breast cancer, Hodgkin lymphoma, non-Hodgkin’s lymphoma, testicular cancer, early-stage non-small cell lung cancer, small cell lung cancer): ESAs not recommended ▪ The ESA dose should be adjusted for each patient to maintain the lowest hemoglobin level sufficient to avoid red blood transfusion and/or to bring about gradual improvement in anemia related symptoms ▪ Studies have reported decreased survival in patients with cancer receiving ESA for anemia where target Hb levels are greater than 12 g/dL ▪ Patients with ferritin values greater than 800 ng/mL or a transferrin saturation (TSAT) greater than or equal to 50% and are not iron deficient do not require iron supplementation or ESA therapy

	ASCO/ASH guidelines recommend the following:(16) • ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose HgB has declined to less than 10 g/dL. RBC transfusion is also an option, depending on the severity of the anemia or clinical circumstances • ESAs should not be offered to patients with chemotherapy-associated anemia whose cancer treatment is curative in intent • Before offering an ESA, clinicians should conduct an appropriate history, physical examination, and diagnostic tests to identify alternative causes of anemia aside from chemotherapy. Such cases should be appropriately addressed before considering the use of ESAs • Starting and modifying doses of ESAs follow FDA guidelines • Among adult patients who will receive an ESA for chemotherapy-associated anemia, HgB may be increased to the lowest concentration needed to avoid or reduce the need for RBC transfusions • ESAs should be discontinued in patients who do not respond to therapy (i.e., less than 1 to 2 g/dL increase in HgB or no decrease in transfusion requirements) within 6 to 8 weeks • Iron replacement may be used to improve HgB response and reduce RBC transfusions for patients receiving ESA with or without iron deficiency
Myelodysplastic Syndrome (MDS)	NCCN Clinical Practice Guideline for Myelodysplastic Syndromes states:(13) • ESA have been used safely in large numbers of adult MDS patients and have become important for symptomatic improvement of those affected by the anemia caused by this disease often with a decrease in RBC transfusion requirements. Studies assessing the long-term use of epoetin with or without G-CSF in MDS compared to historical or randomized controls haven't shown a negative impact on survival or AML evolution. Studies have shown improved survival in low-risk MDS patients with low transfusion need treated with these agents • An alternative option to lenalidomide may include an initial trial of ESAs in patients with serum erythropoietin (Epo) levels of 500 mU/ml or less. Patients with or without normal cytogenetics and with less than 15% ringed sideroblasts and serum Epo levels 500 mU/mL or less may respond to Epo if relatively high doses are used (40,000-60,000 units 1-2 times a week). Darbepoetin alfa should be given subcutaneously at a dose of 150-300 mcg every other week.

	The ASCO/ASH guidelines recommend that ESAs not be offered to most patients with nonchemotherapy-associated anemia to reduce the need for RBC transfusions. The exception is they may be offered to patients with lower-risk MDSs and a serum erythropoietin level less than or equal to 500 IU/L.(16)
Surgery	Epoetin alfa is indicated for the treatment of anemic patients (hemoglobin greater than 10 to less than or equal to 13 g/dL) who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions.(2,4,5)
Anemia in HIV	The causes of HIV-related anemia are multifactorial. HIV may directly affect bone marrow stromal cell or cause cytokine secretion, leading to decreased production of red blood cells (RBCs) and other bone marrow elements. Many drugs used to treat HIV-related disorders are myelosuppressive but severe anemia is most often related to the use of zidovudine.(14) Patients most likely to respond to ESA treatment have a serum erythropoietin level less than 500 iu/L.(14-15)

Safety	The prescribing information for the ESAs notes that in controlled trials, patients experienced a greater risk of death, serious adverse cardiovascular reactions, and stroke when given ESAs to a target hemoglobin level of greater than 11 g/dL. Additionally, no trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.(1-5)
	
	• Aranesp (darbepoetin alfa) is contraindicated in:
	  ○ Uncontrolled hypertension
	  ○ Pure red cell aplasia (PRCA) that begins after treatment with any ESA
	  ○ Serious allergic reactions to Aranesp
	• Epogen (epoetin alfa) is contraindicated in:
	  ○ Uncontrolled hypertension
	  ○ Pure red cell aplasia (PRCA) that begins after treatment with any ESA
	  ○ Serious allergic reactions to Epogen
	  ○ Use of multi-dose vials containing benzoyl alcohol in neonates, infants, pregnant women, and lactating women
	• Mircera (methoxy polyethylene glycol – epoetin beta) is contraindicated in:
	  ○ Uncontrolled hypertension
	  ○ Pure red cell aplasia (PRCA) that begins after treatment with Mircera or other erythropoietin protein drugs
	  ○ History of serious or severe allergic reactions to Mircera (e.g. anaphylactic reactions, angioedema, bronchospasm, skin rash, and urticaria)

	• Procrit (epoetin alfa) is contraindicated in:
	  ○ Uncontrolled hypertension
	  ○ Pure red cell aplasia (PRCA) that begins after treatment with any ESA
	  ○ Serious allergic reactions to Procrit
	  ○ Use of multi-dose vials containing benzoyl alcohol in neonates, infants, pregnant women, and lactating women
	• Retacrit (epoetin alfa-epbx) is contraindicated in:
	  ○ Uncontrolled hypertension
	  ○ Pure red cell aplasia (PRCA) that begins after treatment with Retacrit or other erythropoietin protein drugs
	  ○ Serious allergic reactions to Retacrit or other epoetin alfa products
	  ○ Use of multiple-dose vials containing benzyl alcohol in neonates, infants, pregnant women, and lactating women

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Preferred epoetin alfa containing agents: **Retacrit** (epoetin alfa-epbx) **Non-preferred epoetin alfa containing agents:** **Epogen** (epoetin alfa) **Procrit** (epoetin alfa) **Other erythropoietin agents** **Aranesp** (darbepoetin alfa) **Mircera** (methoxy polyethylene glycol – epoetin beta)

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when BOTH of the following are met: 1. The patient's hemoglobin was measured within the previous 4 weeks **AND** 2. ONE of the following: A. The patient will use the requested agent as part of dialysis AND ONE of the following: 1. The patient is initiating an erythropoietin stimulating agent (ESA) AND the patient's hemoglobin level is less than 10 g/dL **OR** 2. The patient is stabilized on an ESA AND the patient's hemoglobin is less than or equal to 11 g/dL **OR** B. ALL of the following: 1. ONE of the following: A. The requested agent is being prescribed to reduce the possibility of allogeneic blood transfusion in a surgery patient AND the patient's hemoglobin level is greater than 10 g/dL but less than or equal to 13 g/dL **OR** B. The requested agent is being prescribed for anemia due to myelosuppressive chemotherapy for a non-myeloid malignancy AND ALL of the following: 1. The requested agent is NOT Mircera **AND** 2. ONE of the following: A. The patient is initiating an erythropoietin stimulating agent (ESA) AND the patient's hemoglobin level is less than 10 g/dL **OR** B. The patient is stabilized on an ESA AND the patient's hemoglobin is less than or equal to 12 g/dL **AND** 3. The patient is concurrently treated with chemotherapy (with or without radiation) **AND** 4. Chemotherapy is being used for palliative intent **AND** 5. The patient's serum ferritin and transferrin saturation have been evaluated within the previous 4 weeks AND BOTH of the following: A. The patient's serum ferritin is NOT greater than 800 ng/mL **AND** B. The patient's transferrin saturation is NOT greater than 50% **OR** C. The requested agent is being prescribed for anemia associated with chronic kidney disease in a patient NOT on dialysis AND ALL of the following: 1. ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient is initiating an erythropoietin stimulating agent (ESA) AND the patient's hemoglobin level is less than 10 g/dL OR B. The patient is stabilized on an ESA AND the patient's hemoglobin is less than or equal to 11 g/dL **AND** 2. The rate of hemoglobin decline is likely to result in a red blood cell (RBC) transfusion **AND** 3. The intent of therapy is to reduce the risk of alloimmunization and/or other RBC transfusion related risks **OR** D. The requested agent is being prescribed for anemia due to myelodysplastic syndrome, or for anemia resulting from zidovudine treatment of HIV infection AND ONE of the following: 1. The patient is initiating an erythropoietin stimulating agent (ESA) AND the patient's hemoglobin level is less than 12 g/dL **OR** 2. The patient is stabilized on an ESA AND the patient's hemoglobin is less than or equal to 12 g/dL **OR** E. The requested agent is being prescribed for another FDA labeled indication or another indication that is supported in compendia AND the patient's hemoglobin level is within the FDA labeling or compendia recommended range for the requested indication for patients initiating ESA therapy OR for patients stabilized on therapy for the requested indication **AND** 2. The patient's serum ferritin and transferrin saturation have been evaluated within the previous 4 weeks **AND** 3. ONE of the following: A. The patient's serum ferritin is greater than or equal to 100 ng/mL AND the patient's transferrin saturation is greater than or equal to 20% **OR** B. The patient has started supplemental iron therapy **AND** 4. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 5. If the requested agent is Epogen or Procrit, then ONE of the following: A. The patient has tried and had an inadequate response to ONE preferred agent (listed below) (medical records required) **OR** B. The patient has an intolerance or hypersensitivity to ONE preferred agent that is NOT expected to occur with the requested agent (medical records required) **OR**

Module	Clinical Criteria for Approval
	C. The patient has an FDA labeled contraindication to ALL preferred agents that is NOT expected to occur with the requested agent (medical records required) **AND** **Preferred Epoetin Alfa Containing Agent(s)** Retacrit (epoetin alfa-epbx) 6. If the client has preferred agents not addressed previously, then ONE of the following: A. The requested agent is a preferred agent (Preferred and Nonpreferred Agents to be determined by client) **OR** B. The patient has tried and had an inadequate response to ONE preferred agent **OR** C. The patient has an intolerance or hypersensitivity to ONE preferred agent that is NOT expected to occur with the requested agent **OR** D. The patient has an FDA labeled contraindication to ALL preferred agent(s) that is NOT expected to occur with the requested agent **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence, NCCN 1 or 2a recommended use **Length of Approval**: 1 month for allogenic blood transfusion in a surgery patient; 6 months for anemia due to myelosuppressive chemotherapy for a non-myeloid malignancy 12 months for anemia associated with chronic kidney disease in patients on/not on dialysis, anemia due to myelodysplastic syndrome, anemia resulting from zidovudine treatment of HIV infection 6 months for all other diagnoses

Fabhalta (iptacopan)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
FABHALTA® (iptacopan) Capsule	Treatment of adults with paroxysmal nocturnal hemoglobinuria (PNH) Reduction of proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to creatinine ratio (UPCR) greater than or equal to 1.5 g/g		1

CLINICAL RATIONALE

Paroxysmal Nocturnal Hemoglobinuria	Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic, progressive, life-threatening, rare, multi-systemic disease developing as a result of a somatic mutation of hematopoietic stem cells, and characterized by clonal, complement-mediated intravascular hemolysis. PNH is mainly a disease of adults with a median age of onset in the thirties. High precision flow cytometry is the most useful and accepted diagnostic test to confirm the diagnosis of PNH. Flow cytometry is performed by incubating the patient's peripheral blood cells with fluorescently-labeled monoclonal antibodies that bind to glycosylphosphatidylinositol (GPI) anchored proteins, which are reduced or absent on blood cells in PNH. Since different blood cell lineages display different combinations of GPI-linked proteins, and some proteins bind to cell surfaces via both GPI-linked and GPI-independent mechanisms, it is recommended that at least two independent flow cytometry reagents be used on at least two cell lineages (e.g., red blood cells [RBCs] and white blood cells [WBCs]) to establish a diagnosis of PNH.(2) The lack of the complement inhibitor CD59 on RBCs surface is mostly responsible for the clinical manifestations in PNH. These patients manifest with chronic intravascular hemolysis, paroxysmal flares of hemolysis, and a propensity for thrombosis. Intravascular hemolysis leads to release of free hemoglobin (Hb) into the blood. Free Hb, in turn, can cause various toxic effects,

	including hypercoagulability, changes in vascular tone from reduction of circulating nitric oxide, and renal damage.(3) Extravascular hemolysis also occurs in patients with PNH because C3 fragments that are not destroyed by the membrane attack complex (MAC) intravascularly can accumulate on the GPI-negative RBCs (lacking CD55) surface and these fragments opsonize the RBCs, causing reticuloendothelial destruction in the liver and spleen.(3) The main clinical situations or diseases that should be considered in the differential diagnosis of PNH are:(3) • Coombs-negative hemolytic anemia (e.g., hemoglobinopathies, hereditary spherocytosis), microangiopathic hemolytic anemias, drug- or toxin-induced hemolysis/anemias, disseminated intravascular coagulation, and autoimmune hemolysis • Venous thrombosis in atypical sites, including myeloproliferative disorders; solid tumors associated with hypercoagulability; extrinsic compression of vessels, and; inherited/acquired thrombophilias • Anemia and/or other cytopenias related to bone marrow failure syndrome (e.g., aplastic anemia, myelodysplastic syndrome [MDS]) PNH is classified into three different categories:(3) • Classic PNH (PNH with clinical and laboratory findings of intravascular hemolysis without any evidence of bone marrow deficiency) • PNH in the setting of another specified bone marrow disorder (evidence of hemolysis, as well as another specified bone marrow disorder [e.g., aplastic anemia, MDS]) • Subclinical PNH (patients with a small population of PNH cells and no clinical or laboratory evidence of hemolysis or thrombosis) Historically, patients with PNH had a median survival of ten years after diagnosis however, since the development of complement inhibitors survival rates have improved to approximately 75%(4). The approach to therapy depends on the severity of symptoms and the degree of hemolysis. The treatment options for PNH are supportive care, allogenic hematopoietic stem cell transplantation (HSCT), and a complement blockade.(2,3)
Immunoglobulin A Nephropathy	Immunoglobulin A nephropathy (IgAN), also known as Berger's disease, is a kidney disease that occurs when IgA deposits build up in the kidneys, causing inflammation that damages the glomeruli, in turn causing the kidneys to leak blood and protein into the urine. The damage may lead to scarring of the

	nephrons that progresses slowly over may years. Eventually, IgAN can lead to end-stage renal disease (ESRD).(5) Kidney biopsy is required to confirm the diagnosis of IgAN as there are no validated diagnostic serum or urine biomarkers. Biopsy is indicated when a patient has signs of a severe or progressive disease. After a diagnosis has been established, guidelines recommend that all patients with IgAN be assessed for secondary causes (e.g., liver cirrhosis, HIV, hepatitis, inflammatory bowel disease).(5) The primary focus of IgAN management should be optimized supportive care (e.g., blood pressure management, maximally tolerated angiotensin-converting-enzyme inhibitor [ACEI] or angiotensin II blocker [ARB], lifestyle modification, address cardiovascular risk). Guidelines recommend that all patients with proteinuria greater than 0.5 g/d be treated with an ACEI or ARB irrespective of whether they have hypertension.(5) Guidelines define high risk of progression in IgAN as proteinuria greater than 0.75–1 g/d despite at least 90 days of optimized supportive care. It is suggested that patients who remain at high risk despite maximal supportive care be considered for a 6-month course of glucocorticoid therapy. Guidelines stress the importance of discussing treatment-emergent toxicity, particularly in those who have an estimated glomerular filtration rate (eGFR) less than 50 mL/min/1.73 m^2. It is further noted that glucocorticoids should be given with extreme caution or avoided entirely in the following situations:(5) • eGFR less than 30 mL/min/1.73 m^2 • Diabetes • Obesity (BMI greater than 30 kg/m^2) • Latent infections (e.g., viral hepatitis, tuberculosis) • Secondary disease (e.g., cirrhosis) • Active peptic ulceration • Uncontrolled psychiatric illness • Severe osteoporosis The goal of treatment for these patients that remain at high risk for progressive disease is a reduction of proteinuria to less than 1 g/d.(5)
Efficacy	FABHALTA binds to Factor B of the alternative complement pathway and regulates the cleavage of C3, generation of downstream effectors, and the amplification of the terminal pathway. In PNH, intravascular hemolysis (IVH) is mediated by the downstream membrane attack complex, while extravascular

	hemolysis (EVH) is facilitated by C3b opsonization. FABHALTA acts proximally in the alternative pathway of the complement cascade to control both C3b-mediated EVH and terminal complement mediated IVH.(1) The efficacy of FABHALTA in adults with PNH was evaluated in a multi-center, open-label, 24-week active comparator-controlled trial (APPLY-PNH; NCT04558918). The study enrolled adults with PNH and residual anemia (Hb < 10 g/dL) despite previous treatment with a stable regimen of anti-C5 treatment (either eculizumab or ravulizumab) for at least 6 months prior to randomization. Efficacy primary endpoints were established based on demonstration of superiority of switching to FABHALTA compared to continuing on anti-C5 therapy in achieving hematological response after 24 weeks of treatment, without a need for transfusion, by assessing the proportion of patients demonstrating:(1) • Sustained increase of greater than or equal to 2 g/dL in Hb levels from baseline (Hb improvement) • Sustained hemoglobin levels greater than or equal to 12 g/dL Secondary endpoints included:(1) • Transfusion avoidance • Change from baseline in Hb levels • Change from baseline in absolute reticulocyte counts Patients with sustained increase of Hb levels greater than or equal to 2 g/dL in the FABHALTA arm had an 82.3% response rate (95% CI) and the response rate in the Anti-C5 arm was 0%. Patients with sustained Hb level greater than or equal to 12 g/dL in the absence of transfusions in the FABHALTA arm had a 67.7% response rate (95% CI) and the response rate in the Anti-C5 arm was 0%.(1) FABHALTA was studied in a single arm study in adults with PNH who were not previously treated with a complement inhibitor (APPOINT-PNH; NCT04820530). Adult patients with PNH (RBC clone size greater than or equal to 10%), Hb less than 10 g/dL, and LDH greater than 1.5 times the upper limit of normal received FABHALTA during the 24-week open-label core treatment period. In total, 77.5% (95% CI: 61.5%, 89.2%) of patients achieved a sustained increase (between Day 126 and Day 168) in Hb levels from baseline of greater than or equal to 2 g/dL in the absence of RBC transfusions.(1) Additionally, the effect of FABHALTA was evaluated in a multicenter, randomized, double-blind study (APPLAUSE-IgAN, NCT04578834) in adults with biopsy-proven IgAN, eGFR greater than or equal to 20 mL/min/1.73 m^2, and urine

	protein-to-creatinine ratio (UPCR) greater than or equal to 1 g/g on a stable dose of maximally-tolerated renin-angiotensin system (RAS) inhibitor therapy with or without a stable dose of an SGLT2 inhibitor. Patients were randomized (1:1) to either FABHALTA 200 mg or placebo twice daily. Rescue immunosuppressive treatment could be initiated per investigator discretion during the trial. The efficacy analysis was based on the first 250 patients with an eGFR greater than or equal to 30 mL/min/1.73 m^2 (Main Study Population), who had completed or discontinued the study prior to the Month 9 visit. The primary endpoint was the percent reduction in UPCR (sampled from a 24-hr urine collection) at Month 9 relative to baseline. The FABHALTA treatment arm showed a 44% (95% CI; 36%, 51%) reduction in UPCR while the placebo treatment arm showed a 9% (95% CI; -5%, 21%) reduction in UPCR from baseline at month 9.(1)
Safety	FABHALTA contains the following boxed warnings:(1) FABHALTA increases the risk of serious infections, especially those caused by encapsulated bacteria, such as *Streptococcus pneumoniae, Neisseria meningitidis, and Haemophilus influenzae type* B. Life-threatening and fatal infections have occurred and these infections may become rapidly life-threatening or fatal if not recognized and treated early. • Vaccinate patients against encapsulated bacteria as recommended at least 2 weeks prior to administering the first dose of FABHALTA, unless the risks of delaying therapy with FABHALTA outweigh the risk of developing a serious infection • Comply with the most current Advisory Committee on Immunization Practices (ACIP) recommendations for vaccinations against encapsulated bacteria • Patients receiving FABHALTA are at increased risk for invasive disease caused by encapsulated bacteria, even if they develop antibodies following vaccination. Monitor patients for early signs and symptoms of serious infections and evaluate immediately if infection is suspected FABHALTA is contraindicated in the following:(1) • Serious hypersensitivity to iptacopan or any of the excipients • Initiation in patients with unresolved serious infection caused by encapsulated bacteria, including *Streptococcus pneumoniae, Neisseria meningitidis,* or *Haemophilus influenzae* type B FABHALTA is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called FABHALTA REMS.(1)

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of Paroxysmal Nocturnal Hemoglobinuria (PNH) as confirmed by flow cytometry with at least 2 independent flow cytometry reagents on at least 2 cell lineages (e.g., RBCs and WBCs) demonstrating that the patient's peripheral blood cells are deficient in glycosylphosphatidylinositol (GPI) – linked proteins (lab tests required) **OR** B. The patient has a diagnosis of primary immunoglobulin A nephropathy (IgAN) confirmed by kidney biopsy AND ALL of the following: 1. The patient has a urine protein-to-creatinine ratio (UPCR) greater than or equal to 1.5 g/g **AND** 2. The patient's eGFR is greater than or equal to 30 mL/min/1.73 m^2 **AND** 3. ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient has tried and had an inadequate response after at least 3 months of therapy with a maximally tolerated angiotensin-converting-enzyme inhibitor (ACEI, e.g., benazepril, lisinopril) or angiotensin II blocker (ARB, e.g., losartan), or a combination medication containing an ACEI or ARB **OR** B. The patient has an intolerance or hypersensitivity to an ACEI or ARB, or a combination medication containing an ACEI or ARB **OR** C. The patient has an FDA labeled contraindication to ALL ACEI or ARB agents **AND** 4. ONE of the following: A. The patient has tried and had an inadequate response after a 6-month course of glucocorticoid therapy (e.g., methylprednisolone, prednisolone, prednisone) **OR** B. The patient has an intolerance or hypersensitivity to a glucocorticoid therapy **OR** C. The patient has an FDA labeled contraindication to ALL glucocorticoid therapies **OR** D. There is support that glucocorticoid therapy is NOT appropriate for the patient **AND** 5. The patient will continue on standard of care IgAN therapy (e.g., ACEI, ARB, SGLT2, aliskiren) **OR** C. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist, nephrologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with Empaveli (pegcetacoplan), Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), or Piasky (crovalimab-akkz) **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months for PNH, 9 months for IgAN, 12 months for all other indications NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Clinical Criteria for Approval
	Renewal Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. ONE of the following: A. The patient has a diagnosis of primary immunoglobulin A nephropathy (IgAN) AND BOTH of the following: 1. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following: A. Decrease from baseline (prior to treatment with the requested agent) of urine protein-to-creatinine (UPCR) ratio **OR** B. Decrease from baseline (prior to treatment with the requested agent) in proteinuria **AND** 2. The patient will continue standard of care IgAN therapy (e.g., ACEI, ARB, SGLT2, aliskiren) **OR** B. The patient has a diagnosis Paroxysmal Nocturnal Hemoglobinuria (PNH) AND has had improvements or stabilization with the requested agent (e.g., decreased requirement of RBC transfusions, stabilization/improvement of hemoglobin, reduction of lactate dehydrogenase (LDH), stabilization/improvement of symptoms) (medical records required) **OR** C. The patient has a diagnosis other than IgAN or PNH AND has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist, nephrologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with Empaveli (pegcetacoplan), Soliris (eculizumab), Ultomiris (ravulizumab-cwvz), or Piasky (crovalimab-akkz) **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months

Factor VIII and von Willebrand Factor

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#

Advate®
 	
(antihemophilic Factor [recombinant])
 	
Lyophilized powder for reconstitution, for intravenous injection
	• Children and adults with hemophilia A (congenital factor VIII deficiency) for:
	  ○ Control and prevention of bleeding episodes
	  ○ Perioperative management
	  ○ Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
	
	Advate is not indicated for treatment of von Willebrand disease
		Recombinant Factor VIII concentrate	1

Adynovate®
 	
(antihemophilic Factor [recombinant], PEGylated)
 	
Lyophilized powder for solution for intravenous injection
	• Children and adults with hemophilia A (congenital factor VIII deficiency) for:
	  ○ On-demand treatment and control of bleeding episodes
	  ○ Perioperative management
	  ○ Routine prophylaxis to reduce the frequency of bleeding episodes
	
	Limitation of Use:
	
	Adynovate is not indicated for treatment of von Willebrand disease
		Recombinant Factor VIII concentrate	2

Afstyla®
 	
(antihemophilic Factor [recombinant], Single Chain)
	• Adults and children with hemophilia A (congenital Factor VIII deficiency) for:
	  ○ On-demand treatment and control of bleeding episodes
	  ○ Routine prophylaxis to reduce the frequency of bleeding episodes
	  ○ Perioperative management of bleeding
		Recombinant Factor VIII concentrate	3

Agent(s)	FDA Indication(s)	Notes	Ref#
Lyophilized powder for solution for intravenous injection	Limitation of Use: Afstyla is not indicated for treatment of von Willebrand disease		
Alphanate® (antihemophilic Factor/von Willebrand Factor Complex [human]) Lyophilized powder for solution for intravenous use	• Control and prevention of bleeding in adult and pediatric patients with hemophilia A • Surgical and/or invasive procedures in adult and pediatric patients with von Willebrand disease (VWD) in whom desmopressin (DDAVP) is either ineffective or contraindicated. Alphanate is not indicated for patients with severe VWD (Type 3) undergoing major surgery	Pooled human plasma antihemophilic Factor/von Willebrand Factor complex	4

Altuviiio®
 	
(antihemophilic factor [recombinant], Fc-VWF-XTEN fusion protein-ehtl)
 	
Lyophilized powder foe intravenous use
	• Use in adults and children with hemophilia A (congenital Factor VIII deficiency) for
	  ○ Routine prophylaxis to reduce the frequency of bleeding episodes
	  ○ On-demand treatment & control of bleeding episodes
	  ○ Perioperative management of bleeding
	
	Limitation of Use:
	Altuviiio is not indicated for the treatment of von Willebrand disease
		Recombinant antihemophilic Factor	34

Eloctate®
 	
(antihemophilic Factor [recombinant], Fc fusion protein)
 	
Lyophilized powder for solution for intravenous injection
	• Adults and children with Hemophilia A (congenital Factor VIII deficiency) for:
	  ○ On-demand treatment and control of bleeding episodes
	  ○ Perioperative management of bleeding
	  ○ Routine prophylaxis to reduce the frequency of bleeding episodes
	
	Limitation of Use:
	
	Eloctate is not indicated for treatment of von Willebrand disease
		Recombinant Factor VIII concentrate	5

Agent(s)	FDA Indication(s)	Notes	Ref#

Esperoct®
 	
(antihemophilic Factor [recombinant], glycopegylated-exei)
 	
Lyophilized powder for solution for intravenous injection
	• Adults and children with hemophilia A for:
	  ○ On-demand treatment and control of bleeding episodes
	  ○ Perioperative management of bleeding
	  ○ Routine prophylaxis to reduce the frequency of bleeding episodes
	
	Esperoct is not indicated for the treatment of von Willebrand disease
		Recombinant Factor VIII concentrate	6

Hemofil M® (antihemophilic Factor [human], method M, monoclonal) Dried preparation for reconstitution for intravenous use	• Indicated in hemophilia A (classical hemophilia) for the prevention and control of hemorrhagic episodes. Hemofil M is not indicated in von Willebrand disease	Human Plasma-Derived Immunoaffinity-Purified Factor VIII concentrate	7
Humate-P® (antihemophilic Factor/von Willebrand Factor Complex [human]) Lyophilized powder for reconstitution for intravenous use	• Treatment and prevention of bleeding in adults with hemophilia A • Treatment of spontaneous and trauma-induced bleeding episodes in adult and pediatric patients with von Willebrand disease (VWD) • Prevention of excessive bleeding during and after surgery in adult and pediatric patients with VWD Use in VWD applies to patients with severe VWD as well as patients with mild to moderate VWD where the use of desmopressin is known or suspected to be inadequate Humate-P is not indicated for the prophylaxis of spontaneous bleeding episodes in VWD	Human plasma antihemophilic Factor/von Willebrand Factor complex	8
Jivi®	• Use in previously treated adults and adolescents (12 years of age and older) with hemophilia A (congenital Factor VIII deficiency) for:	Recombinant Factor VIII concentrate	9

Agent(s)	FDA Indication(s)	Notes	Ref#
(antihemophilic Factor [recombinant], PEGylated-aucl) Lyophilized powder for solution for intravenous use	○ On-demand treatment and control of bleeding episodes ○ Perioperative management of bleeding ○ Routine prophylaxis to reduce the frequency of bleeding episodes Limitations of Use: • Jivi is not indicated for use in children less than 12 years of age due to a greater risk for hypersensitivity reactions • Jivi is not indicated for use in previously untreated patients (PUPs) • Jivi is not indicated for the treatment of von Willebrand disease		
Koāte® (antihemophilic Factor [human]) Lyophilized powder for solution for intravenous injection	• Control or prevention of bleeding episodes or in order to perform emergency and elective surgery on individuals with hemophilia Limitations of Use: Koāte is not indicated for the treatment of von Willebrand disease	Human Plasma-Derived Immunoaffinity-Purified Factor VIII concentrate	10
Kogenate FS® (antihemophilic Factor [recombinant], formulated with sucrose) Lyophilized powder for reconstitution with vial adapter for intravenous use	• On-demand treatment and control of bleeding episodes in adults and children with hemophilia A • Perioperative management of bleeding in adults and children with hemophilia A • Routine prophylaxis to reduce the frequency of bleeding episodes in adults with hemophilia A • Routine prophylaxis to reduce the frequency of bleeding episodes in children with hemophilia A and to reduce the risk of joint damage in children without pre-existing joint damage Kogenate FS is not indicated for the treatment of von Willebrand disease	Recombinant Factor VIII concentrate	11

Agent(s)	FDA Indication(s)	Notes	Ref#

Kovaltry®
 	
(antihemophilic Factor [recombinant])
 	
Lyophilized powder for solution for intravenous injection
	• Indicated for use in adults and children with hemophilia A (congenital Factor VIII deficiency) for:
	  ○ On-demand treatment and control of bleeding episodes
	  ○ Perioperative management of bleeding
	  ○ Routine prophylaxis to reduce the frequency of bleeding episodes
	
	Kovaltry is not indicated for the treatment of von Willebrand disease
		Recombinant Factor VIII concentrate	12

NovoEight®
 	
(antihemophilic Factor [recombinant])
 	
Lyophilized powder for solution for intravenous use
	• Adults and children with hemophilia A for:
	  ○ On-demand control and prevention of bleeding
	  ○ Perioperative management
	  ○ Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.
	
	NovoEight is not indicated for the treatment of von Willebrand disease
		Recombinant Factor VIII concentrate	13

Nuwiq®
 	
(antihemophilic Factor [recombinant])
 	
Lyophilized powder for solution for intravenous injection
	• Adults and children with Hemophilia A for:
	  ○ On-demand treatment and control of bleeding episodes
	  ○ Perioperative management of bleeding
	  ○ Routine prophylaxis to reduce the frequency of bleeding episodes
	
	Nuwiq is not indicated for the treatment of von Willebrand disease.
		Recombinant Factor VIII concentrate	14

Recombinate® (antihemophilic Factor [recombinant]) Lyophilized powder for reconstitution for intravenous injection	• Indicated in hemophilia A (classical hemophilia) for the prevention and control of hemorrhagic episodes • Perioperative management of patients with hemophilia A (classical hemophilia)	Recombinant Factor VIII concentrate	15

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Recombinate can be of therapeutic value in patients with acquired Factor VIII inhibitors not exceeding 10 Bethesda Units per mL. Recombinate is not indicated for the treatment of von Willebrand disease.		

Vonvendi®
 	
(von Willebrand Factor [recombinant])
 	
Solution for intravenous use
	• Adults (age 18 and older) diagnosed with von Willebrand disease (VWD) for:
	  ○ On-demand treatment and control of bleeding episodes
	  ○ Perioperative management of bleeding
	  ○ Routine prophylaxis to reduce the frequency of bleeding episodes in patients with severe Type 3 von Willebrand disease receiving on-demand therapy
		Recombinant von Willebrand Factor	16

Wilate® (von Willebrand Factor/Coagulation Factor VIII Complex [human]) Lyophilized powder for solution for intravenous use	• On-demand treatment and control of bleeding episodes in children and adults with von Willebrand disease (VWD) • Perioperative management of bleeding in children and adults with VWD • Routine prophylaxis to reduce the frequency of bleeding episodes in adolescents and adults with hemophilia A • On-Demand treatment and control of bleeding episode in adolescents and adults with hemophilia A	Human plasma-derived, sterile, purified, double virus inactivated von Willebrand Factor/Coagulation Factor VIII complex	17

Xyntha®/Xyntha® Solofuse®
 	
(antihemophilic Factor [recombinant])
 	
Lyophilized powder for solution for intravenous injection
	• Indicated for use in adults and children with hemophilia A for:
	  ○ On-demand treatment for control and prevention of bleeding episodes
	  ○ Perioperative management
	  ○ Routine prophylaxis to reduce the frequency of bleeding episodes
		Recombinant Factor VIII concentrate	18

Agent(s)	FDA Indication(s)	Notes	Ref#
	Xyntha/Xyntha Solofuse is not indicated in patients with von Willebrand's disease		

CLINICAL RATIONALE

Hemophilia A	Hemophilia A, also called Factor VIII (FVIII) deficiency or classic hemophilia, is a genetic disorder caused by missing or defective Factor VIII (FVIII), a clotting protein. Although it is passed down from parents to children, about 1/3 of cases found have no previous family history.(19) Treatment for hemophilia A is dependent on several factors and there is not a universal therapy that will work for all patients. Clinically the hallmark of bleeding in hemophilia is bleeding into the joints, muscles, and soft tissues. The severity and the risk of that bleeding can be correlated to the residual amount of factor activity that can be measured in the blood. Patients with severe disease have less than 1% residual activity, and often have zero. These are the patients who are at risk for spontaneous as well as traumatic bleeding. Having over 5% residual amount makes bleeding into the joints very unusual (although not inconceivable), and most bleeding is triggered only by trauma. Residual activity of 1-5% appears for the most part to prevent spontaneous bleeding, but patients can still be at risk for joint bleeds with even relatively minor trauma.(25) The main goal of any therapy is to completely prevent bleeding. The current World Hemophilia Federation Guidelines for the Management of Hemophilia state:(26) • Both virus-inactivated plasma-derived and recombinant clotting factor concentrates (CFCs), as well as other hemostasis products when appropriate can be used for treatment of bleeding and prophylaxis in people with hemophilia • Prophylaxis is the standard of care for people with severe hemophilia, and for some people with moderate hemophilia or for those with a severe bleeding phenotype and/or a high risk of spontaneous life-threatening bleeding • Episodic CFC replacement should not be considered a long-term option for the management of hemophilia as it does not alter its natural history of spontaneous bleeding and related complications

	• Emerging therapies in development with alternative modes of delivery (e.g., subcutaneous injection) and novel targets may overcome the limitations of standard CFC replacement therapy (i.e., need for intravenous administration, short half-life, risk of inhibitor formation) • The development of gene therapies for hemophilia has advanced significantly, with product registration likely in the near future • Gene therapy should make it possible for some people with hemophilia to aspire to and attain much better health outcomes and quality of life than that attainable with currently available hemophilia therapies • Given the ongoing advances transforming the hemophilia treatment landscape, it is important to establish systems to constantly monitor developments in emerging and gene therapies for hemophilia and make them available as soon as possible following approval by regulatory authorities The National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC) suggests the number of doses required for provision of home therapy varies greatly and is dependent upon the type of hemophilia (FVIII, FIX), the level of severity (severe, moderate, mild), the presence of an inhibitor, the prescribed regimen (on-demand, prophylaxis, immune tolerance), the number of bleeding episodes experienced regardless of the prescribed regimen, individual pharmacokinetics, the products utilized, and the level of physical activity. For patients on prophylaxis, a minimum of one major dose and two minor doses should be available in addition to the prophylactic doses utilized monthly. For patients with severe or moderate hemophilia treated on-demand, the number of doses required to be available at home may be based upon historical bleeding patterns, with at least one major and two minor doses added to assure a level of safety.(20) A major dose is defined as a correction of clotting factor that achieves a level of 60-100+% clotting factor activity that is utilized to treat a bleeding episode that is expected to require a higher hemostatic level such as when bleeds occur in a target joint, or joint/area with a risk of significant sequelae (e.g., hip, head, GI bleed). A minor dose is defined as a correction of clotting factor that achieves a level of 30-60% clotting factor activity that is utilized to treat a bleeding episode that is treated early, in a non-critical area and treatable with a lower hemostatic level (e.g., early non-major joints, small muscle bleeds, and skin/soft tissue, etc.).(20) Recombinant FVIII (rFVIII) products are treatment of choice for hemophilia A as recommended by MASAC. First generation rFVIII products contain animal and/or human plasma-derived proteins in the cell culture medium and in the final

	formulation vial (Recombinate). Second generation rFVIII products contain animal or human plasma proteins in the culture medium but not in the final formulation (Helixate, Kogenate). Third/fourth generation rFVIII products do not contain any animal or human plasma-derived proteins in the culture medium or in the final formulation vial.(22) In view of the demonstrated benefits of prophylaxis (regular/scheduled administration of clotting factor concentrate to prevent bleeding) begun at a young age in persons with hemophilia A or B, MASAC recommends that prophylaxis be considered standard of care therapy for individuals with severe hemophilia A (FVIII less than 1%) including those with inhibitors. Prophylactic therapy may also be considered for persons with moderate and mild hemophilia with a severe phenotype. Prophylactic therapy should be instituted early (prior to the onset of frequent bleeding).(35) Approximately 1 in 5 people with hemophilia A will develop an antibody – called an inhibitor – to the clotting factor concentrate(s) used to treat or prevent their bleeding episodes. Developing an inhibitor is one of the most serious and costly medical complications of a bleeding disorder because it becomes more difficult to treat bleeds. Inhibitors most often appear in the first 50 exposure days of clotting factor concentrates.(25,27) The National Hemophilia Foundation classifies inhibitors as low responding and high responding in addition to low titer (less than 5 BU) and high titer (greater than or equal to 5 BU). In low responding inhibitors when the patient receives Factor VIII the inhibitor titer does not rise. These patients can be treated with higher doses of the CFC. If the inhibitor titer increases with CFC it is considered high-responding. For high-responding inhibitors, the situation becomes much more complicated as even large doses of infused CFC are often rendered ineffectual by the sheer potency of the antibody response.(26) In the cases of high-responding inhibitors treatment is based on several components including the type of hemophilia and the nature of the bleed. During a life or limb-threatening bleeding episode, physicians can remove antibodies from the body using plasmapheresis. This is only a temporary solution however as within a few days the body will produce large amounts of new antibodies. For the person with a high responding inhibitor there are therapies that can effectively treat bleeds by circumventing the need to replace FVIII. These agents are commonly referred to as bypassing agents (BPAs) and include activated prothrombin complex concentrate (aPCC) and recombinant activated Factor VII

	concentrates. Hemlibra, a therapy that does not function by FVIII or Factor IX replacement, is a newer therapy that can be used for these patients.(26) If left unchecked, a persistent inhibitor will present a severe burden on patients and families, as the ongoing physical, emotional, and in many cases financial toll continue to intensify. Healthcare providers will often attempt to proactively stamp out an inhibitor through immune tolerance therapy (ITI). ITI is an approach to inhibitor eradication where the body's immune system begins to tolerate a therapy after daily doses of factor are administered over time. The majority of people who undergo ITI therapy will see an improvement within 12 months, but more difficult cases can take two years or longer.(27) There is a general consensus that failure of ITI is the inability to achieve successful tolerance within 2-3 years of initiation of an ITI regimen.(26) ITI can take several months to several years to be effective. The Hemophilia Federation of America recommends that if success has not occurred within 33 months of beginning ITT and there is a lack of a 20% decrease in the inhibitor titer over a 6 month period, that it is considered a failure.(23) Emicizumab-kxwh is a recombinant, humanized, bispecific immunoglobulin G4 monoclonal antibody that substitutes for part of the cofactor function of activated factor VIII (FVIII) by bridging activated factor IX and Factor X. Emicizumab-kxwh is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children of all ages, newborn and older, with hemophilia A with and without Factor VIII inhibitors. There is significant reduction in annualized bleeding rates at all doses for all age groups, with or without inhibitors.(24) There is limited data on the concomitant use of emicizumab prophylaxis during ITI. There is a case series of children with hemophilia A and inhibitors who underwent ITI in combination with emicizumab prophylaxis (Atlanta Protocol), and a larger clinical trial of this protocol is underway [MOTIVATE study (NCT04023019)].(24) The MOTIVATE study is a non-interventional, multicenter, observational, international study in male persons with hemophilia A who have developed inhibitors to any replacement coagulation Factor VIII (FVIII product). The purpose of the study is to capture different approaches in the management and to evaluate the efficacy and safety of immune tolerance induction, including the combination of FVIII and emicizumab. Patients will be assigned to 1 of 3 groups based on the treatments they receive and may switch to another group if their treatment is changed. The 3 groups are:(30) • ITI with Nuwiq, Octanate, or Wilate

	• ITI with Nuwiq, Octanate, or Wilate with emicizumab • Prophylaxis with emicizumab, aPCC, or recombinant FVIIIa without immune tolerance induction
von Willebrand disease	von Willebrand disease (VWD) is a common, inherited bleeding disorder. VWD affects males and females equally in up to 1% of the population. There are several classification types of VWD which includes types 1 and 2 which are characterized by quantitative deficiencies of von Willebrand Factor (VWF) and types 2A, 2B, 2M, and 2N which are qualitative variants. Clinically, VWD patients experience several symptoms including: (32) • Excessive mucocutaneous bleeding including heavy menstrual bleeding • Epistaxis • Easy bruising • Prolonged bleeding from minor wounds and the oral cavity • Gastrointestinal bleeding • Bleeding after dental work, childbirth, and surgery • Musculoskeletal bleeding in severe cases Persons with type 1, 2A, 2M and 2N VWD may be treated with desmopressin (DDAVP Injection or Stimate Nasal Spray) if they have been shown by a DDAVP trial to be responsive. Response to DDAVP should be assessed one and four hours after DDAVP; the one-hour assessment is particularly important for patients suspected of having type 1 C VWD. A desmopressin response requires an increase of at least greater than 2 times the baseline VWF activity level and a sustained increase of both VWF and Factor VIII:C levels greater than 0.50 IU/mL for at least 4 hours.(33) Persons with type 2B and type 3 VWD and those with type 1, 2A, 2M, and 2N who have been shown to be nonresponsive to DDAVP, should be treated with a Factor VIII/VWF concentrate that is known to contain the higher molecular weight multimers of von Willebrand Factor and that has been virally attenuated to eliminate transmission of HIC and hepatitis A, B, and C.(33) In patients with VWD with a history of major and frequent bleeds, the American Society of Hematology (ASH), the International Society for Thrombosis and Haemostasis (ISTH), the National Hemophilia Foundation (NHF), and the World Federation of Hemophilia (WFH) guideline panel suggests using long-term prophylaxis with Factor replacement rather than no prophylaxis. Prophylaxis in VWD is defined as a period of at least 3 months of treatment of VWF concentrate

	at least once weekly, or for women with heavy menstrual bleeding, the use of VWF concentrate at least once per menstrual cycle.(33) Prior to surgery in a patient with VWD, consultation should be obtained with a pediatric or adult hematologist who specializes in the management of individuals with inherited bleeding disorders. This consultation should cover risk of bleeding with procedure and duration of risk. Treatment plan should be developed including such issues as the need for a DDAVP trial; type of fluid replacement or fluid restriction; dose and duration of DDAVP to be used; appropriate dose, timing, and duration of factor replacement therapy; and use of adjunctive medications (antifibrinolytics and topical agents). The ASH ISRH NHF WFH 2021 guidelines on the management of VWD conditionally recommend that desmopressin should not be used for major surgery and factor replacement should contain both FVIII and VWF activity levels of 0.50 IU/mL for at least 3 days after surgery.(33)

Safety	• **Advate** is contraindicated in:(1)
	  ○ Patients who have life-threatening hypersensitivity reactions, including anaphylaxis, to mouse or hamster protein or other constituents of the product (mannitol, trehalose, sodium chloride, histidine, Tris, calcium chloride, polysorbate 80, and/or glutathione)
	• **Adynovate** is contraindicated in:(2)
	  ○ Patients who have had prior anaphylactic reaction to Adynovate, the parent molecule (Advate), mouse or hamster protein, or excipients of Adynovate
	• **Afstyla** is contraindicated in:(3)
	  ○ Patients who have had life-threatening hypersensitivity reactions, including anaphylaxis to Afstyla or its excipients, or hamster proteins
	• **Alphanate** is contraindicated in:(4)
	  ○ Patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product of its components
	• **Altuviiio** is contraindicated in:(34)
	  ○ Patients who have had severe hypersensitivity reactions, including anaphylaxis, to Altuviiio or excipients of Altuviiio
	• **Eloctate** is contraindicated in:(5)
	  ○ Patients who have had life-threatening hypersensitivity reactions, including anaphylaxis, to Eloctate or excipients of Eloctate (sucrose, sodium chloride, L-histidine, calcium chloride and polysorbate 20)

	• **Esperoct** is contraindicated in:(6)
	  ○ Patients who have known hypersensitivity to Esperoct or its components, including hamster protein
	• **Hemofil M** is contraindicated in:(7)
	  ○ Patients with a known hypersensitivity to the active substance, to excipients, or to mouse proteins
	• **Humate-P** is contraindicated in:(8)
	  ○ Anaphylactic or severe systemic reaction to antihemophilic factor or VWF preparations
	• **Jivi** is contraindicated in:(9)
	  ○ Patients who have a history of hypersensitivity reactions to the active substance, polyethylene glycol (PEG), mouse or hamster proteins, or other constituents of the product
	• **Koāte** is contraindicated in:(10)
	  ○ Patients who have had hypersensitivity reactions, including anaphylaxis, to Koāte or its components
	• **Kogenate FS** is contraindicated in:(11)
	  ○ Patients who have life-threatening hypersensitivity reactions, including anaphylaxis to mouse or hamster protein or other constituents of the product
	• **Kovaltry** is contraindicated in:(12)
	  ○ Patients who have history of hypersensitivity reactions to the active substance, mouse or hamster protein, or other constituents of the product
	• **NovoEight** is contraindicated in:(13)
	  ○ Patients who have had life-threatening hypersensitivity reactions, including anaphylaxis, to NovoEight or its components, including hamster proteins
	• **Nuwiq** is contraindicated in:(14)
	  ○ Patients who have manifested life-threatening hypersensitivity reactions, including anaphylaxis, to the product or its components
	• **Recombinate** is contraindicated in:(15)
	  ○ Patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including bovine, mouse or hamster protein
	• **Vonvendi** is contraindicated in:(16)
	  ○ Patients who have had life-threatening hypersensitivity reactions to Vonvendi or its components (tri-sodium citrate dihydrate, glycine, mannitol, trehalose-dihydrate polysorbate 80m and hamster or mouse proteins)
	• **Wilate** is contraindicated in:(17)

	○ Patients with known hypersensitivity reactions, including anaphylactic or severe systemic reaction, to human plasma-derived products, any ingredient in the formulation, or components of the container • **Xyntha** is contraindicated in:(18) ○ Patients who have manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including hamster proteins

REFERENCES

Number	Reference
1	Advate prescribing information. Takeda Pharmaceuticals America, Inc. March 2023.
2	Adynovate prescribing information. Takeda Pharmaceuticals America, Inc. August 2023.
3	Afstyla prescribing information. CSL Behring Lengnau AG. June 2023.
4	Alphanate prescribing information. Grifols USA, LLC. November 2022.
5	Eloctate prescribing information. Bioverativ Therapeutics Inc. May 2023.
6	Esperoct prescribing information. Novo Nordisk. August 2022.
7	Hemofil M prescribing information. Takeda Pharmaceuticals America, Inc. March 2023.
8	Humate-P prescribing information. Takeda Pharmaceuticals America, Inc. March 2023.
9	Jivi prescribing information. Bayer HealthCare LLC. August 2018.
10	Koāte prescribing information. Kedrion Biopharma, Inc. January 2022.
11	Kogenate FS prescribing information. Bayer HealthCare LLC. December 2019.
12	Kovaltry prescribing information. Bayer HealthCare LLC. December 2022.
13	NovoEight prescribing information. Novo Nordisk. July 2020.

Number	Reference
14	Nuwiq prescribing information. Octapharma USA Inc. June 2021.
15	Recombinate prescribing information. Takeda Pharmaceuticals America, Inc. March 2023.
16	Vonvendi prescribing information. Takeda Pharmaceuticals America, Inc. March 2023.
17	Wilate prescribing information. Octapharma USA Inc. November 2019.
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21	Reference no longer used
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26	Srivastave A, Santagostino E, Dougall A, et al. World Federation of Hemophilia Guidelines for the Management of Hemophilia. 3rd edition. August 2020.
27	CDC Centers for Disease Control and Prevention. Inhibitors and Hemophilia. https://www.cdc.gov/ncbddd/hemophilia/inhibitors.html

Number	Reference
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29	National Hemophilia Foundation. Bleeding Disorders A-Z/ Overview/ Inhibitors/ Immune Tolerance. https://www.hemophilia.org/bleeding-disorders-a-z/overview/inhibitors/immune-tolerance
30	Clinicatrials.gov. NCT04023019. Treatment of Hemophilia A Patients With FVIII Inhibitors (MOTIVATE). https://clinicaltrials.gov/ct2/show/NCT04023019?term=NCT04023019&draw=2&rank=1
31	Reference no longer used
32	James PD, Connell NT, Ameer B, et al. ASH ISTH NHF WFH 2021 guidelines on the diagnosis of von Willebrand disease. Blood Advances 12 January 2021. Volume 5, Number 1. 280-300.
33	Medical and Scientific Advisory Committee. MASAC Document 266 – MASAC Recommendations Regarding the Treatment of von Willebrand Disease. March 2021.
34	Altuviiio prescribing information. Bioverativ Therapeutics Inc. March 2023.
35	Medical and Scientific Advisory Council. MASAC Document 267 - Recommendation Concerning Prophylaxis for Hemophilia A and B with and without inhibitors. April 2022.

ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
85100010252 1	Advate ; Kovaltry	antihemophilic factor recomb (rahf-pfm) for inj	1000 UNIT ; 1500 UNIT ; 2000 UNIT ; 250 UNIT ; 3000	Dependent on patient weight and			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
			UNIT ; 4000 UNIT ; 500 UNIT	number of doses			
85100010402 1	Adynovate	antihemophilic factor recomb pegylated for inj	1000 UNIT ; 1500 UNIT ; 2000 UNIT ; 250 UNIT ; 3000 UNIT ; 500 UNIT ; 750 UNIT	Dependent on patient weight and number of doses			
85100010556 4	Afstyla	antihemophilic fact rcmb single chain for inj kit	1000 UNIT ; 1500 UNIT ; 2000 UNIT ; 250 UNIT ; 2500 UNIT ; 3000 UNIT ; 500 UNIT	Dependent on patient weight and number of doses			
85100015102 1	Alphanate ; Humate-p	antihemophilic factor/vwf (human) for inj	1000 UNIT ; 1000-2400 UNIT ; 1500 UNIT ; 2000 UNIT ; 250 UNIT ; 250-600 UNIT ; 500 UNIT ; 500-1200 UNIT	Dependent on patient weight and number of doses		02-17-2022	
85100010312 1	Altuviiio	antihemophilic fact rcmb fc-vwf-xten-ehtl for inj	1000 UNIT ; 2000 UNIT ; 250 UNIT ; 3000 UNIT ; 4000 UNIT ; 500 UNIT ; 750 UNIT	Dependent on patient weight and number of doses			
85100010302 1	Eloctate	antihemophilic factor rcmb (bdd-rfviiifc) for inj	1000 UNIT ; 1500 UNIT ; 2000 UNIT ; 250 UNIT ; 3000 UNIT ; 4000 UNIT ; 500 UNIT ; 5000	Dependent on patient weight and number of doses			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
			UNIT ; 6000 UNIT ; 750 UNIT				
85100010352 1	Esperoct	antihemophilic factor recomb glycopeg-exei for inj	1000 UNIT ; 1500 UNIT ; 2000 UNIT ; 3000 UNIT ; 500 UNIT	Dependent on patient weight and number of doses			
85100010002 1	Hemofil m ; Koate ; Koate-dvi	antihemophilic factor (human) for inj	1000 UNIT ; 1700 UNIT ; 250 UNIT ; 500 UNIT	Dependent on patient weight and number of doses			
85100010412 1	Jivi	antihemophil fact rcmb(bdd-rfviii peg-aucl) for inj ; antihemophil fact rcmb(bdd-rfviii peg-aucl)for inj	1000 UNIT ; 2000 UNIT ; 3000 UNIT ; 500 UNIT	Dependent on patient weight and number of doses			
85100010206 4	Kogenate fs	antihemophilic factor recomb (rfviii) for inj kit	1000 UNIT ; 2000 UNIT ; 250 UNIT ; 3000 UNIT ; 500 UNIT	Dependent on patient weight and number of doses			
85100010332 1	Novoeight	antihemophilic fact rcmb (bd trunc-rfviii) for inj	1000 UNIT ; 1500 UNIT ; 2000 UNIT ; 250 UNIT ; 3000 UNIT ; 500 UNIT	Dependent on patient weight and number of doses			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
85100010226 4	Nuwiq	antihemophil fact rcmb (bdd-rfviii,sim) for inj kit ; antihemophil fact rcmb(bdd-rfviii,sim) for inj kit	1000 UNIT ; 1500 UNIT ; 2000 UNIT ; 250 UNIT ; 2500 UNIT ; 3000 UNIT ; 4000 UNIT ; 500 UNIT	Dependent on patient weight and number of doses			
85100010222 1	Nuwiq	antihemophilic fact rcmb (bdd-rfviii,sim) for inj ; antihemophilic factor rcmb (bdd-rfviii,sim) for inj	1000 UNIT ; 1500 UNIT ; 2000 UNIT ; 250 UNIT ; 2500 UNIT ; 3000 UNIT ; 4000 UNIT ; 500 UNIT	Dependent on patient weight and number of doses			
85100010202 1	Recombinate	antihemophilic factor recomb (rfviii) for inj	1241 -1800 UNIT ; 1801 -2400 UNIT ; 220 -400 UNIT ; 401 -800 UNIT ; 801 - 1240 UNIT	Dependent on patient weight and number of doses			
85100070202 1	Vonvendi	von willebrand factor (recombinant) for inj	1300 UNIT ; 650 UNIT	Dependent on patient weight and number of doses		02-17-2022	
85100015106 4	Wilate	antihemophilic factor/vwf (human) for inj	1000-1000 UNIT ; 500-500 UNIT	Dependent on patient weight and number of doses		02-17-2022	

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
85100010266 4	Xyntha ; Xyntha solofuse	antihemophil fact rcmb (bdd-rfviii,mor) for inj kit ; antihemophil fact rcmb(bdd-rfviii,mor) for inj kit	1000 UNIT ; 2000 UNIT ; 250 UNIT ; 3000 UNIT ; 500 UNIT	Dependent on patient weight and number of doses			

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Preferred and Non-Preferred Agents to be determined by client**

Preferred Agents for Hemophilia A	Non-Preferred Agents for Hemophilia A
Advate Adynovate Afstyla Altuviiio Eloctate Esperoct Jivi Kogenate FS Kovaltry NovoEight Nuwiq Recombinate Wilate Xyntha/Xyntha solofuse	Alphanate Hemofil-M Humate-P Koāte

Module	Clinical Criteria for Approval

Preferred Agents for von Willebrand disease	Non-Preferred Agents for von Willebrand disease
Vonvendi Wilate	Alphanate Humate-P

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Agents Eligible for Continuation of Therapy
All target agents are eligible for continuation of therapy

1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR**
2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR**

B. BOTH of the following:
1. ONE of the following:
A. The patient has a diagnosis of hemophilia A (also known as Factor VIII deficiency or classic hemophilia) AND ONE of the following:
1. The patient is currently experiencing a bleed AND BOTH of the following:
A. The patient is out of medication **AND**
B. The patient needs to receive a ONE TIME emergency supply of medication **OR**
2. ALL of the following:
A. The requested agent is FDA labeled or compendia supported for a diagnosis of hemophilia A **AND**

Module	Clinical Criteria for Approval
	B. The requested agent is being used for ONE of the following: 1. Prophylaxis AND the patient will NOT be using the requested agent in combination with Hemlibra (emicizumab-kxwh) **OR** 2. As a component of Immune Tolerance Therapy (ITT)/Immune Tolerance Induction (ITI) AND BOTH of the following: A. The patient will NOT be using the requested agent in combination with Hemlibra (emicizumab-kxwh) **AND** B. ONE of the following: (medical records required) 1. The patient has NOT had more than 33 months of ITT/ITI therapy **OR** 2. There is support for the continued use of ITT/ITI therapy (i.e., the patient has had a greater than or equal to 20% decrease in inhibitor level over the last 6 months and needs further treatment to eradicate inhibitors) **OR** 3. On-demand use for bleeds **OR** 4. Peri-operative management of bleeding **AND** C. If the client has a preferred agent(s), then ONE of the following: 1. The requested agent is a preferred agent **OR** 2. The patient has tried and had an inadequate response to ALL of the preferred agent(s) for the requested indication **OR** 3. The patient has an intolerance or hypersensitivity to ALL of the preferred agent(s) for the requested indication **OR** 4. The patient has an FDA labeled contraindication to ALL of the preferred agents for the requested indication **OR**

Module	Clinical Criteria for Approval
	B. The patient has a diagnosis of von Willebrand disease (VWD) AND ALL of the following: 1. The requested agent is FDA labeled or compendia supported for a diagnosis of von Willebrand disease **AND** 2. ONE of the following: A. The patient is currently experiencing a bleed AND BOTH of the following: 1. The patient is out of medication **AND** 2. The patient needs to receive a ONE TIME emergency supply of medication **OR** B. The patient has type 1, 2A, 2M or 2N VWD AND ONE of the following: 1. The patient has tried and had an inadequate response to desmopressin (e.g., DDAVP injection, Stimate nasal spray) **OR** 2. The patient did not respond to a DDAVP trial with 1 and 4 hour post infusion bloodwork **OR** 3. The patient has an intolerance or hypersensitivity to desmopressin **OR** 4. The patient has an FDA labeled contraindication to desmopressin **OR** 5. The patient cannot use desmopressin (e.g., shortage in marketplace) **OR** C. The patient has type 2B or 3 VWD **AND** 3. The requested agent will be used for ONE of the following: A. Prophylaxis AND ONE of the following: 1. The requested agent is Vonvendi AND ONE of the following: A. The patient has severe Type 3 VWD **OR** B. The patient has another subtype of VWD AND the subtype is FDA labeled for prophylaxis use **OR** 2. The requested agent is NOT Vonvendi **OR** B. On-demand use for bleeds **OR** C. Peri-operative management of bleeding **AND** 4. If the client has a preferred agent(s), then ONE of the following: A. The requested agent is a preferred agent **OR**

Module	Clinical Criteria for Approval
	B. The patient has tried and had an inadequate response to ALL of the preferred agent(s) for the requested indication **OR** C. The patient has an intolerance or hypersensitivity to ALL of the preferred agent(s) for the requested indication **OR** D. The patient has an FDA labeled contraindication to ALL of the preferred agents for the requested indication **AND** 2. If the patient has an FDA labeled indication, ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis [e.g., prescriber working in a hemophilia treatment center (HTC), hematologist with hemophilia experience] or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 4. The prescriber must provide the actual prescribed dose with ALL of the following: A. Patient's weight **AND** B. Intended use/regimen: (e.g., prophylaxis, ITT/ITI, on-demand, peri-operative) **AND** C. If the patient has a diagnosis of hemophilia A BOTH of the following: 1. Severity of the factor deficiency (i.e., severe is less than 1% factor activity, moderate is greater than or equal to 1 to less than or equal to 5% factor activity, mild is greater than 5 to 40% factor activity) **AND** 2. Inhibitor status **AND** 5. ONE of the following: A. The patient will NOT be using the requested agent in combination with another agent in the same category (e.g., Factor VIII agents, Factor VIII and von Willebrand Factor combination agents) included in this program **OR** B. There is support for the use of more than one unique agent in the same category (medical records required) **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** One time emergency use: up to 2 weeks, Peri-operative dosing: 1 time per request, On-demand: up to 3 months, Prophylaxis: up to 12 months ITT/ITI: up to 6 months - or up to a total of 33 months ITT/ITI therapy, or requested duration, whichever is shortest

Module	Clinical Criteria for Approval
	NOTE: If Quantity Limit applies, please see Quantity Limit criteria **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process (if current request is for ONE TIME emergency use or if patient ONLY has previous approval(s) for emergency use, must use Initial Evaluation) **AND** 2. If the patient is using the requested agent for prophylaxis, then ONE of the following: A. The patient has a diagnosis of hemophilia A AND the patient will NOT be using the requested agent in combination with Hemlibra (emicizumab-kxwh) **OR** B. The patient has another diagnosis **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis [e.g., prescriber working in a hemophilia treatment center (HTC), hematologist with hemophilia experience] or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The prescriber must provide the actual prescribed dose with ALL of the following: A. Patient's weight **AND** B. Intended use/regimen: (e.g., prophylaxis, ITT/ITI, on-demand, peri-operative) **AND** C. If the patient has a diagnosis of hemophilia A BOTH of the following: 1. Severity of the factor deficiency (i.e., severe is less than 1% factor activity, moderate is greater than or equal to 1 to less than or equal to 5% factor activity, mild is greater than 5 to 40% factor activity) **AND** 2. Inhibitor status **AND** 6. ONE of the following: A. The prescriber communicated with the patient (via any means) regarding the frequency and severity of the patient's bleeds and has verified that the patient does not have greater than 5 on-demand doses on hand **OR** B. There is support for the patient having more than 5 on-demand doses on hand **AND** 7. ONE of the following: A. The patient will NOT be using the requested agent in combination with another agent in the same category (e.g., Factor VIII agents, Factor VIII and von Willebrand Factor combination agents) included in this program **OR** B. There is support for the use of more than one unique agent in the same category (medical records required) **AND** 8. If the patient is using Immune Tolerance Therapy (ITT)/Immune Tolerance Induction (ITI), then BOTH of the following: A. The patient will NOT be using the requested agent in combination with Hemlibra (emicizumab-kxwh) **AND**

Module	Clinical Criteria for Approval
	B. ONE of the following: (medical records required) 1. The patient has NOT had more than 33 months of ITT/ITI therapy **OR** 2. There is support for the continued use of ITT/ITI therapy (i.e., the patient has had a greater than or equal to 20% decrease in inhibitor level over the last 6 months and needs further treatment to eradicate inhibitors) **Length of Approval:** Peri-operative dosing: 1 time per request On-demand: up to 3 months Prophylaxis: up to 12 months ITT/ITI: up to 6 months, or up to a total of 33 months of ITT/ITI therapy, or requested duration, whichever is shortest NOTE: If Quantity Limit applies, please see Quantity Limit criteria

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the requested agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit defined by BOTH of the following: A. The requested dose is within the FDA labeled dosing **AND** B. The requested quantity (number of doses) is appropriate based on intended use (e.g., prophylaxis, ITT/ITI, on-demand, peri-operative) **OR** 2. There is support for exceeding the defined program quantity limit (dose and/or number of doses) (medical records required) **Length of Approval:** For initial one-time emergency use: up to 2 weeks Prophylaxis: up to 12 months Both initial and renewal peri-operative dosing: 1 time per request Both initial and renewal on-demand: up to 3 months Both initial and renewal: ITT/ITI: up to 6 months, or up to a total of 33 months of ITT/ITI therapy, or requested duration, whichever is shortest

Filspari (sparsentan)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Filspari® (sparsentan) Tablet	Reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) greater than or equal to 1.5 g/g		1

CLINICAL RATIONALE

Immunoglobulin A Nephropathy	Immunoglobulin A nephropathy (IgAN), also known as Berger's disease, is a kidney disease that occurs when IgA deposits build up in the kidneys, causing inflammation that damages the glomeruli, in turn causing the kidneys to leak blood and protein into the urine. The damage may lead to scarring of the nephrons that progresses slowly over may years. Eventually, IgAN can lead to end-stage renal disease (ESRD).(4) Kidney biopsy is required to confirm the diagnosis of IgAN as there are no validated diagnostic serum or urine biomarkers for IgAN. Biopsy is indicated when a patient has signs of a severe or progressive disease. After a diagnosis has been established, guidelines recommend that all patients with IgAN be assessed for secondary causes (e.g., liver cirrhosis, HIV, hepatitis, inflammatory bowel disease).(4) The primary focus of IgAN management should be optimized supportive care [e.g., blood pressure management, maximally tolerated angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin II blocker (ARB), lifestyle modification, address cardiovascular risk]. Guidelines recommend that all patients with proteinuria greater than 0.5 g/d be treated with an ACEI or ARB irrespective of whether they have hypertension.(4) Guidelines define high risk of progression in IgAN as proteinuria greater than 0.75–1 g/d despite at least 90 days of optimized supportive care. It is suggested that patients who remain at high risk despite maximal supportive care be

	considered for a 6 month course of glucocorticoid therapy. They stress the importance of discussing treatment-emergent toxicity, particularly those who have an estimated glomerular filtration rate (eGFR) less than 50 mL/min/1.73 m^2. It is further noted that glucocorticoids should be given with extreme caution or avoided entirely in the following situations:(4) • eGFR less than 30 mL/min/1.73 m^2 • Diabetes • Obesity (BMI greater than 30 kg/m^2) • Latent infections (e.g., viral hepatitis, tuberculosis) • Secondary disease (e.g., cirrhosis) • Active peptic ulceration • Uncontrolled psychiatric illness • Severe osteoporosis The goal of treatment for these patients that remain at high risk for progressive disease is a reduction of proteinuria to less than 1 g/d.(4)
Efficacy	Filspari (sparsentan) is an endothelin and angiotensin II receptor antagonist. The effect of Filspari on proteinuria was assessed in a randomized, double-blind, active-controlled, multicenter, global study (PROTECT, NCT03762850) in adults with biopsy-proven IgAN, eGFR greater than or equal to 30 mL/min/1.73 m^2, and total urine protein greater than or equal to 1.0 g/day on a maximized stable dose of renin-angiotensin- system (RAS) inhibitor treatment for at least 12 weeks that was at least 50% of maximum labeled dose.(1,2) Patients with other glomerulopathies or those who had been recently treated with systemic immunosuppressants were excluded. Patients were randomized (1:1) to either Filspari (400 mg once daily following 200 mg once daily for 14 days) or irbesartan (300 mg once daily following 150 mg once daily for 14 days). Rescue immunosuppressive treatment could be initiated per investigator discretion during the trial, but use of SGLT2 inhibitors was prohibited. The 281 patients who reached week 36 had a mean (SD) baseline eGFR of 56 (24) mL/min/1.73 m^2. Rescue immunosuppressive treatment was initiated in 1.4% and 5.7% of Filspari and irbesartan patients, respectively. The primary endpoint of the interim analysis was the relative change from baseline in urine protein to creatinine ratio (UPCR) at week 36. The adjusted geometric mean percent change (GMPC) from baseline was -45% in the Filspari arm and -15% in the irbesartan arm, a statistically significant reduction. The ratio of adjusted geometric mean (GM) relative to baseline at week 36 was 0.65 (0.55, 0.77; 95% CI; p less than 0.0001). The treatment effect on UPCR at Week 36 was consistent across subgroups including age, sex, race, and baseline eGFR and proteinuria levels.(1)

Safety	Filspari (sparsentan) has a boxed warning for hepatotoxicity and embryo-fetal toxicity and is available only through a risk evaluation and mitigation strategy (REMS) program (Filspari REMS):(1) • Elevations in aminotransferases (ALT or AST) of at least 3 times the upper limit of normal (ULN) were observed in up to 2.5% of Filspari treated patients in clinical studies. Transaminases and bilirubin should be measured before initiating treatment, monthly for the first 12 months, and then every 3 months during treatment. Interrupt treatment and closely monitor patients who develop aminotransferase elevations more than 3x ULN. Filspari should be avoided in patients with elevated aminotransferases greater than 3 times ULN at baseline because monitoring for hepatoxicity may be more difficult and these patients may be at increased risk for serious hepatotoxicity. • Because Filspari can cause major birth defects if used by pregnant patients, pregnancy testing is required before initiation of treatment, during treatment, and one month after discontinuation of treatment with Filspari. Patients who can become pregnant must use effective contraception before the initiation of treatment, during treatment, and for one month after the discontinuation of treatment with Filspari. Filspari is contraindicated in patients who are pregnant. Filspari is contraindicated to be coadministered with ARBs, endothelin receptor antagonists (ERAs), or aliskiren.(1) Prior to initiating treatment with Filspari, discontinue use of renin-angiotensin-aldosterone system (RAAS) inhibitors, ERAs, and aliskiren.(1)

REFERENCES

Number	Reference
1	Filspari prescribing information. Travere Therapeutics, Inc. February 2023
2	Heerspink HJL, Radhakrishnan J, Alpers CE, et al. Sparsentan in patients with IgA nephropathy: a prespecified interim analysis from a randomised, double-blind, active-controlled clinical trial. The Lancet. 2023;401(10388):1584-1594. doi:10.1016/s0140-6736(23)00569-x

Number	Reference
3	Reference no longer used.
4	Rovin BH, Adler SG, Barratt J, et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. Kidney International. 2021;100(4):S1-S276. doi:10.1016/j.kint.2021.05.021
5	Reference no longer used.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of primary immunoglobulin A nephropathy (IgAN) confirmed by kidney biopsy **AND** 2. ONE of the following: A. The patient has a urine protein-to-creatinine ratio (UPCR) greater than or equal to 1.5 g/g **OR** B. The patient has proteinuria greater than or equal to 1 g/day **AND** 3. The patient's eGFR is greater than or equal to 30 mL/min/1.73 m^2 **AND** 4. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 5. ONE of the following: A. The patient has tried and had an inadequate response after at least 3 months of therapy with a maximally tolerated angiotensin-converting-enzyme inhibitor (ACEI, e.g., benazepril, lisinopril) or angiotensin II blocker (ARB, e.g., losartan), or a combination medication containing an ACEI or ARB **OR** B. The patient has an intolerance or hypersensitivity to an ACEI or ARB, or a combination medication containing an ACEI or ARB **OR** C. The patient has an FDA labeled contraindication to ALL ACEI or ARB **AND** 6. ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient has tried and had an inadequate response after a 6 month course of glucocorticoid therapy (e.g., methylprednisolone, prednisolone, prednisone) **OR** B. The patient has an intolerance or hypersensitivity to a glucocorticoid **OR** C. The patient has an FDA labeled contraindication to ALL glucocorticoids **OR** D. There is support that glucocorticoid therapy is NOT appropriate for the patient **AND** 7. The patient will NOT use the requested agent in combination with an ACEI, ARB, endothelin receptor antagonist (ERA, e.g., bosentan), or aliskiren **AND** 8. The prescriber is a specialist in the area of the patient's diagnosis (e.g., nephrologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 9. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 9 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following: A. Decrease from baseline (prior to treatment with the requested agent) of urine protein-to-creatinine (UPCR) ratio **OR** B. Decrease from baseline (prior to treatment with the requested agent) in proteinuria **AND** 3. The patient will NOT use the requested agent in combination with an angiotensin-converting-enzyme inhibitor (ACEI, e.g., benazepril, lisinopril), angiotensin II blocker (ARB, e.g., losartan), endothelin receptor antagonist (ERA, e.g., bosentan), or aliskiren **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., nephrologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Filsuvez (birch triterpenes)

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Filsuvez® (birch triterpenes) Topical gel	For the treatment of wounds associated with dystrophic and junctional epidermolysis bullosa in adult and pediatric patients 6 months of age and older		1

CLINICAL RATIONALE

Epidermolysis bullosa (EB)	Epidermolysis bullosa (EB) encompasses a number of disorders characterized by recurrent blister formation as the result of structural fragility within the skin and selected other tissues caused by mutations in CLO7A1, the gene encoding the anchoring fibril component, collagen VII. All types and subtypes of EB are rare; the overall incidence and prevalence of the disease within the United States is approximately 19 per one million live births and 8 per one million population, respectively. Clinical manifestations range widely, from localized blistering of the hands and feet to generalized blistering of the skin and oral cavity, and injury to many internal organs.(2) EB types are divided into four main groups according to the depth below the skin surface at which the blisters occur. Approximately 20% of EB cases are dystrophic (DEB), 10% junctional (JEB), and 70% simplex (EBS); Kindler syndrome is very rare. The genetic errors in EB result in defects in the proteins that make the outer skin layer (epidermis) adhere to the deeper layer (dermis). Some types of EB are inherited dominantly, others are inherited recessively. There are more than 30 clinical subtypes. Each EB subtype is known to arise from mutations within the genes encoding for several different proteins, each of which is intimately involved in the maintenance of keratinocyte structural stability or adhesion of the keratinocyte to the underlying dermis. EB is best diagnosed and subclassified by the collective findings obtained via detailed personal and family history, in concert with the results of immunofluorescence antigenic

	mapping, transmission electron microscopy, and in some cases, by DNA analysis.(2,4) Optimal patient management requires a multidisciplinary approach and revolves around the protection of susceptible tissues against trauma, use of sophisticated wound care dressings, aggressive nutritional support, and early medical or surgical interventions to correct whenever possible the extracutaneous complications. Prognosis varies considerably and is based on both EB subtype and the overall health of the patient. Currently, there is no cure for EB. Supportive care includes daily wound care, bandaging, and pain management as needed.(2)
Efficacy	The efficacy of Filsuvez for the treatment of partial-thickness wounds associated with inherited EB was evaluated in a randomized, double-blind, placebo-controlled trial in adults and pediatric subjects 6 months of age and older (EASE; NCT03068780) with dystrophic EB (DEB) and junctional EB (JEB). Subjects were randomized 1:1 to receive FILSUVEZ (n=109) or placebo topical gel (n=114) and instructed to apply approximately 1 mm (0.04 inch) of the investigational product to all their wounds at each dressing change (every 1 to 4 days) for 90 days (+/- 7 days). If a treated wound became infected, it was advised to discontinue treatment to that wound until the infection had resolved. At randomization, 1 wound was selected by the investigator as the target wound for the evaluation of the primary efficacy endpoint. The target wound was defined as a partial-thickness wound of 10-50 cm^2 in surface area and present for 21 days to 9 months prior to screening. Of the 223 subjects randomized, the median age was 12 years (range: 6 months to 81 years), 70% were under 18 years of age, and 60% were male and 40% were female. Eighty three (83)% of subjects were White, 5% were Asian, 1% were Black or African American, and 10% were other races or did not have race recorded. For ethnicity, 35% identified as Hispanic or Latino and 65% identified as not Hispanic or Latino. Of these 223 subjects, 195 had DEB, of which 175 subjects had recessive DEB (RDEB) and 20 had dominant DEB (DDEB); in addition, there were 26 subjects with JEB and 2 subjects with EB simplex. Squamous cell carcinoma of the skin (SCC) was reported as an adverse event in the double-blind and open-label periods of EASE. Four subjects with recessive dystrophic EB each reported one SCC.(1) EASE's top-line findings showed that the trial met its main goal, with a significantly greater proportion of Filsuvez-treated patients exhibiting wound closure within 45 days, compared with those using a placebo gel (41.3% vs. 28.9%). This benefit was exclusive to participants with recessive DEB, who showed a 72% higher likelihood of wound closure within 45 days with Filsuvez relative to a placebo gel. No significant differences in wound closure were detected between Filsuvez and a placebo among participants with dominant DEB

	or JEB. Recessive DEB is commonly more severe than dominant DEB. While a greater proportion of patients using Filsuvez showed wound closure within three months, faster than those on the placebo gel, these differences failed to reach statistical significance. All participants who completed the three-month period entered the study's extension phase, in which all are using Filsuvez for two years to heal their wounds. The goal is to evaluate the therapy's safety over the long-term.(3)
Safety	Filsuvez has no FDA labeled contraindications for use.(1)

REFERENCES

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1	Filsuvez prescribing information. Lichtenheldt GmbH. December 2023.
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3	Figueiredo, M. Filsuvez gel becomes 1st therapy approved in EU for EB wounds. Epidermolysis Bullosa News. June 2022. https://epidermolysisbullosanews.com/news/filsuvez-gel-becomes-1st-therapy-approved-eu-eb-wounds.
4	EB Research Network. EB research network: understanding EB & its classification. 2022. https://www.eb-researchnetwork.org/research/what-is-eb/.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Module	Clinical Criteria for Approval

Agents Eligible for Continuation of Therapy
All agents are eligible for continuation of therapy

1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR**
2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR**

B. The patient has a diagnosis of dystrophic or junctional epidermolysis bullosa confirmed by genetic testing (medical records required) **OR**

C. The patient has another FDA labeled indication for the requested agent **AND**

2. If the patient has an FDA approved indication, then ONE of the following:
   A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**
   B. There is support for using the requested agent for the patient's age for the requested indication **AND**
3. The patient does NOT have current evidence or a history of squamous cell carcinoma on the area to be treated **AND**
4. The patient does NOT have an active infection on the area to be treated **AND**
5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., dermatologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**
6. The patient will NOT be using the requested agent in combination with a gene therapy agent on the area to be treated **AND**
7. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 4 months

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Prior Authorization criteria [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND**
2. The patient has had clinical benefit with the requested agent **AND**

Module	Clinical Criteria for Approval
	3. The patient does NOT have current evidence or a history of squamous cell carcinoma on the area to be treated **AND** 4. The patient does NOT have an active infection on the area to be treated **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., dermatologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. The patient will NOT be using the requested agent in combination with a gene therapy agent on the area to be treated **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 month

Fintepla

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Fintepla® (fenfluramine) Oral solution	Treatment of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older		1

CLINICAL RATIONALE

Dravet Syndrome	Dravet syndrome (DS) is a severe form of epilepsy with an onset of recurrent, prolonged seizures in infancy that are often triggered by fever or overheating. DS is characterized by lifelong comorbidities, including neurodevelopmental problems and intellectual disability.(2,3,4,9) Mutations in the alpha-1 subunit of the voltage-gated sodium channel (SCN1A) gene are identified in at least 80% of patients with DS.(2,3,9) Status epilepticus is common and is one of the leading causes of premature mortality seen with DS. Patients with DS have an elevated risk of premature mortality, with the most common cause being sudden unexpected death in epilepsy (SUDEP).(2,3,4) Other types of seizures appear before age 5 years and include myoclonic, focal, and atypical absence seizures.(2,3,9) Valproate is considered first-line therapy, with clobazam added if needed.(2,3,4,9) Additional agents include stiripentol, topiramate, cannabidiol, and fenfluramine.(3,4,9) For patients with symptoms refractory to drug therapy, ketogenic diet and vagal nerve stimulation may be beneficial.(2,3,4,9)
Lennox-Gastaut Syndrome	Lennox-Gastaut syndrome (LGS) is a severe form of epilepsy involving several seizure types, with an onset during infancy or early childhood. Many causes of LGS have been identified, including genetic disorders, trauma, cortical malformations, perinatal hypoxia, and meningitis. Tonic, atonic, and atypical absence seizures are the most common seizure types associated with LGS. Clinical features that may be present include cognitive dysfunction, behavioral abnormalities, and neurodevelopmental impairment. Management of LGS is

	difficult because it is refractory to many treatments, and no specific therapy is effective for all patients. Valproate is generally considered first-line therapy, and if monotherapy is ineffective another drug such as lamotrigine or rufinamide is added to valproate therapy.(7,8) Alternative adjunctive antiseizure medications include topiramate, clobazam, cannabidiol, fenfluramine, or felbamate.(8) Additional therapies, for patients who do not respond to antiseizure medications, include the ketogenic diet and vagal nerve stimulation.(7,8)
Efficacy	The effectiveness of fenfluramine for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older was established in two randomized, double-blind, placebo-controlled trials in patients 2 to 18 years of age. Study 1 (N = 117) compared a 0.7 mg/kg/day and a 0.2 mg/kg/day dose of fenfluramine with placebo in patients who were NOT receiving stiripentol. Study 2 (N = 85) compared a 0.4 mg/kg/day dose of fenfluramine with placebo in patients who were receiving stiripentol and either clobazam, valproate, or both. In both studies, patients had a clinical diagnosis of Dravet syndrome and were inadequately controlled on at least one antiepileptic drug (AED) or other antiseizure treatment including vagal nerve stimulation or a ketogenic diet. In Study 1, 98% of patients were taking 1-4 concomitant AEDs; in Study 2, 100% were taking 2-4 concomitant AEDs.(1) The primary efficacy endpoint in both studies was the change from baseline in the frequency of convulsive seizures per 28 days during the treatment period. For Study 1, the percent reduction in monthly convulsive seizure frequency was 70% for the 0.7 mg/kg/day dose (p less than 0.001) and 31.7% for the 0.2 mg/kg/day dose (p=0.043); for Study 2 it was 59.5% reduction (p less than 0.001). A reduction in convulsive seizures was observed within 3-4 weeks of starting fenfluramine, and the effect remained generally consistent over the 14- or 15-week treatment period.(1) A secondary endpoint was longest seizure-free interval, for which the median longest seizure-free intervals in the 0.7 mg/kg/day, 0.4 mg/kg/day, and 0.2 mg/kg/day groups were 25 days, 22 days, and 15 days, respectively.(5,6) The effectiveness of fenfluramine for the treatment of seizures associated with LGS in patients 2 years of age and older was established in a randomized, double-blind, placebo-controlled trial in patients 2 to 35 years of age. Study 3 (N=263) compared a 0.7 mg/kg/day and a 0.2 mg/kg/day dose of fenfluramine with placebo in patients with a diagnosis of LGS who were inadequately controlled on at least one antiepileptic drug (AED) or other antiseizure treatment including vagal nerve stimulation and/or a ketogenic diet.(1)

	The primary efficacy endpoint was the median percent change from baseline (reduction) in the frequency of seizures per 28 days during the treatment period. The median percent change from baseline (reduction) in the frequency of seizures per 28 days was significantly greater for the 0.7 mg/kg/day group compared with placebo (23.7%; p=0.0037). The effect remained generally consistent over the 14-week treatment period.(1)
Safety	Fintepla carries a boxed warning for valvular heart disease and pulmonary arterial hypertension. There is an association between serotonergic drugs with 5-HT2B receptor agonist activity, including fenfluramine, and valvular heart disease and pulmonary arterial hypertension. Echocardiogram assessments are required before, during, and after treatment with Fintepla; benefits versus risks of initiating or continuing must be considered based on echocardiogram findings. Because of these risks, Fintepla is available only through the Fintepla REMS program.(1) Fintepla has the following contraindications:(1) • Concomitant use of, or within 14 days of the administration of, monoamine oxidase inhibitors because of an increased risk of serotonin syndrome. • Hypersensitivity to fenfluramine or any of the excipients in Fintepla.

REFERENCES

Number	Reference
1	Fintepla prescribing information. Zogenix, Inc. December 2023.
2	Wirrell EC, Laux L, Donner E, et al. Optimizing the Diagnosis and Management of Dravet Syndrome: Recommendations from a North American Consensus Panel. Pediatr Neurol. 2017;68:18-34.
3	Sullivan J, Knupp K, Wirrell E, et al. Dravet Syndrome. National Organization for Rare Disorders (NORD). Last updated July 2020. Available at https://rarediseases.org/rare-diseases/dravet-syndrome-spectrum/.
4	Andrade DM, Nascimento FA, et al. Dravet Syndrome: Management and Prognosis. UpToDate. Last updated November 2022. Literature review current through December 2023.

Number	Reference
5	Lagae L, Sullivan J, Knupp K, et al. Fenfluramine Hydrochloride for the Treatment of Seizures in Dravet Syndrome: A Randomized, Double-Blind, Placebo-Controlled Trial. Lancet. 2019;394(10216):2243-2254.
6	Nabbout R, Mistry A, Zuberi S, et al. Fenfluramine for Treatment-Resistant Seizures in Patients with Dravet Syndrome Receiving Stiripentol-Inclusive Regimens: A Randomized Clinical Trial. JAMA Neurol. 2020;77(3):300-308.
7	Wheeless JW. Lennox-Gastaut Syndrome. National Organization for Rare Disorders (NORD). Last updated June 2020. Available at https://rarediseases.org/rare-diseases/lennox-gastaut-syndrome/.
8	Wilfong A, et al. Lennox-Gastaut syndrome. UpToDate. Last updated June 2023. Literature review current through December 2023.
9	Wirrell E, Hood V, Knupp KG, et al. International consensus on diagnosis and management of Dravet syndrome. Epilepsia. 2022;63(7):1761-1777.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. BOTH of the following: 1. ONE of the following: A. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** B. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **AND** 2. The patient has an FDA labeled indication for the requested agent **OR** B. BOTH of the following: 1. ONE of the following: A. If the patient has a diagnosis of Dravet syndrome (DS), then ONE of the following:

Module	Clinical Criteria for Approval
	1. The patient has tried and had an inadequate response to TWO generic antiseizure agents used in the treatment of DS (e.g., valproate, clobazam, stiripentol, topiramate) **OR** 2. The patient has an intolerance or hypersensitivity to therapy with generic antiseizure agents used in the treatment of DS **OR** 3. The patient has an FDA labeled contraindication to ALL generic antiseizure agents used in the treatment of DS **OR** B. If the patient has a diagnosis of Lennox-Gastaut syndrome (LGS), then ONE of the following: 1. The patient has tried and had an inadequate response to TWO generic antiseizure agents used in the treatment of LGS (e.g., valproate, lamotrigine, rufinamide, topiramate, clobazam, felbamate) **OR** 2. The patient has an intolerance or hypersensitivity to therapy with generic antiseizure agents used in the treatment of LGS **OR** 3. The patient has an FDA labeled contraindication to ALL generic antiseizure agents used in the treatment of LGS **OR** C. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. If the patient has a diagnosis of seizures associated with Dravet syndrome (DS) or Lennox-Gastaut syndrome (LGS), the requested agent will NOT be used as monotherapy for seizure management **AND** 3. An echocardiogram assessment will be obtained before and during treatment with the requested agent to evaluate for valvular heart disease and pulmonary arterial hypertension **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Clinical Criteria for Approval
	Renewal Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. If using for seizure management associated with Dravet syndrome (DS) or Lennox-Gastaut syndrome (LGS), the requested agent will NOT be used as monotherapy **AND** 4. An echocardiogram assessment will be obtained during treatment with the requested agent to evaluate for valvular heart disease and pulmonary arterial hypertension **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months

Furoscix (furosemide)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Furoscix® (furosemide) Subcutaneous cartridge kit	Treatment of congestion due to fluid overload in adults with NYHA Class II/III chronic heart failure Limitations of Use: Furoscix is not indicated for emergency situations or in patients with acute pulmonary edema. The On-Body Infusor will deliver only an 80-mg dose of Furoscix		1

CLINICAL RATIONALE

Management of Heart Failure

The 2022 AHA/ACC/HFSA Guidelines for the Management of Heart Failure (HF) recommends the following on diuretic and decongestion strategies in patient with HF (Strong evidence):(8)

- In patients with HF who have fluid retention, diuretics are recommended to relieve congestion, improve symptoms, and prevent worsening HF
- For patients with HF and congestive symptoms, addition of a thiazide (eg, metolazone) to treatment with a loop diuretic should be reserved for patients who do not respond to moderate or high-dose loop diuretics to minimize electrolyte abnormalities

Commonly Used Oral Loop Diuretics in Treatment of Congestion for Chronic HF include the following:(8)

Loop Diuretic	Duration of Action	Initial Daily Dose	Maximum Dosage
Bumetanide	4-6 hours	0.5–1.0 mg once or twice	10mg

Furosemide	6-8 hours	20–40 mg once or twice	600 mg
Torsemide	12-16 hours	10–20 mg once	200mg

Effective diuretic action in HF requires four discrete steps: 1) ingestion and gastrointestinal absorption (if given orally), 2) delivery to the kidney, 3) secretion into the tubule lumen; and 4) binding to the transport protein.(5) Controlled trials with diuretics showed their effects to increase urinary sodium excretion, decrease physical signs of fluid retention, and improve symptoms, quality of life, and exercise tolerance. Recent data from the nonrandomized OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry revealed reduced 30-day all-cause mortality and hospitalization for HF with diuretic use compared with no diuretic use after hospital discharge for HF. The most commonly used loop diuretic for the treatment of HF is furosemide, but some patients respond more favorably to other agents in this category (e.g., bumetanide, torsemide), potentially because of their increased oral bioavailability.(8)

Parenteral loop diuretics form the cornerstone of treatment of acute decompensated HF when patients respond insufficiently to oral diuretics alone. HF syndrome is characterized by unpredictable periods of decompensation, which require escalation of oral diuretic doses and/or frequency of dosing. When such oral treatment adjustment fails, IV diuretics are usually prescribed. Furthermore, many patients appear to temporarily have a reduced response to oral medication due to impaired absorption because of fluid overload and other factors affecting gastric and intestinal absorptive functions.(6)

For patients on long-term loop diuretic agents, it is suggested that patients hospitalized with HF and congestion initially start loop diuretic dosage at 2.5 times their outpatient dose on a mg per mg basis. For example, for patients taking 40 mg of oral furosemide twice daily as an outpatient, initial intravenous (IV) dosing would be 100 mg of furosemide IV twice daily. For patients not receiving long-term loop diuretic agents, 40-80 mg IV BID of furosemide or the equivalent is a reasonable, empiric, starting dose. Due to post-dosing sodium retention, IV loop-diuretic agents should usually be given at least twice daily.(5)

The average bioavailability after oral administration of furosemide is highly variable and has been reported to range between 49% and 72%, while individual

	differences range from below 20% to over 90%. Parenteral furosemide therapy not only reduces hypervolemia, but in many patients, it also restores oral bioavailability, allowing them to transition more readily back to oral maintenance therapy.(6) Parenteral therapy routinely requires emergency room or inpatient care. A novel buffered furosemide formulation (Furoscix) with neutral pH was developed to offer diuresis for outpatient use, including self-administration at home. Subcutaneous infusion using a biphasic delivery profile resulted in complete bioavailability (99.65%) and equivalent diuresis when compared with intravenous administration. Subcutaneous administration of buffered furosemide was well tolerated with no evidence of any drug-induced skin reactions. Subcutaneous infusion of buffered furosemide in the outpatient setting or home may help to reduce the burden of heart failure.(6)
Efficacy	Furoscix is a proprietary furosemide solution formulated to a neutral pH, designed to allow for subcutaneous infusion via a wearable, pre-programmed on-body infusor, for outpatient self-administration. It was developed for the treatment of congestion due to fluid overload in adult patients with New York Heart Association (NYHA) Class II and Class III chronic heart failure who display reduced responsiveness to oral diuretics and who do not require hospitalization.(1,4) The PK/PD Pivotal (Crossover Study to Compare the Pharmacokinetics and Bioavailability of a Novel Furosemide Regimen Administered Subcutaneously vs. the Same Dose Administered Intravenously in Subjects With Chronic Heart Failure; NCT02329834) study compared the pharmacokinetics and bioavailability of an 80-mg buffered furosemide solution administered via the SC route with an equivalent 80-mg dose of IV furosemide in a similar subject population. The main findings of this study were: 1) typical therapeutic levels of furosemide were reached within 30 min of SC administration and maintained for more than 5 h; 2) absolute bioavailability of SC furosemide was complete at 99.65%; 3) SC furosemide was as effective as IV furosemide in achieving diuresis; and 4) SC furosemide was well tolerated, with minimal erythema and edema at the site of injection.(6) These results suggest that SC furosemide administration may offer a “hospital-strength” diuretic option for patients with HF who require a shift of their oral diuretic treatment, when hospitalization is not strictly warranted. These results also suggest that the reformulation combined with the slow infusion rate has resulted in a product that is free from the stinging and discomfort that had been reported with the administration of conventional furosemide injection.(6)

	The AT HOME-HF Pilot study (NCT04593823), a Phase 2 multicenter, randomized study that compared Furoscix with a "treatment as usual" approach in chronic heart failure patients presenting to a heart failure clinic with worsening congestion and requiring augmented diuresis. The study enrolled 63 subjects, of which 34 received FUROSCIX and 17 received "treatment as usual. Results indicated a 37% reduction in heart failure hospitalizations relative to 'treatment as usual' and improvement in congestion signs and symptoms.(11) The FREEDOM-HF was a multicenter, adaptive clinical trial that included a prospective treatment arm (i.e., Furoscix administered via the Furoscix Infusor) administered outside the hospital that was compared to a propensity-matched historical control arm of patients admitted to the hospital for less than or equal to 72 hours (i.e., Treatment As Usual (TAU)) that was derived from administrative claims data. Eligible patients for the Furoscix arm had NYHA Class II or III heart failure and were exhibiting signs of volume expansion defined as: jugular venous distention, pitting edema (greater than or equal to 1+), abdominal distension, pulmonary congestion on chest x-ray, or pulmonary rales.(4) Results of the FREEDOM-HF study showed positive results demonstrating the average 30-day heart failure related costs were reduced in the Furoscix arm compared to historically matched comparators ($p<0.0001$). Comparators were hospitalized for less than or equal to 72 hours and were selected from a claims database matched to seven variables associated with HF-related hospitalization and severity.(9) Analyses of additional secondary endpoints have been conducted that provide additional insights into the clinical effectiveness of Furoscix. Patients who received Furoscix had a median reduction of heart failure peptide biomarkers from study entry (day 0) to first visit (day 2 to 4), and to last visit (day 30), of 42.3% and 28%, respectively (p less than or equal to 0.01). Patients who received Furoscix had a 12.8-point improvement in the Kansas City Cardiomyopathy Questionnaire (KCCQ-12) Summary Score 30 days after study entry.(10)
Safety	Furoscix is contraindicated in patients with:(1) • anuria • a history of hypersensitivity to furosemide or medical adhesives • hepatic cirrhosis or ascites

REFERENCES

Number	Reference
1	Furoscix prescribing information. scPharmaceuticals, Inc. November 2023.
2	Reference no longer used
3	Reference no longer used
4	Furoscix Real-World Evaluation for Decreasing Hospital Admissions in Heart Failure (FREEDOM-HF). Available at https://beta.clinicaltrials.gov/study/NCT03458325
5	Felker GM, Ellison DH, Mullens W, Cox ZL, Testani JM. Diuretic Therapy for Patients With Heart Failure: JACC State-of-the-Art Review. J Am Coll Cardiol 2020;75:1178-1195.
6	Sica DA, Muntendam P, Myers RL, Ter Maaten JM, Sale ME, de Boer RA, Pitt B. Subcutaneous Furosemide in Heart Failure: Pharmacokinetic Characteristics of a Newly Buffered Solution. JACC Basic Transl Sci. 2018 Feb 7;3(1):25-34. doi: 10.1016/j.jacbts.2017.10.001. PMID: 30062191; PMCID: PMC6059009.
7	Reference no longer used
8	Heidenreich, Paul A. Heidenreich, MD, MS, FACC, FAHA, FHFSA, Chair, Bozkurt, Biykem Bozkurt, MD, PhD, FACC, FAHA, FHFSA, Vice Chair, et.al, 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. 2022;145:e895–e1032. Available at: https://doi.org/10.1161/CIR.0000000000001063Circulation.
9	scPharmaceuticals Inc. Presents Late-breaking FREEDOM-HF Study Data at the Heart Failure Society of America Annual Scientific Meeting 2021. Available at: https://scpharmaceuticalsinc.gcs-web.com/news-releases/news-release-details/scpharmaceuticals-inc-presents-late-breaking-freedom-hf-study.
10	Effect of Subcutaneous Furosemide (Furoscix) on Natriuretic Peptides, Quality of Life and Patient/Caregiver Satisfaction in Heart Failure Patients: Secondary Outcomes of the FREEDOM-HF Trial. Presented at The American Association of Heart Failure Nurses 18thAnnual Meeting in Orlando, FL on June 18, 2022. Available at: http://ir.scpharma.com/static-files/0fdebb90-5032-4f86-afc1-a8279df9c74e

Number	Reference
11	Avoiding Treatment in the Hospital With Furoscix for the Management of Congestion in Heart Failure - A Pilot Study (AT HOME-HF). Available at https://clinicaltrials.gov/ct2/show/NCT04593823

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of New York Heart Association (NYHA) Class II or Class III chronic heart failure with congestion due to fluid overload **AND** 2. The patient has ONE of the following: A. An estimated creatinine clearance of greater than 30 mL/min **OR** B. An estimated glomerular filtration rate of greater than 20 mL/min/1.73m^2 **AND** 3. The requested agent will NOT be used in emergency situations **AND** 4. BOTH of the following: A. The patient was currently treated with a loop diuretic (e.g., bumetanide, furosemide, torsemide) equivalent to a total daily oral furosemide dose of at least 40-160 mg for 4 weeks **AND** B. The patient will NOT be using the requested agent in combination with another loop diuretic agent and will be transitioned back to oral diuretic maintenance therapy after discontinuation of requested agent **AND** 5. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: Up to 12 months

Gabapentin ER

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Gralise® (gabapentin)* Extended-release tablet	Management of postherpetic neuralgia (PHN)	*generic available	2
Horizant® (gabapentin) Extended-release tablet	Treatment of moderate-to-severe primary Restless Legs Syndrome (RLS) in adults Management of postherpetic neuralgia (PHN) in adults		1

CLINICAL RATIONALE

Restless Legs Syndrome (RLS)	Restless legs syndrome (RLS) is a movement disorder characterized by an urge to move the legs or arms, commonly in response to uncomfortable dysesthesia.(5) Pramipexole, ropinirole, and rotigotine transdermal system are recommended by the American Academy of Sleep Medicine (AASM) and the European Federation of Neurological Societies/European Neurological Society/European Sleep Research Society as first-line treatment for RLS.(3,4) The non-ergot dopamine agonists, pramipexole and ropinirole, are effective in the treatment of RLS and are less likely to cause side effects than other dopamine agonists (e.g., cabergoline and pergolide) and levodopa. Gabapentin and pregabalin may be useful in RLS in patients with comorbid pain.(3) The American Academy of Neurology recommends that the choice of agent for the treatment of primary RLS be based on goal of treatment and patient comorbidities. The level of evidence for use of pramipexole, rotigotine, cabergoline, gabapentin, IV ferric carboxymaltose, levodopa, and pregabalin in RLS varies depending on those goals and comorbidities.(5)

Postherpetic Neuralgia (PHN)	Postherpetic neuralgia (PHN) is the most common complication of herpes zoster. PHN is defined as pain in the dermatomal distribution that is sustained for at least 90 days after the rash. PHN is caused by nerve damage secondary to an inflammatory response induced by viral replication within a nerve. Pain-management strategies should focus on symptom control. Some patients have complete resolution of symptoms at several years while others continue medications indefinitely.(7) Both topical (capsaicin and lidocaine) and systemic treatments can be effective in the management of PHN. The anticonvulsants gabapentin and pregabalin are approved for treatment of PHN. Tricyclic antidepressants are also effective in treating PHN, but up to one-fourth of patients discontinue treatment due to adverse reactions. Opioids are considered third-line treatment with two systematic reviews finding tramadol provided significant pain relief in patients with PHN.(6,7) Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are generally considered to be ineffective for neuropathic pain.(7)
Safety	Gralise is contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients. Horizant has no FDA labeled contraindications for use.

REFERENCES

Number	Reference
1	Horizant prescribing information. Azurity Pharmaceuticals, Inc. August 2022.
2	Gralise prescribing information. Almatica Pharma LLC. March 2023.
3	Aurora RN, Kristo DA, Bista SR, et al. The Treatment of Restless Legs Syndrome and Periodic Limb Movement Disorder in Adults - An Update for 2012: Practice Parameters with an Evidence-Based Systematic Review and Meta-Analyses. An American Academy of Sleep Medicine Clinical Practice Guideline. *Sleep.* 2012;35(8):1039-1062. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3397811/
4	Garcia-Borreguero D, Ferini-Strambi L, Kohnen R, et al. European guidelines on management of restless legs syndrome: report of a joint task force by the European Federation of Neurological Societies, the European Neurological Society and the European Sleep Research Society. *European Journal of*

Number	Reference
	Neurology. 2012, 19(11):1385-1396. Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/j.1468-1331.2012.03853.x
5	Winkelman WJ, Armstrong MJ, Chaudhuri KR. Practice guideline summary: Treatment of restless legs syndrome in adults. Neurology. December 13, 2016;87(24). Reaffirmed October 2022.
6	Johnson, RW, Rice AS. Postherpetic Neuralgia. *N Engl J Med.* 2014;371:1526-1533. Available at: https://www.nejm.org/action/showPdf?downloadfile=showPdf&doi=10.1056/NEJMcp1403062&loaded=true
7	Saguil AS, Kane S, Mercado M, et al. Herpes Zoster and Postherpetic Neuralgia: Prevention and Management. *Am Fam Physician.* 2017;96(10):656-663. Available at: https://www.aafp.org/afp/2017/1115/p656.pdf

ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
62540030000325	Gralise	gabapentin (once-daily) tab	450 MG	Gralise dosage must be titrated up over 15 days			
62540030000345	Gralise	gabapentin (once-daily) tab	750 MG	Gralise dosage must be titrated up over 15 days			
62540030000360	Gralise	gabapentin (once-daily) tab	900 MG	Gralise dosage must be titrated up over 15 days			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
62540030000320	Gralise	Gabapentin (Once-Daily) Tab 300 MG	300 MG	Gralise dosage must be titrated up over 15 days			
62540030000330	Gralise	Gabapentin (Once-Daily) Tab 600 MG	600 MG	Gralise dosage must be titrated up over 15 days			

ALLOWED EXCEPTIONS QUANTITY LIMIT

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Allowed Exceptions	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
62540030000325	Gralise	gabapentin (once-daily) tab	450 MG	*The patient requires increased quantities of Gralise to accommodate a titration schedule. The increased quantity will be approved for 1 month only.			
62540030000345	Gralise	gabapentin (once-daily) tab	750 MG	*The patient requires increased quantities of Gralise to accommodate a titration schedule. The increased quantity will be approved for 1 month only.			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Allowed Exceptions	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
62540030000360	Gralise	gabapentin (once-daily) tab	900 MG	*The patient requires increased quantities of Gralise to accommodate a titration schedule. The increased quantity will be approved for 1 month only.			
62540030000320	Gralise	Gabapentin (Once-Daily) Tab 300 MG	300 MG	*The patient requires increased quantities of Gralise to accommodate a titration schedule. The increased quantity will be approved for 1 month only.			
62540030000330	Gralise	Gabapentin (Once-Daily) Tab 600 MG	600 MG	*The patient requires increased quantities of Gralise to accommodate a titration schedule. The increased quantity will be approved for 1 month only.			

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The patient requires increased quantities of Gralise to accommodate a titration schedule. The increased quantity will be approved for 1 month only **OR** 3. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Galafold (migalastat)

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Galafold® (migalastat) Capsule	Treatment of adults with a confirmed diagnosis of Fabry disease and an amenable galactosidase alpha gene (*GLA*) variant based on in vitro assay data		1

CLINICAL RATIONALE

Fabry Disease	Fabry disease, also called Anderson-Fabry disease, is a rare X-linked lysosomal storage disorder caused by pathogenic mutations in the *GLA* (galactosidase alpha) gene, resulting in functional deficiency of the enzyme alpha-galactosidase A (alpha-Gal A).(4) Markedly reduced, or absent, activity of alpha-Gal A results in progressive accumulation of glycolipids, primarily globotriaosylceramide (GL-3, Gb3), within lysosomes in multiple cell types throughout the body.(2,4,5) This includes those particularly relevant to disease pathology (e.g., vascular endothelial cells, podocytes, cardiomyocytes, arterial smooth muscle cells) and other cell types in the kidneys, nervous system, and other organs.(2,5,6) Although some *GLA* variants do not appear to cause disease, more than a thousand disease-causing *GLA* variants have been identified. The severity of symptoms may vary among individuals depending upon the specific *GLA* mutation within their family. In general, mutations that result in little to no alpha-Gal A activity cause the classic Fabry phenotype, and those mutations that result in residual alpha-Gal A activity cause the atypical later-onset phenotype.(2,4,5) The "classic" form of Fabry disease is the most severe clinical phenotype and occurs predominantly in males. These patients are characterized by absent or severely reduced alpha-Gal A activity, with childhood or adolescent onset of symptoms including severe neuropathic or limb pain, abdominal pain, telangiectasias and angiokeratomas, corneal opacities, renal involvement that may progress to end-stage renal disease (ESRD), and hearing loss, with cardiac and cerebrovascular involvement occurring by adulthood. The spectrum of disease severity in heterozygous female patients ranges from asymptomatic to a

	severe phenotype resembling the male "classic" phenotype and is, in part, dependent on the mutation and the X chromosome inactivation (Lyonization) profile. The prevalence of signs and symptoms at any given age is lower in females, though increasing age will result in development of cardiac and cerebrovascular involvement.(2,5,6) Fabry disease should be suspected in patients with a family history of Fabry disease or those who present with the clinical manifestations or laboratory abnormalities associated with the disease. The diagnosis is typically confirmed by biochemical and/or molecular genetic testing, with the latter approach being the final determinant.(5) An initial evaluation includes baseline documentation of renal function (e.g., proteinuria, glomerular filtration rate [GFR]), cardiac function (e.g., left ventricular hypertrophy, conduction defects, mitral and/or aortic valve abnormalities), ophthalmological signs (e.g., corneal verticillate, subcapsular cataracts, conjunctival and/or retinal vasculopathy), peripheral nerve symptoms (e.g., neuropathic pain, heat and/or cold intolerance, impaired sweat function), and gastrointestinal involvement (e.g., nausea, vomiting, abdominal pain, diarrhea, constipation).(2,5,6) After a thorough clinical evaluation, mutational analysis of the *GLA* gene is the gold-standard assay to confirm the diagnosis of Fabry disease in males and females. For male patients suspected of having Fabry disease, an initial measurement of alpha-Gal A activity (in leukocytes, plasma, fibroblasts, or dried blood spots [DBS]) may be performed. However, the alpha-Gal A activity assay is not definitive confirmation of Fabry disease, since the assay will identify less than 50% of female carriers. Additionally, for patients with residual alpha-Gal A activity on assay (3-35%), genetic testing for a pathogenic *GLA* gene will confirm the Fabry disease diagnosis, and establish the patient's amenability to treatment with chaperone therapy.(2,5) There is no cure for Fabry disease. Available Fabry-specific therapies include intravenous enzyme replacement therapy (ERT) and pharmacologic chaperone therapy. ERT with Fabrazyme (agalsidase beta) or Elfabrio (pegunigalsidase alfa) focuses on replacing the missing or deficient enzyme (alpha-Gal A). Galafold (migalastat, an oral capsule) is approved as first-line therapy in patients with amenable *GLA* gene variants.(3,4,6) Migalastat is a pharmacologic chaperone that binds to and stabilizes specific (amenable) mutant forms of alpha-Gal A, thereby facilitating proper trafficking of the enzyme to lysosomes. Once in the lysosome, migalastat dissociates from alpha-Gal A allowing it to then catabolize accumulated glycolipids.(1,3,4)

	Certain *GLA* mutations causing Fabry disease result in the production of abnormally folded and less stable forms of the alpha-Gal A protein which retain residual enzymatic activity. These *GLA* variants, referred to as amenable variants, produce alpha-Gal A proteins that may be stabilized by migalastat thereby restoring their trafficking to lysosomes and their intralysosomal activity.(1) A complete list of amenable variants is available in the Galafold prescribing information or a specific variant can be verified as amenable at http://www.galafoldamenabilitytable.com/hcp. Patients on ERT or migalastat should have a clinical evaluation every 6-12 months. Renal function, cardiac function, ophthalmological signs, peripheral nerve symptoms, and gastrointestinal involvement should all be assessed to monitor disease manifestations, disease severity, and/or side effects of therapy.(3,5)
Efficacy	Study AT1001-011 (NCT00925301) included a 6-month randomized, double-blind, placebo-controlled phase followed by a 6-month open-label treatment phase and a 12-month open-label extension phase. A total of 67 patients with Fabry disease who were naïve to migalastat and enzyme replacement therapy (ERT) or who were previously treated with ERT and had been off ERT for at least 6 months were randomized in a 1:1 ratio to receive migalastat every other day or placebo for the first 6 months. In the second 6 months, all patients were treated with migalastat. At 6 months, patients treated with migalastat had lower plasma globotriaosylceramide (GL-3, Gb3) levels compared with placebo. No changes in these parameters occurred in patients with non-amenable GLA mutations.(1) A second trial, 18-month, randomized, active-controlled, with 57 adults, compared migalastat with ERT in patients who were previously treated with ERT. Primary objective was to assess renal function and secondary endpoints of cardiovascular and patient-reported outcomes. At 18 months, migalastat and ERT had comparable effects on kidney function. Left ventricular mass index decreased from baseline in patients on migalastat but did not change significantly in those on ERT.(3)
Safety	Migalastat has no FDA labeled contraindications for use.(1)

REFERENCES

Number	Reference
1	Galafold prescribing information. Amicus Therapeutics US, Inc. June 2023.
2	Mauer M, Wallace E, Schiffmann R, et al. Fabry Disease: Clinical Features and Diagnosis. UpToDate. Last updated July 2023. Literature review current through December 2023.
3	Mauer M, Wallace E, Schiffmann R, et al. Fabry Disease: Treatment and Prognosis. UpToDate. Last updated November 2023. Literature review current through December 2023.
4	Germain DP, Nicholls K, Giugliani R, et al. Efficacy of the Pharmacologic Chaperone Migalastat in a Subset of Male Patients with the Classic Phenotype of Fabry Disease and Migalastat-Amenable Variants: Data from the Phase 3 Randomized, Multicenter, Double-Blind Clinical Trial and Extension Study. Genet Med. 2019 Feb;21(9):1987-1997.
5	Ortiz A, Germain DP, Desnick RJ, et al. Fabry Disease Revisited: Management and Treatment Recommendations for Adult Patients. Mol Genet Metab. 2018 Apr;123(4):416-427.
6	Ganesh J, et al. Fabry Disease. National Organization for Rare Disorders (NORD): Rare Disease Database. 2019. Available at: https://rarediseases.org/rare-diseases/fabry-disease/.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** Galafold

Module	Clinical Criteria for Approval
	1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. The patient has a diagnosis of Fabry disease AND BOTH of the following: A. The diagnosis was confirmed by mutation in the galactosidase alpha (*GLA*) gene **AND** B. The patient has a confirmed amenable *GLA* variant based on in vitro assay data (a complete list of amenable variants is available in the Galafold prescribing information, or a specific variant can be verified as amenable at http://www.galafoldamenabilitytable.com/hcp **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The prescriber has assessed current status of ALL of the following: renal function (e.g., proteinuria, glomerular filtration rate [GFR]), cardiac function (e.g., left ventricular hypertrophy, conduction defects, mitral and/or aortic valve abnormalities), ophthalmological signs (e.g., corneal verticillate, subcapsular cataracts, conjunctival and/or retinal vasculopathy), peripheral nerve symptoms (e.g., neuropathic pain, heat and/or cold intolerance, impaired sweat function), and gastrointestinal involvement (e.g., nausea, vomiting, abdominal pain, diarrhea, constipation) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist, nephrologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with enzyme replacement therapy (ERT) (e.g., Elfabrio, Fabrazyme) for the requested indication **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation**

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following: A. Renal function (e.g., proteinuria, glomerular filtration rate [GFR]) **OR** B. Cardiac function (e.g., left ventricular hypertrophy, conduction defects, mitral and/or aortic valve abnormalities) **OR** C. Ophthalmological signs (e.g., corneal verticillate, subcapsular cataracts, conjunctival and/or retinal vasculopathy) **OR** D. Peripheral nerve symptoms (e.g., neuropathic pain, heat and/or cold intolerance, impaired sweat function) **OR** E. Gastrointestinal symptoms (e.g., nausea, vomiting, abdominal pain, diarrhea, constipation) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist, nephrologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with enzyme replacement therapy (ERT) (e.g., Elfabrio, Fabrazyme) for the requested indication **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** Initial - up to 6 months; Renewal - up to 12 months

Gattex (teduglutide)

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Gattex® (teduglutide) Single use vial kit	Short Bowel Syndrome (SBS) in adults and pediatric patients 1 year of age and older patients who are dependent of parenteral support		1

CLINICAL RATIONALE

Short Bowel Syndrome	Short bowel syndrome (SBS) results from the physical or functional loss of intestinal length due to disease or surgical resection. This leads to malabsorption of nutrients, water, and electrolytes relative to the amount of functional intestine remaining and which sections of the bowel are involved. Typically patients with SBS have a residual small intestine length of 200cm or less.(2,4,5) SBS can result in significant morbidity and mortality, reduced quality of life, and high health care costs. The symptoms, prognosis, and treatment of SBS can vary depending on which of the three groups it is classified into: jejunocolonic, jejunoileocolonic, and end jejunostomy. Typical signs and symptoms of SBS include diarrhea, dehydration, electrolyte abnormalities, malnutrition, and weight loss. (3,5) The goals of treatment are to:(4) • Provide nutrition, water, and electrolytes necessary to maintain health, with normal body weight or growth • Use oral/enteral nutrition in preference to parenteral nutrition whenever the gut is functional and can absorb sufficient nutrients, water, and electrolytes • Reduce the complications resulting from the underlying disease, intestinal failure, and/or nutritional/fluid support • Achieve a good quality of life

	Diarrhea can be a bothersome and debilitating consequence for patients with SBS, having a negative impact on their quality of life. Several factors can contribute to diarrhea, including loss of gut surface area, gastric hypersecretion, and reduced gut hormone feedback mechanisms.(3) The use of antimotility agents long-term to control fluid and stool losses is a cornerstone of SBS therapy since limiting food intake to reduce diarrhea will exacerbate nutritional issues.(2,3,4,5) Loperamide is the preferred drug to treat diarrhea, but objective measures of stool output should guide the use of specific antidiarrheals. Other agents used include diphenoxylate, codeine, and tincture of opium.(5) Dehydration is also critical to avoid since it can result in rapid weight loss, fatigue, and kidney injury. Patients without a colon in continuity typically use a glucose-electrolyte oral rehydration solution (ORS) to enhance absorption of fluids and reduce secretion. Most patients with a colon do not require ORS for hydration since the colon has a large capacity to absorb water and sodium.(3,4,5) Long-term parenteral nutrition (PN) is often required to manage SBS, especially during the initial period following resection. Over 50% of adults with SBS can completely wean off PN within 5 years of diagnosis, but if not successfully accomplished within the first 2 years following resection the probability is less than 6%.(3,5) During the first 2 years following intestinal resection, intestinal adaptation occurs and the remaining bowel undergoes macroscopic and microscopic changes in order to increase its absorptive capacity. However, independence from PN may be accomplished through the use of intestinotrophic agents as part of a multidisciplinary approach.(3) Glucagon-like peptide-2 (GLP-2) analogs can be used to help wean patients with SBS off of PN after the period of maximal intestinal adaptation and work by aiding in absorption. They also help with the management of chronic diarrhea, malnutrition, dehydration, and electrolyte deficiencies. GLP-2 analogs should only be used after optimizing diet and more conventional SBS treatments.(3,5)
Efficacy	Treatment of SBS in Adults Gattex (teduglutide) is a recombinant, degradation-resistant analog of naturally occurring human glucagon-like peptide-2 (GLP-2). GLP-2 is a peptide secreted by L-cells of the distal intestine in response to postprandial stimulation. GLP-2 is known to increase intestinal and portal blood flow, improve intestinal absorption, and inhibit gastric acid secretion. Gattex binds to the glucagon-like peptide-2 receptors, and activation results in the local release of multiple mediators including insulin-like growth factor (IGF)-1, nitric oxide, and keratinocyte growth factor (KGF).(1,3,5)

The efficacy, safety, and tolerability of Gattex was evaluated in a randomized, double-blind, placebo-controlled, clinical study (Study 1) in adults with short bowel syndrome (SBS) who were dependent on parenteral nutrition/intravenous (PN/IV) support for at least 12 months and required PN at least 3 times per week. Investigators optimized the PN/I.V. volume of all patients, followed by a 4-week to 8-week period of fluid stabilization, prior to randomization. Patients were randomized (1:1) to placebo or Gattex 0.05mg/kg/day (subcutaneously once daily) for 24 weeks. PN/IV volume adjustments (up to 30% decrease) and clinical assessments were made at 2, 4, 8, 12, 20, and 24 weeks. Mean duration of PN/IV dependency prior to enrollment was 6 years, mean length of remaining small intestine was 77.3cm, and the colon was not in continuity in 44% of patients at baseline.(1) The primary efficacy endpoint was the percentage of patients who demonstrated a response at week 20 and maintained that response at week 24 (responder). A response was defined as a reduction from baseline in weekly PN/IV of 20% or greater (20%-100%). In the Gattex treatment group, 63% of patients were responders compared to only 30% of the placebo-treated patients (p=0.002). At Week 24, the mean reduction in weekly PN/IV volume was 4.4 Liters for Gattex-treated patients (from pre-treatment baseline of 12.9 Liters) versus 2.3 Liters for placebo-treated patients (from pre-treatment baseline of 13.2 Liters/week) (p<0.001).(1,6)

Study 2 was a 2-year open-label extension of Study 1 in which 88 patients received Gattex 0.05 mg/kg/day. 76 patients who completed Study 1 elected to enroll in Study 2, and an additional 12 patients entered Study 2 who had been optimized and stabilized but not randomized in Study 1 because of closed enrollment. Patients who completed Study 2 are split into three groups for assessment of results: 30 patients received Gattex in Study 1 and Study 2 (TED/TED - 30 months of treatment), 29 patients received placebo in Study 1 and Gattex in Study 2 (PBO/TED - 24 months of treatment), and 6 were not in Study 1 but received Gattex in Study 2 (NT/TED - 24 months of treatment). Unique to the TED/TED group, 22 of the 30 patients in the group were considered responders from Study 1, and of those 22 patients, 21 (96%) sustained their response to Gattex in Study 2. Other results are shown in the table below:(1,7)

Completers (n=65)			
	TED/TED (n=30)	PBO/TED (n=29)	NT/TED (n=6)
Clinical Response*, n(%)	28(93)	16(55)	4(67)

Mean PN/IV reduction from baseline, L/week(SD)	7.6(4.9)	3.1(3.9)	4.0(2.9)
Total patients weaned off of PN/IV while treated with Gattex, n(%)	10 (33%)	2 (69%)	1 (17%)
*Clinical response is defined as a reduction from baseline in weekly PN/IV of 20% or greater (20%-100%)			

Study 3 was a randomized, double-blind, placebo-controlled, three parallel-group, study in adults with SBS who were dependent on PN/IV support for at least 12 months and required PN at least 3 times per week. After a period of optimization and stabilization similar to Study 1, patients were randomized to receive 24 weeks of one of the following treatment regimens: Gattex 0.05 mg/kg/day (n=35), Gattex 0.1 mg/kg/day (twice the recommended dose) (n=33), or placebo (n=16). Evaluation of the efficacy endpoint of response (defined as at least 20% reduction in PN/IV fluid from Baseline to Weeks 20 and 24) showed 46% of patient treated with Gattex 0.05mg/kg/day responded versus 6% on placebo. Study 4 was a blinded, uncontrolled extension of Study 3, in which 65 patients from Study 3 received Gattex for up to an additional 28 weeks of treatment. In the Gattex 0.05 mg/kg/day dose group, a 20% or greater reduction of PN/IV was achieved in 68% (17/25) of patients.(1)

Treatment of SBS in Pediatrics

Study 5 was a 24-week, multicenter study conducted in 59 pediatric patients aged 1 year through 17 years with SBS who were dependent on parenteral support (PS). Patients chose whether to receive Gattex or standard of care (SOC). Patients who chose to receive Gattex treatment were subsequently randomized in a double-blind manner to 0.025 mg/kg/day (n=24) or 0.05 mg/kg/day (n=26), while 9 patients enrolled in the SOC arm. At baseline, the mean PS volume was 60mL/kg/day and the mean PS infusion time was 7 days/week and 11 hours/day. At week 24 in patients treated with Gattex 0.05mg/kg/day (n=26), 69%(18/26) had a reduction in PS volume of at least 20,

	38%(10/26) had a reduction in PS infusion time of greater than or equal to 1 day/week, and 12%(3/26) achieved enteral autonomy.(1) Study 6 was a prospective, open-label, long-term extension study of pediatric patients who completed Study 5. Patients received additional treatment with Gattex 0.05 mg/kg subcutaneously once daily if they deteriorated or stopped improving after discontinuation of prior Gattex treatment. 87% (13/15) of patients required additional treatment with Gattex. At the end of week 24 (total treatment for a mean of 40 weeks), efficacy results were similar to those achieved at the end of 24 weeks treatment in Study 5. One additional patient achieved enteral autonomy during follow-up in Study 6.(1)
Safety	Gattex has no FDA labeled contraindications for use but does carry warnings concerning neoplastic growth, intestinal obstruction, biliary and pancreatic disease, and fluid overload.(1) Gattex is a growth factor and has the potential to enhance the growth of gastrointestinal polyps, accelerate cancer growth, and cause hyperplastic changes including neoplasia.(1,5) Due to this risk, a colonoscopy of the entire colon should be done within 6 months prior to starting therapy in adult patients. If polyps are present, they should be removed and adherence to current polyp follow-up guidelines is recommended. If colorectal cancer is diagnosed, discontinue Gattex. In patients at increased risk for malignancy or patients who develop active non-gastrointestinal malignancy, the clinical decision to use Gattex should be made based on benefit-risk considerations. In pediatric patients, a fecal occult blood test should be performed within 6 months prior to starting therapy. If there is unexplained blood in the stool, a colonoscopy/sigmoidoscopy should be performed. For all patients, a follow-up colonoscopy (or alternate imaging) is recommended at the end of 1 year of Gattex therapy and at least every 5 years thereafter while on therapy.(1) Intestinal obstruction has been reported with Gattex in clinical trials. In patients who develop intestinal or stromal obstruction, Gattex should be temporarily discontinued while the patient is clinically managed. Gattex may be restarted when the obstructive presentation resolves.(1) Cholecystitis, cholangitis, cholelithiasis, and pancreatitis have been reported in clinical studies with Gattex treatment. Patients should undergo laboratory assessment of bilirubin, alkaline phosphatase, lipase, and amylase within 6 months prior to starting Gattex and at least every 6 months while on Gattex.(1) Fluid overload and congestive heart failure have been observed in clinical trials, which were felt to be related to enhanced fluid absorption associated with

	Gattex. If fluid overload occurs, parenteral support should be adjusted and Gattex treatment should be reassessed, especially in patients with underlying cardiovascular disease.(1) Gattex has the potential to increase absorption of concomitant oral medications. Agents that require titration or have a narrow therapeutic index require careful monitoring and possible dose adjustments.(1)

REFERENCES

Number	Reference
1	Gattex prescribing information. Takeda Pharmaceuticals America, Inc. February 2024.
2	American Gastroenterological Association medical position statement: Short bowel syndrome and intestinal transplantation. *Gastroenterology*. 2003;124(4):1105-1110. doi:10.1053/gast.2003.50139
3	Parrish CR, DiBaise JK. Managing the adult patient with short bowel syndrome. PubMed. 2017;13(10):600-608.
4	Nightingale J, Woodward J. Guidelines for management of patients with a short bowel. *Gut*. 2006;55(suppl_4):iv1-iv12. doi:10.1136/gut.2006.091108
5	DiBaise JK, Iyer K, Rubio–Tapia A. AGA Clinical Practice Update on Management of Short Bowel Syndrome: Expert Review. Clinical Gastroenterology and Hepatology. 2022;20(10):2185-2194.e2. doi:10.1016/j.cgh.2022.05.032
6	Jeppesen PB, Pertkiewicz M, Messing B, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. *Gastroenterology*. 2012;143(6):1473-1481.e3. doi:10.1053/j.gastro.2012.09.00
7	Schwartz LK, O'Keefe SJD, Fujioka K, et al. Long-Term teduglutide for the treatment of patients with intestinal failure associated with short bowel syndrome. *Clinical and Translational Gastroenterology*. 2016;7(2):e142. Doi:10.1038/ctg.2015.69

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of short bowel syndrome (SBS) and ALL of the following: 1. The patient has less than 200 cm of functional small intestine **AND** 2. The patient has tried and had an inadequate response to maximal use of TWO anti-diarrheal agents (e.g., loperamide, diphenoxylate) used concomitantly with oral rehydration solution **AND** 3. The patient is currently receiving parenteral nutrition/intravenous fluids (PN/IV) at least 3 days per week **AND** 4. ONE of the following: A. The patient is a pediatric patient at least 1 year of age AND BOTH of the following: 1. A fecal occult blood test has been performed within 6 months prior to initiating treatment with the requested agent **AND** 2. ONE of the following: A. There was no unexplained blood in the stool **OR** B. There was unexplained blood in the stool AND a colonoscopy or a sigmoidoscopy was performed **OR** B. The patient is an adult AND BOTH of the following: 1. The patient has had a colonoscopy within 6 months of initiating treatment with the requested agent **AND** 2. If polyps were present at this colonoscopy, the polyps were removed **OR** B. The patient has another FDA labeled indication for the requested agent **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) is within FDA labeled dosing for the requested indication

Module	Clinical Criteria for Approval
	Length of Approval: 6 months **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient has had clinical benefit with the requested agent **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months

GLP-1 (glucagon-like peptide-1) Agonists

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Adlyxin® (lixisenatide) Subcutaneous injection	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Limitations of Use: • Has not been studied in patients with chronic pancreatitis or a history of unexplained pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis • Should not be used in patients with type 1 diabetes • Has not been studied in patients with gastroparesis and is not recommended in patients with gastroparesis.		8
Bydureon® (exenatide) Subcutaneous injection	Adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus. Limitations of Use: • Not recommended as first-line therapy for patients inadequately controlled on diet and exercise • Is not indicated for use in patients with type 1 diabetes mellitus • Bydureon is an extended-release formulation of exenatide and should not be used with other products containing the active ingredient exenatide. • Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.		3

Agent(s)	FDA Indication(s)	Notes	Ref#
Bydureon BCise® (exenatide) Subcutaneous injection	Adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus. Limitations of Use: • Not recommended as first-line therapy for patients inadequately controlled on diet and exercise. • Is not indicated for use in patients with type 1 diabetes mellitus • Bydureon BCise is an extended-release formulation of exenatide. It should not be used with other products containing the active ingredient exenatide. • Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.		4
Byetta® (exenatide) Subcutaneous injection	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Limitations of Use: • Should not be used for the treatment of type 1 diabetes. • Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.		1
Mounjaro® (tirzepatide) Subcutaneous injection	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of Use • Has not been studied in patients with a history of pancreatitis • Is not indicated for use in patients with type 1 diabetes mellitus		11

Agent(s)	FDA Indication(s)	Notes	Ref#
Ozempic® (semaglutide) Subcutaneous injection	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease Limitations of Use: • Has not been studied in patients with a history of pancreatitis. Consider another antidiabetic therapy • Not for treatment of type 1 diabetes mellitus		5
Rybelsus® (semaglutide) Tablet	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of Use: • Not recommended as first-line therapy for patients who have inadequate glycemic control on diet and exercise • Has not been studied in patients with a history of pancreatitis • Not indicated for use in patients with type 1 diabetes mellitus		6
Trulicity® (dulaglutide) Subcutaneous injection	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. To reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus who have established cardiovascular disease or multiple cardiovascular risk factors Limitations of Use: • Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in these patients • Not for treatment of type 1 diabetes		7

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Not recommended in patients with severe gastrointestinal disease, including severe gastroparesis.		
Victoza®, Liraglutide Subcutaneous injection	Adjunct to diet and exercise to improve glycemic control in patients 10 years and older with type 2 diabetes mellitus. To reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease Limitations of Use: • Should not be used in patients with type 1 diabetes mellitus. • Contains liraglutide and should not be coadministered with other liraglutide containing products		2

CLINICAL RATIONALE

Diabetes Mellitus	The American Diabetes Association (ADA) recommends the following guidelines:(9,10) • Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. • In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. • Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy. • Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals.

	• Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. A Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. • The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (greater or equal to 300 mg/dL) are very high. • A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. • Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. • In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. • An A1C level of greater than or equal to 6.5% is recommended for most nonpregnant adults, if it can be achieved safely. Glucose targets should be individualized with consideration for life expectancy, disease duration, presence or absence of micro- and macrovascular complications, cardiovascular disease (CVD) risk factors, comorbid conditions, and risk for hypoglycemia, as well as a person's cognitive and psychological status. • Adopt less stringent glycemic goals (A1C 7% to 8%) in persons with a history of severe hypoglycemia, hypoglycemia unawareness, limited life expectancy, advanced renal disease, extensive comorbid conditions, or long-standing DM in which the A1C goal has been difficult to attain despite intensive efforts, so long as the person remains free of hyperglycemia-associated symptoms. Healthy lifestyle behaviors, diabetes self-management, education, and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. Pharmacotherapy should be started at the time type 2 diabetes is diagnosed unless there are

	contraindications. Pharmacologic approaches that provide the efficacy to achieve treatment goals should be considered, such as metformin or other agents, including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals. In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and/or chronic kidney disease (CKD), the treatment regimen should include agents that reduce cardiorenal risk. Pharmacologic approaches that provide the efficacy to achieve treatment goals should be considered, specified as metformin or agent(s), including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals. In general, higher-efficacy approaches have greater likelihood of achieving glycemic goals, with the following considered to have very high efficacy for glucose lowering: the GLP-1 RAs dulaglutide (high dose) and semaglutide, the gastric inhibitory peptide (GIP) and GLP-1 RA tirzepatide, insulin, combination oral therapy, and combination injectable therapy. Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals, with very high efficacy for weight loss seen with semaglutide and tirzepatide. Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death. Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release form that can be given once daily. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, weight, and cardiovascular mortality. For people with type 2 diabetes and established ASCVD or indicators of high ASCVD risk, HF, or CKD, an SGLT2 inhibitor and/or GLP-1 RA with demonstrated CVD benefit is recommended as part of the glucose-lowering regimen independent of A1C, independent of metformin use and in consideration of person-specific factors. For people without established ASCVD, indicators of high ASCVD risk, HF, or CKD, medication choice is guided by efficacy in support of individualized glycemic and weight management goals, avoidance of side effects (particularly hypoglycemia and weight gain), cost/access, and individual preferences.(10) The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) recommend glucagon-like peptide 1 receptor agonists (GLP-1) as an add-on therapy to oral agents and in combination with insulin for the treatment of diabetes. Current guidelines by the ADA and AACE do not support combination therapy of GLP-1 and dipeptidyl peptidase 4 inhibitors (DPP-4) due to lack of added clinical benefit. The mechanism of action by which GLP-1 and DPP-4 medications control blood glucose is by

	targeting the body's incretin system. GLP-1 agonists act as "incretin mimetics" and DPP-4 inhibitors prevent the breakdown of endogenous incretin. Unlike endogenous incretin, GLP-1 is not broken down by the DPP-4 enzyme. Therefore, using these medications at the same time yields no additional benefit due to the simliar mechanism of action. (10,12,13)

Safety	Bydureon, Bydureon BCise, Mounjaro, Ozempic, Rybelsus, Trulicity, and Victoza all share the same boxed warning and contraindications:(2-7,11)
	
	• Causes thyroid C-cell tumors at clinically relevant exposures in rats. It is unknown whether these agents cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) in humans, as the human relevance of induced rodent thyroid C-cell tumors has not been determined.
	• Contraindicated in:
	  ○ Patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
	  ○ Prior serious hypersensitivity reaction to the active ingredient or any of the product components
	
	Adlyxin and Byetta are contraindicated in patients with severe hypersensitivity to the active product ingredient or any component. (1,8)

REFERENCES

Number	Reference
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2	Victoza prescribing information. Novo Nordisk A/S. July 2023.
3	Bydureon prescribing information. AstraZeneca Pharmaceuticals, Inc. December 2022.
4	Bydureon BCise prescribing information. AstraZeneca Pharmaceuticals, Inc. December 2022.
5	Ozempic prescribing information. Novo Nordisk. September 2023.
6	Rybelsus prescribing information. Novo Nordisk A/S. January 2022.
7	Trulicity prescribing information. Eli Lilly and Company. November 2022.

Number	Reference
8	Adlyxin prescribing information. Sanofi-Aventis US. LLC. June 2022.
9	American Diabetes Association. 6. Glycemic Targets: Standards of Care in Diabetes-2024. Diabetes Care. 2024 Jan;47(Suppl 1):S97-S1https://doi.org/10.2337/dc24-S00610.
10	American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2023. Diabetes Care 1 January 2023; 47 (Supplement_1): S158–S178. https://doi.org/10.2337/dc23-S009.
11	Mounjaro prescribing information. Lilly, USA. June 2023.
12	Nauck, Michael A. Addition of dipeptidyl peptidase-4 inhibitor, sitagliptin, to ongoing therapy with the glucagon-like peptide-1 receptor agonist liraglutide: A randomized controlled trial in patients with type 2 diabetes. Diabetes Obesity and Metabolism. (2):200-207. dom-pubs.onlinelibrary.wiley.com/doi/10.1111/dom.12802.
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14	American Diabetes Association. Understanding A1C. https://diabetes.org/about-diabetes/a1c.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td>CoT with Dx check</td><td>
<table>
<tr><th>Preferred Target Agent(s)</th><th>Non-Preferred Target Agent(s)</th></tr>
<tr><td>Bydureon (exenatide)
Mounjaro (tirzepatide)
Ozempic (semaglutide)
Rybelsus (semaglutide)
Trulicity (dulaglutide)</td><td>Adlyxin (lixisenatide)
Byetta (exenatide)
Victoza, Liraglutide</td></tr>
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<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
Target Agent(s) will be approved when BOTH of the following are met:

1. The patient has a diagnosis of type 2 diabetes AND
2. The patient's diagnosis has been confirmed by lab tests (e.g., A1C greater than or equal to 6.5%) (lab test results required) AND
3. ONE of the following:
A. The requested agent eligible for continuation of therapy AND ONE of the following:

<table>
<tr><th>Agents Eligible for Continuation of Therapy</th></tr>
<tr><td>Ozempic, Rybelsus, Trulicity, Mounjaro, Bydureon</td></tr>
</table>

1. The patient has been treated with a preferred agent (starting on samples is not approvable) within the past 90 days OR
2. The prescriber states the patient has been treated with a preferred agent within the past 90 days (starting on samples is not approvable) AND is at risk if therapy with a preferred agent is discontinued OR
B. BOTH of the following:
1. ONE of the following:
A. The patient has tried and had an inadequate response to an agent containing metformin or insulin OR
B. The patient has an intolerance or hypersensitivity to metformin or insulin OR
C. The patient has an FDA labeled contraindication to BOTH metformin AND insulin OR
D. The patient has a diagnosis of type 2 diabetes with/or at high risk for atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease AND
2. ONE of the following:
A. The requested agent is a preferred GLP-1 or GLP-1/GIP OR
B. The agent is a non-preferred GLP-1 and TWO of the following:
1. The patient has tried and had an inadequate response after at least a 90 day trial of therapy, has an intolerance, has a hypersensitivity, or has an FDA labeled contraindication to semaglutide (Ozempic OR Rybelsus) OR
2. The patient has tried and had an inadequate response after at least a 90 day trial of therapy, has an intolerance, has a
</td></tr>
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Module	Clinical Criteria for Approval
	hypersensitivity, or has an FDA labeled contraindication to dulaglutide (Trulicity) **OR** 3. The patient has tried and had an inadequate response after at least a 90 day trial of therapy, has an intolerance, has a hypersensitivity, or has an FDA labeled contraindication to tirzepatide (Mounjaro) **AND** 4. The patient will NOT be using the requested agent in combination with a DPP-4 containing agent for the requested indication **AND** 5. The patient will NOT be using the requested agent in combination with another GLP-1 receptor agonist agent **Length of Approval:** 12 months NOTE: If Quantity Limit program also applies, please refer to Quantity Limit criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Glucose Test Strips and Meters

Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Accu-Chek® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
Advocate® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
CareSens® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
Choice® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
Contour® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
CVS® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1

Agent(s)	FDA Indication(s)	Notes	Ref#
Diathrive® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
EasyGluco® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
Easymax® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
Embrace® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
Fifty50® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
Fora® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
FortisCare® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
Freestyle® products		NOTE: This table is not inclusive of all	1

Agent(s)	FDA Indication(s)	Notes	Ref#
(Blood glucose test strip, Blood glucose test meter)		available diabetic test strips	
GHT® Blood Glucose products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
Glucocard® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
iGlucose® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	
Infinity® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
MyGlucoHealth® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
Nova Max® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
OneTouch® products		NOTE: This table is not inclusive of all	1

Agent(s)	FDA Indication(s)	Notes	Ref#
(Blood glucose test strip, Blood glucose test meter)		available diabetic test strips	
POGO Automatic® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
Precision® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
Prodigy® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
ReliOn® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
Sidekick® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
Smart® Gluco-Monitoring poducts (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1
Telcare® products		NOTE: This table is not inclusive of all	1

Agent(s)	FDA Indication(s)	Notes	Ref#
(Blood glucose test strip, Blood glucose test meter)		available diabetic test strips	
Verasens® products (Blood glucose test strip, Blood glucose test meter)		NOTE: This table is not inclusive of all available diabetic test strips	1

CLINICAL RATIONALE

Glucose Test Strips and Meters	Glucose Test Strips and appropriate meters are indicated to be used for quantitatively measuring glucose in indicated blood samples. Strips and associated meters are intended for use outside the body by people with diabetes for self-monitoring of blood glucose at home and healthcare professionals in the clinical setting, as an aid to monitor the effectiveness of diabetes control.(1) There are many choices of meters and test strips to choose from. Individuals should choose the device based on ease of use, cost and insurance coverage, information retrieval, flexibility.(1) The evidence is insufficient regarding when to prescribe blood glucose monitors (BGM) and how often testing is needed for insulin-treated people with diabetes who do not use intensive insulin regimens, such as those with type 2 diabetes using basal insulin with or without oral agents and/or non-insulin injectables. In people with type 2 diabetes not using insulin, routine glucose monitoring may be of limited additional clinical benefit. For some individuals, glucose monitoring can provide insight into the impact of nutrition, physical activity, and medication management on glucose levels. Glucose monitoring may also be useful in assessing hypoglycemia, glucose levels during intercurrent illness, or discrepancies between measured A1C and glucose levels when there is concern an A1C result may not be reliable in specific individuals. For patients using basal insulin, assessing fasting glucose with blood glucose monitoring to inform dose adjustments to achieve blood glucose targets results in lower A1C. For many individuals on intensive insulin regimens using BGM, this requires checking up to 6-10 times daily.(2)

REFERENCES

Number	Reference
1	American Diabetes Association Consumer Guide. Meters. https://consumerguide.diabetes.org/collections/meters.
2	American Diabetes Association Professional Practice Committee; 7. Diabetes Technology: Standards of Care in Diabetes—2024. Diabetes Care 1 January 2024; 47 (Supplement_1): S126–S144. https://doi.org/10.2337/dc24-S007.

OBJECTIVE

Glucose Test Strips Quantity Limit

The intent of the Glucose Test Strips Quantity Limit program is to determine appropriate prescribing quantities as recommended by Food and Drug Administration (FDA) approved product labeling or as otherwise clinically appropriate. The quantity limit will allow 3-4 times a day testing with meals plus 1-2 additional testing to accommodate for snacks. Allowing for 204 tests/30 days accommodates for not only the 50-100 packs, but also the 51 & 102 that is used for some drums.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Traditional QL	Quantities above the program quantity limit for the **Target Agent(s)** will be approved when ONE of the following is met: 1. There is support indicating the need for additional blood glucose testing **Length of Approval:** up to 12 months

Gonadotropin Hormones

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Cetrotide® (cetrorelix acetate)* Injection	Inhibition of premature luteinizing hormone (LH) surges in women undergoing controlled ovarian stimulation	*generic available Gonadotropin Releasing Hormone (GnRH) analogs	1
Follistim® AQ (follitropin beta) Injection	Induction of ovulation and pregnancy in anovulatory infertile women whom the cause of infertility is functional and not due to primary ovarian failure Pregnancy in normal ovulatory women undergoing controlled ovarian stimulation as part of an in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) cycle Induction of spermatogenesis in men with primary and secondary hypogonadotropic hypogonadism (HH) in whom the cause of infertility is not due to primary testicular failure	Follicle Stimulating Hormone (FSH)	2
Ganirelix acetate* Injection	Inhibition of premature LH surges in women undergoing controlled ovarian hyperstimulation	*generic available Gonadotropin Releasing Hormone (GnRH) analogs	3
Gonal-F® (follitropin alpha) Injection	Induction of ovulation and pregnancy in oligo-anovulatory infertile women for whom the cause of infertility is functional and not due to primary ovarian failure	Follicle Stimulating Hormone (FSH)	4

Agent(s)	FDA Indication(s)	Notes	Ref#
	Development of multiple follicles in ovulatory infertile women as part of an assisted reproductive technology (ART) cycles Induction of spermatogenesis in infertile men with primary and secondary hypogonadotropic hypogonadism for whom the cause of infertility is not due to primary testicular failure		
GONAL-F RFF® (follitropin alfa) Injection	Induction of ovulation and pregnancy in oligo-anovulatory infertile women for whole the cause of infertility is function and not due to primary ovarian failure Development of multiple follicles in ovulatory infertile women as part of assisted reproductive technology (ART) cycles	Follicle Stimulating Hormone (FSH)	14
Menopur® (menotropins) Injection	Development of multiple follicles and pregnancy in ovulatory women as part of an assisted reproductive technology (ART) cycle	Menotropins	5
Novarel® (chorionic gonadotropin) Injection	Prepubertal cryptorchidism not due to anatomic obstruction Selected cases of hypogonadotropic hypogonadism (hypogonadism secondary to a pituitary deficiency) in males Induction of ovulation and pregnancy in the anovulatory, infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure, and who has been appropriately pretreated with human menotropins	Human Chorionic Gonadotropin (hCG)	6
Ovidrel® (choriogonadotropin alfa) Injection	Induction of final follicular maturation and early luteinization in infertile women who have undergone pituitary desensitization and who have been appropriately pretreated with follicle simulating	Human Chorionic Gonadotropin (hCG)	7

Agent(s)	FDA Indication(s)	Notes	Ref#
	hormones as part of an assisted reproductive technology (ART) program Induction of ovulation (OI) and pregnancy in anovulatory infertile patients in whom the cause of infertility is functional and not due to primary ovarian failure		
Pregnyl®, Chorionic Gonadotropin Injection	Prepubertal cryptorchidism not due to anatomical obstruction Selected cases of hypogonadotropic hypogonadism (hypogonadism secondary to a pituitary deficiency) in males Induction of ovulation and pregnancy in the anovulatory, infertile woman in whom the cause of anovulation is secondary and not due to primary ovarian failure, and who have been appropriately treated with human gonadotropins	Human Chorionic Gonadotropin (hCG)	8,17

CLINICAL RATIONALE

Infertility	Infertility is a disease, condition, or status characterized by any of the following:(20) • Inability to achieve a successful pregnancy based on a patient's medical, sexual, and reproductive history, age, physical findings, diagnostic testing, or any combination of these factors • Need for medical intervention, such as use of donor gametes or donor embryos in order to achieve a successful pregnancy as an individual or with a partner • Patients having regular, unprotected intercourse and without any known etiology for either partner suggestive of impaired reproductive ability, evaluation should be initiated at 12 months for females under 35 years of age and 6 months if over 35 years of age Infertility is a multifactorial condition and may be due to either the male or female partner or a combination of both. Some causes of infertility are easily identifiable; however, the situation is less clear in most couples. The most

	common causes of infertility are combined factors, male factor (hypogonadism, post-testicular defects, seminiferous tubule dysfunction), ovulatory dysfunction, tubal damage, endometriosis, coital problems, and cervical factor. Up to 25-28% of infertility is unexplained.(15) Because infertility could be due to one partner or both it is recommended that an evaluation of both partners is performed concurrently. In addition to a complete initial diagnostic evaluation including a complete history and physical exam the following tests are useful in most couples with infertility:(15) • Semen analysis to assess male factors • Menstrual history, assessment of luteinizing hormone (LH) surge in urine prior to ovulation, and/or luteal phase progesterone level to assess ovulatory function • Hysterosalpingogram or sonohysterogram with a test of tubal patency such as hysterosalpingo-contrast-sonography to assess tubal patency and the uterine cavity • Assessment of ovarian reserve with day 3 serum follicle-stimulating hormone (FSH) and estradiol levels, anti-Müllerian hormone, and/or antral follicle count • Thyroid-stimulating hormone In select couples, the following additional tests may be warranted:(15) • Pelvic ultrasound to assess for uterine myomas and ovarian cysts • Laparoscopy to identify endometriosis or other pelvic pathology Once the cause of infertility is identified, therapy aimed at correcting reversible etiologies and overcoming irreversible factors can be implemented. Therapeutic interventions for treatment of male and female infertility may involve drug therapy, surgery, and/or procedures such as intrauterine insemination (IUI) or invitro fertilization (IVF). In women with ovulatory failure or those who have unexplained infertility with normal estradiol and gonadotropin levels, clomiphene is considered a reasonable first approach to ovulation induction. It may be combined with IUI to increase the likelihood of conception, particularly in couples with oligospermia. If 3 or 4 cycles of clomiphene fail to result in a pregnancy, or the woman is of advanced fertility age, injectable FSH/LH may be tried for ovulation induction. When this approach also fails, assisted reproductive technologies (ART) can be tried. ART is used from the beginning in women with tubal factor infertility.(16)

Assisted Reproductive Technology	The CDC definition of ART includes all fertility treatments in which both eggs and embryos are handled. ART procedures involve surgically removing eggs from a woman's ovaries, combining them with sperm in the laboratory, and returning them to the woman's body or donating them to another woman. They do not include treatments in which only sperm are handled (i.e., intrauterine or artificial insemination) or procedures in which a woman takes medicine only to stimulate egg production without the intention of having eggs retrieved.(9)
Hypogonadotropic Hypogonadism	Hypogonadism is defined as inadequate gonadal function, as manifested by deficiencies in gametogenesis and/or the secretion of gonadal hormones. Hypogonadotropic hypogonadism is also known as secondary or central hypogonadism.(10) Secondary hypogonadism is associated with decreased secretion of the gonadotropins, LH and FSH, resulting in reductions in testosterone secretion and sperm production. This disorder should, in theory, respond to the administration of LH and FSH. In practice, testosterone secretion virtually always increases to normal after replacement of LH, and sperm production more often than not increases after replacement of LH alone or LH plus FSH. Testosterone replacement will not restore spermatogenesis. Sperm production can usually be stimulated to a level sufficient to restore fertility in men who are infertile as a result of secondary hypogonadism through the use of gonadotropins or gonadotropin-releasing hormone.(10) The American Urological Association/American Society for Reproductive Medicine (AUA/ASRM) guideline recommends that clinicians should obtain hormonal evaluation, including FSH and testosterone, for infertile men with impaired libido, erectile dysfunction, oligozoospermia, atrophic testes, or evidence of hormonal abnormality on physical examination.(18) Testosterone levels should be defined based on a blood sample drawn in the morning, since levels drop during the day.(10) If the morning total testosterone level is low (less than 300 ng/dL), a more extensive evaluation should include a second testosterone level, measurements of free testosterone, LH, estradiol, and prolactin. The relationships among serum testosterone, LH, FSH, and prolactin concentrations helps to identify the clinical condition. The infertile male presenting with HH be treated with aromatase inhibitors, hCG, selective estrogen receptor modulators, or a combination thereof, after the etiology of the disorder has been evaluated.(19)
Cryptorchidism	Terms such as undescended testis, retentio testis, cryptorchidism, and maldescended testis describe a testis that is not normally located at the bottom of the scrotum. Cryptorchidism is the most common congenital abnormality of the male genitourinary tract. Most cryptorchid testes are undescended, but some are absent (due to agenesis or atrophy). True undescended testes have stopped

	short along their normal path of descent into the scrotum. They may remain in the abdominal cavity, or they may be palpable in the inguinal canal, or just outside the external ring.(11) The goal of management is to place and fix viable undescended testes in a normal scrotal position or to remove nonviable testicular remnants. Scrotal positioning reduces the risk of torsion and blunt traumatic injury (for intracanalicular testes) and permits easier examination of the testis. If performed sufficiently early, surgical correction also may reduce the risk of infertility and testicular cancer. Finally, having the testis in a normal, dependent scrotal position may improve body satisfaction, although the psychological impact of abnormal testicular position has not been studied.(11) Treatment for undescended testes is almost always surgical. Testicular descent depends upon local concentrations of testosterone considerably greater than can be achieved through systemic administration. However, administration of gonadotropins (either urine-derived human chorionic gonadotropin [hCG] or gonadotropin-releasing hormone [GnRH] analogs) can stimulate the testes to increase production of testosterone sufficiently to achieve the necessary local concentration. Hormonal treatment is controversial. The Nordic consensus on treatment of undescended testes and the 2014 American Urological Association guideline on the evaluation and treatment of cryptorchidism recommend against hormonal treatment, whereas 2016 European guidelines suggest that hormonal treatment before or after surgical treatment may have a beneficial effect on fertility. Although, in some cases, descent following hCG administration is permanent, in most cases, the response is temporary.(11)
Efficacy - Gonadotropins	Follicle-stimulating hormone (FSH) is synthesized and secreted by the gonadotropic cells of the anterior pituitary gland, and regulates the development, growth, pubertal maturation, and reproductive processes of the body. FSH stimulates the maturation of primordial germ cells in both males and females. In males, FSH induces Sertoli cells to secrete androgen-binding proteins and sustains spermatogenesis and stimulates inhibin B secretion. In females, FSH initiates follicular growth and recruitment of immature ovarian follicles on the ovary.(10) Menopur is a preparation of gonadotropins (FSH and LH activity).(5) During the normal menstrual cycle, LH participates with FSH in the development and maturation of the normal ovarian follicle, and the mid-cycle LH surge triggers ovulation.(7)

Human Chorionic Gonadotropin (hCG)	Human chorionic gonadotropin (hCG) is structurally similar to LH, although hCG appears to have a small degree of FSH activity as well. hCG stimulates production of gonadal steroid hormones by stimulating the interstitial cells (Leydig cells) of the testis to produce androgens and the corpus luteum of the ovary to produce progesterone. Androgen stimulation in the male leads to the development of secondary sex characteristics and may stimulate testicular descent when no anatomical impediment to descent is present. This descent is usually reversible when hCG is discontinued.(6,8) During the normal menstrual cycle, LH participates with FSH in the development and maturation of the normal ovarian follicle, and the mid-cycle LH surge triggers ovulation. hCG can substitute for LH in this function.(6-8)
Gonadotropin Releasing Hormone Analogs (GnRH)	Gonadotropin Releasing Hormone (GnRH) analogs compete with natural GnRH for binding to membrane receptors on pituitary cells and thus control the release of LH and FSH. GnRH stimulates the synthesis and release of LH and FSH from the gonadotrophic cells of the anterior pituitary. Due to a positive estradiol (E2) feedback at midcycle, GnRH liberation is enhanced resulting in an LH-surge. Thus LH-surge induces the ovulation of the dominant follicle, resumption of oocyte meiosis and subsequently luteinization as indicated by rising progesterone levels.(1,3)
Clomiphene citrate	The majority of patients who are going to ovulate will do so after the first course of therapy with clomiphene citrate. If ovulation does not occur after three courses of therapy, further treatment with clomiphene citrate is not recommended and the patient should be reevaluated.(13)
Safety	Ovarian hyperstimulation syndrome (OHSS) is not common but can be a serious complication associated with controlled ovarian stimulation during assisted reproductive technology (ART). Moderate-to-severe OHSS occurs in approximately 1-5% of cycles. However, the true incidence is difficult to delineate as a strict, consensus definition is lacking. Symptoms of OHSS are often qualified by their severity (mild, moderate, or severe) and by the timing of onset (early or late). Severe OHSS can lead to serious complications, including pleural effusion, acute renal insufficiency, and venous thromboembolism.(12) OHSS could theoretically occur in any woman undergoing controlled ovarian stimulation with gonadotropins. However, evidence indicates there are some women who are at higher risk. These risk factors may include:(12) • Younger age (less than 35 years old) • Lower body mass index (BMI)

	• Diagnosis of an ovulation disorder or polycystic ovary syndrome (PCOS) • Serum antimüllerian hormone (AMH) levels greater than 10 ng/mL • Antral follicle count (AFC) greater than or equal to 24 • Serum estradiol concentrations Chorionic Gonadotropin has the following contraindications:(17) • Precocious puberty • Prostatic carcinoma or other androgen-dependent neoplasm • Prior allergic reaction to HCG Cetrotide has the following contraindications:(1) • Hypersensitivity to cetrorelix acetate, extrinsic peptide hormones or mannitol • Known hypersensitivity to GnRH or any other GnRH analogs • Known or suspected pregnancy, and lactation • Severe renal impairment Follistim AQ has the following contraindications:(2) • Women and men who exhibit: • Prior hypersensitivity to recombinant hFSH products • High levels of FSH indicating primary gonadal failure • Presence of uncontrolled non-gonadal endocrinopathies • Hypersensitivity reactions related to streptomycin or neomycin • Tumors of the ovary, breast, uterus, testis, hypothalamus or pituitary gland • Women who exhibit: • Pregnancy • Heavy or irregular vaginal bleeding of undetermined origin • Ovarian cysts or enlargement not due to polycystic ovary syndrome Ganirelix acetate has the following contraindications:(3) • Known hypersensitivity to Ganirelix Acetate or to any of its components including dry natural rubber/latex • Known hypersensitivity to GnRH or any other GnRH analog • Known or suspected pregnancy Gonal-F has the following contraindications:(4)

	• Hypersensitivity to recombinant FSH products or one of their excipients • High levels of FSH indicating primary gonadal failure • Uncontrolled non-gonadal endocrinopathies (for example, thyroid, adrenal, or pituitary disorders) • Sex hormone dependent tumors of the reproductive tract and accessory organ • Tumors of pituitary gland or hypothalamus • Abnormal uterine bleeding of undetermined origin • Ovarian cyst or enlargement of undetermined origin, not due to poly cystic ovary syndrome Gonal-F RFF has the following contraindications in women:(14) • Prior hypersensitivity to recombinant FSH products or one of their excipients • High levels of FSH indicating primary gonadal failure • Uncontrolled non-gonadal endocrinopathies • Sex hormone dependent tumors of the reproductive tract and accessory organs • Tumors of the pituitary gland or hyperthalamus • Abnormal uterine bleeding of undetermined origin • Ovarian cyst or enlargement of undetermined origin Menopur has the following contraindications:(5) • Prior hypersensitivity to Menopur or menotropins products or one of their excipients • High levels of FSH indicating primary ovarian failure • Pregnancy • Presence of uncontrolled non-gonadal endocrinopathies (e.g., thyroid, adrenal, or pituitary disorders) • Sex hormone dependent tumors of the reproductive tract and accessory organs • Tumors of the pituitary gland or hypothalamus • Abnormal uterine bleeding of undetermined origin • Ovarian cyst or enlargement of undetermined origin, not due to polycystic ovary syndrome Novarel has the following contraindications:(6) • Precocious puberty • Prostatic carcinoma or other androgen-dependent neoplasm

	• Prior allergic reaction to hCG • hCG may cause fetal harm when administered to a pregnant woman • Combined hCG and pregnant mare's serum therapy has been noted to induce high incidences of external congenital anomalies in the offspring of mice, in a dose-dependent manner. The potential extrapolation to humans has not been determined Ovidrel has the following contraindications:(7) • Prior hypersensitivity to hCG preparations or one of their excipients • Primary ovarian failure • Uncontrolled thyroid or adrenal dysfunction • An uncontrolled organic intracranial lesion such as a pituitary tumor • Abnormal uterine bleeding of undetermined origin • Ovarian cyst or enlargement of undetermined origin • Sex hormone dependent tumors of the reproductive tract and accessory organs • Pregnancy Pregnyl has the following contraindications:(8) • Prior hypersensitivity reactions to human gonadotropins, including hCG, or any of the excipients • High serum FSH, indicating primary gonadal failure in women • Presence of uncontrolled non-gonadal endocrinopathies (e.g., thyroid, adrenal, or pituitary disorders) • Tumors of the hypothalamus or pituitary gland and ovary, breast, or uterus in females and breast or prostate in males • Malformations of the reproductive organs incompatible with pregnancy • Fibroid tumors of the uterus incompatible with pregnancy • Abnormal vaginal bleeding of undetermined origin

REFERENCES

Number	Reference
1	Cetrotide prescribing information. EMD Serono, Inc. December 2023.
2	Follistim AQ prescribing information. Merck Sharp & Dohme LLC. March 2023.

Number	Reference
3	Ganirelix acetate prescribing information. Organon LLC. August 2023.
4	Gonal-F prescribing information. EMD Serono, Inc. November 2023.
5	Menopur prescribing information. Ferring Pharmaceuticals Inc. May 2018.
6	Novarel prescribing information. Ferring Pharmaceuticals. May 2023.
7	Ovidrel prescribing information. EMD Serono, Inc. February 2022.
8	Pregnyl prescribing information. Merck Sharp & Dohme LLC. March 2023.
9	Centers for Disease Control and Prevention. Assisted Reproductive Technology (ART). What is Assisted Reproductive Technology? Available at https://www.cdc.gov/art/whatis.html.
10	Petak SM, Nankin HR, Spark RF, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the evaluation and Treatment of Hypogonadism in Adult Male patients—2002 Update. *Endocrine Practice*. 2002;8(6):439-456. doi:10.4158/ep.8.6.439
11	Niedzielski JK, Oszukowska E, Slpwikowska-Hilczer J. Undescended testis - current trends and guidelines: a review of the literature. Arch Med Sci. 2016 June 1; 12(3): 667-677.
12	Practice Committee of the American Society for Reproductive Medicine. Prevention and treatment of moderate and severe ovarian hyperstimulation syndrome: a guideline. Fertility and Sterility, 106(7), 1634-1647. https://doi.org/10.1016/j.fertnstert.2016.08.048
13	Clomiphene citrate prescribing information. Par Pharmaceutical, Inc. December 2021.
14	Gonal-F RFF prescribing information. EMD Serono, Inc. November 2023.
15	Lindsay TJ, Vitrikas KR. Evaluation and Treatment of Infertility. Am Fam Physician. 2015 Mar 1;91(5):308-314.
16	Practice Committee of the American Society for Reproductive Medicine. American Society for Reproductive Medicine, Birmingham, Alabama. Evidence-based treatments for couples with unexplained infertility: a guideline. Fertility and Sterility® Vol. 113, No2, February 2020.

Number	Reference
17	Chorionic Gonadotropin prescribing information. Fresenius Kabi USA, LLC. April 2020.
18	Schlegel PN, Sigman M, Collura B, et al. Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline Part I. *J Urol*. 2021;205(1):36-43. doi:10.1097/JU.0000000000001521.
19	Schlegel PN, Sigman M, Collura B, et al. Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline Part II. J Urol. 2021;205(1):44-51. doi:10.1097/JU.0000000000001521
20	Definition of infertility: A committee opinion (2023). American Society for Reproductive Medicine. (n.d.). https://www.asrm.org/practice-guidance/practice-committee-documents/denitions-of-infertility/

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td>Follicle Stimulating Hormone</td><td>
Follicle Stimulating Hormone Evaluation

Follistim AQ and Gonal-F will be approved when ALL of the following are met:

1. The patient’s benefit plan covers agents for infertility AND
2. ONE of the following:
A. The requested agent will be used for ovulation induction AND ONE of the following:
1. The requested agent is eligible for continuation of therapy AND ONE of the following:

<table>
<tr><th>Agents Eligible for Continuation of Therapy</th></tr>
<tr><td>All target agents are eligible for continuation of therapy</td></tr>
</table>

A. The patient has been treated with the requested agent within the past 90 days OR
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
B. The prescriber states the patient has been treated with the requested agent within the past 90 days AND is at risk if therapy is changed OR
2. ALL of the following:
A. ONE of the following:
1. The patient has tried and had an inadequate response to 3 courses of at least 50 mg daily for 5 days of clomiphene citrate OR
2. The patient has an intolerance or hypersensitivity to clomiphene citrate OR
3. The patient has an FDA labeled contraindication to clomiphene citrate AND
B. The patient is NOT pregnant AND
C. The patient does NOT have primary ovarian failure AND
D. The patient will receive human chorionic gonadotropin (hCG) following completion of the requested agent unless there are risks present for ovarian hyperstimulation syndrome (OHSS) AND
E. ONE of the following:
<table>
<tr><th>Preferred Target Agents</th><th>Non-Preferred Target Agents</th></tr>
<tr><td>Follistim AQ (follitropin beta)</td><td>Gonal F (follitropin alfa)
Gonal F RFF (follitropin alfa)</td></tr>
</table>
1. The requested agent is a preferred agent OR
2. The patient has tried and had an inadequate response to ONE of the preferred agent(s) OR
3. The patient has an intolerance or hypersensitivity to ONE of the preferred agent(s) that is NOT expected to occur with the requested agent OR
4. The patient has an FDA labeled contraindication to ALL of the preferred agent(s) that is NOT expected to occur with the requested agent OR
B. The requested agent will be used for the development of multiple follicles as part of an assisted reproductive technology (ART) [e.g., invitro fertilization (IVF), gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), tubal embryo transfer (TET), cryopreservation, intracytoplasmic sperm injection (ICSI)] AND ONE of the following:
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
1. The requested agent is eligible for continuation of therapy AND ONE of the following:

<table>
<tr><th>Agents Eligible for Continuation of Therapy</th></tr>
<tr><td>All target agents are eligible for continuation of therapy</td></tr>
</table>

A. The patient has been treated with the requested agent within the past 90 days **OR**
B. The prescriber states the patient has been treated with the requested agent within the past 90 days AND is at risk if therapy is changed **OR**

2. ALL of the following:
A. The patient is NOT pregnant **AND**
B. The patient does NOT have primary ovarian failure **AND**
C. The patient will receive human chorionic gonadotropin (hCG) following completion of the requested agent unless there are risks present for ovarian hyperstimulation syndrome (OHSS) **AND**
D. ONE of the following:

<table>
<tr><th>Preferred Target Agents</th><th>Non-Preferred Target Agents</th></tr>
<tr><td>Follistim AQ (follitropin beta)</td><td>Gonal F (follitropin alfa)
Gonal F RFF (follitropin alfa)</td></tr>
</table>

1. The requested agent is a preferred agent **OR**
2. The patient has tried and had an inadequate response to ONE of the preferred agent(s) **OR**
3. The patient has an intolerance or hypersensitivity to ONE of the preferred agent(s) that is NOT expected to occur with the requested agent **OR**
4. The patient has an FDA labeled contraindication to ALL of the preferred agent(s) that is NOT expected to occur with the requested agent **OR**

C. The requested agent will be used for hypogonadotropic hypogonadism AND ALL of the following:
1. The requested agent is Follistim AQ or Gonal-F **AND**
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
2. The patient does not have primary testicular failure AND
3. The requested agent will be used in combination with human chorionic gonadotropin (hCG) AND
4. The requested agent will not be started until the patient's serum testosterone level is at normal levels AND
1. ONE of the following:

<table>
<tr><th>Preferred Target Agents</th><th>Non-Preferred Target Agents</th></tr>
<tr><td>Follistim AQ (follitropin beta)</td><td>Gonal F (follitropin alfa)
Gonal F RFF (follitropin alfa)</td></tr>
</table>

A. The requested agent is a preferred agent OR
B. The patient has tried and had an inadequate response to ONE of the preferred agent(s) OR
C. The patient has an intolerance or hypersensitivity to ONE of the preferred agent(s) that is NOT expected to occur with the requested agent OR
D. The patient has an FDA labeled contraindication to ALL of the preferred agent(s) that is NOT expected to occur with the requested agent AND
3. The patient has undergone a complete medical and endocrinologic evaluation AND
4. The fertility status of the patient's partner has been evaluated (if applicable) AND
5. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of approval: 3 months for ART or ovulation induction
6 months for hypogonadotropic hypogonadism

NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents
</td></tr>
<tr><td>Gonadotropin Releasing Hormone (GnRH) Analogs</td><td>
Gonadotropin Releasing Hormone (GnRH) Analogs Evaluation

Cetrotide and Ganirelix acetate will be approved when BOTH of the following are met:

1. The patient's benefit plan covers agents for infertility AND
1. ONE of the following:
A. The requested agent is eligible for continuation of therapy AND ONE of the following:
</td></tr>
</table>

Module	Clinical Criteria for Approval

Agents Eligible for Continuation of Therapy
All target agents are eligible for continuation of therapy

1. The patient has been treated with the requested agent within the past 90 days **OR**
2. The prescriber states the patient has been treated with the requested agent within the past 90 days AND is at risk if therapy is changed **OR**

B. ALL of the following:

1. The patient is undergoing ovarian stimulation **AND**
2. The patient is NOT pregnant **AND**
3. The patient has undergone a complete medical and endocrinologic evaluation **AND**
4. The fertility status of the patient's partner has been evaluated (if applicable) **AND**
5. The patient will receive human chorionic gonadotropin (hCG) following completion of the requested agent unless there are risks present for ovarian hyper-stimulation syndrome (OHSS) **AND**
6. ONE of the following:

Preferred Target Agents	Non-Preferred Target Agents
Ganirelix acetate* *generic available	Cetrotide (cetrorelix acetate)

A. The requested agent is a preferred agent **OR**
B. The patient has tried and had an inadequate response to ONE of the preferred agent(s) **OR**
C. The patient has an intolerance or hypersensitivity to ONE of the preferred agent(s) that is NOT expected to occur with the requested agent **OR**
D. The patient has an FDA labeled contraindication to ALL of the preferred agent(s) that is NOT expected to occur with the requested agent **AND**

Module	Clinical Criteria for Approval
	2. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 3 months NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents
Human Chorionic Gonadotropin Evaluation	**Human Chorionic Gonadotropin Evaluation** **Novarel, Ovidrel, Pregnyl, and Chorionic gonadotropin** will be approved when BOTH of the following are met: 1. ONE of the following: A. The requested agent will be used for a diagnosis of cryptorchidism AND ALL of the following: 1. The requested agent is Novarel, Pregnyl, or hCG **AND** 2. The diagnosis is not due to an anatomical obstruction **AND** 3. The patient is prepubertal **AND** 4. ONE of the following: A. The patient has had surgery to correct the cryptorchidism **OR** B. The patient will have surgery to correct the cryptorchidism after using the requested agent **OR** C. The patient is unable to have surgery to correct the cryptorchidism **OR** B. The requested agent will be used for a diagnosis of hypogonadotropic hypogonadism AND BOTH of the following: 1. The requested agent is Novarel, Pregnyl, or hCG **AND** 2. ONE of the following: A. The patient is not currently receiving treatment for the diagnosis AND has ONE of the following pretreatment levels 1.Total serum testosterone level that is below the testing laboratory's normal range or is less than 300 ng/dL **OR** 2.Free serum testosterone level that is below the testing laboratory's normal range **OR** B. The patient is currently receiving treatment for the diagnosis AND has ONE of the following current levels: 1.Total serum testosterone level that is within OR below the testing laboratory's normal range OR is less than 300 ng/dL **OR** 2.Free serum testosterone level is within OR below the testing laboratory's normal range **OR**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
C. The requested agent will be used for the development of multiple follicles as part of an assisted reproductive technology (ART) [e.g., invitro fertilization (IVF), gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT), tubal embryo transfer (TET), cryopreservation, intracytoplasmic sperm injection (ICSI)] OR for ovulation induction AND BOTH of the following:
1. The patient’s benefit plan covers agents for infertility AND
2. ONE of the following:
A. The requested agent is eligible for continuation of therapy AND ONE of the following:

<table>
<tr><th>Agents Eligible for Continuation of Therapy</th></tr>
<tr><td>Ovidrel (chorionic gonadotropin)

Pregnyl (chorionic gonadotropin)</td></tr>
</table>

1. The patient has been treated with the requested agent within the past 90 days OR
2. The prescriber states the patient has been treated with the requested agent within the past 90 days AND is at risk if therapy is changed OR
B. ALL of the following:
1. The patient is NOT pregnant AND
2. The patient does NOT have primary ovarian failure AND
3. The patient will receive follicle stimulating hormone (FSH) OR clomiphene before the requested agent unless there are risks present for ovarian hyperstimulation syndrome (OHSS) AND
4. The patient has undergone a complete medical and endocrinologic evaluation AND
5. The fertility status of the partner been evaluated (if applicable) AND
6. ONE of the following:

<table>
<tr><th>Preferred Target Agents</th><th>Non-Preferred Target Agents</th></tr>
<tr><td>Ovidrel (chorionic gonadotropin)

Pregnyl (chorionic gonadotropin)</td><td>Chorionic gonadotropin

Novarel (chorionic gonadotropin)</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>A. The requested agent is a preferred agent OR
B. The patient has tried and had an inadequate response to ONE of the preferred agent(s) OR
C. The patient has an intolerance or hypersensitivity to ONE preferred agent(s) that is NOT expected to occur with the requested agent OR
D. The patient has an FDA labeled contraindication to ALL of the preferred agent(s) that is NOT expected to occur with the requested agent AND
2. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 3 months for ovulation induction or ART
6 months for hypogonadotropic hypogonadism
3 months for cryptorchidism

NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents</td></tr>
<tr><td>Menotropins</td><td>Menotropins Evaluation

Menopur will be approved when ALL of the following are met:

1. The patient’s benefit plan covers agents for infertility AND
2. ONE of the following:
1. The requested agent is eligible for continuation of therapy AND ONE of the following:

<table><tr><th>Agents Eligible for Continuation of Therapy</th></tr><tr><td>All target agents are eligible for continuation of therapy</td></tr></table>
A. The patient has been treated with the requested agent within the past 90 days OR
B. The prescriber states the patient has been treated with the requested agent within the past 90 days AND is at risk if therapy is changed OR
2. ALL of the following:
A. The requested agent will be used for the development of multiple follicles as part of an assisted reproductive technology (ART) [e.g., invitro fertilization (IVF), gamete intrafallopian transfer (GIFT), zygote</td></tr>
</table>

Module	Clinical Criteria for Approval
	intrafallopian transfer (ZIFT), tubal embryo transfer (TET), cryopreservation, intracytoplasmic sperm injection (ICSI) **AND** B. The patient is NOT pregnant **AND** C. The patient does NOT have primary ovarian failure **AND** D. The patient will receive human chorionic gonadotropin (hCG) following completion of the requested agent unless there are risks present for ovarian hyperstimulation syndrome (OHSS) **AND** E. The patient has undergone a complete medical and endocrinologic evaluation **AND** F. The fertility status of the patient's partner has been evaluated (if applicable) **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 3 months NOTE: If Quantity Limit program also applies, please refer to Quantity Limit documents

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Growth Hormone

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Genotropin® (somatropin) Subcutaneous injection	Pediatric: Treatment of children with growth failure due to growth hormone deficiency (GHD), Prader-Willi syndrome (PWS), Small for Gestational Age (SGA), Turner syndrome (TS), and Idiopathic Short Stature (ISS) Adult: Treatment of adults with either adult onset or childhood onset GHD		4
Humatrope® (somatropin) Subcutaneous injection	Pediatric: Growth failure due to inadequate secretion of endogenous growth hormone (GHD); short stature associated with TS; Idiopathic Short Stature (ISS), height standard deviation score (SDS) less than -2.25, and associated with growth rates unlikely to permit attainment of adult height in the normal range; short stature or growth failure in short stature homeobox-containing gene (SHOX) deficiency; short stature born small for gestational age (SGA) with no catch-up growth by 2 years to 4 years of age Adult: Replacement of endogenous GH in adults with GH deficiency		5
Ngenla™ (somatrogon-ghla) Subcutaneous pen-injection	Treatment of pediatric patients aged 3 years and older who have growth failure due to inadequate secretion of endogenous growth hormone		38
Norditropin® (somatropin) Subcutaneous injection	Pediatric: Treatment of pediatric patients with growth failure due to inadequate secretion of endogenous growth hormone (GH), short stature associated with NS, TS, and SGA with no catch-up growth by age 2 to 4 years, ISS, and growth failure due to PWS		6

Agent(s)	FDA Indication(s)	Notes	Ref#
	Adult: Replacement of endogenous GH in adults with growth hormone deficiency		
Nutropin® AQ (somatropin) Subcutaneous injection	Pediatric: Treatment of children with growth failure due to growth hormone deficiency (GHD), ISS, TS, and chronic kidney disease (CKD) up to the time of renal transplantation Adult: Treatment of adults with either childhood-onset or adult onset GHD		8
Omnitrope® (somatropin) Subcutaneous injection	Pediatric: Treatment of children with growth failure due to GHD, PWS, SGA, TS, and ISS Adult: Treatment of adults with either adult onset or childhood onset GHD		7
Saizen® (somatropin) Subcutaneous injection	Pediatric: Treatment of children with growth failure due to GHD Adult: Treatment of adults with either adult onset or childhood onset GHD		1
Serostim® (somatropin) Subcutaneous injection	- Treatment of HIV patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance		2
Skytrofa® (lonapegsomatropin-tcgd) Subcutaneous injection	- Treatment of pediatric patients 1 year and older who weigh at least 11.5 kg and have growth failure due to inadequate secretion of endogenous growth hormone		37
Sogroya® (somapacitan-beco) Subcutaneous injection	Pediatric: Treatment of pediatric patients aged 2.5 years and older who have growth failure due to inadequate secretion of endogenous growth hormone Adult: Replacement of endogenous growth hormone in adults with growth hormone deficiency		38

Agent(s)	FDA Indication(s)	Notes	Ref#
ZOMACTON® (somatropin) Subcutaneous injection	Pediatric: Treatment of pediatric patients with growth failure due to inadequate secretion of endogenous growth hormone (GH), short stature associated with Turner syndrome (TS), idiopathic short stature (ISS), short stature or growth failure in short stature homeobox-containing gene (SHOX) deficiency, and short stature born small for gestational age (SGA) with no catch-up growth by 2 years to 4 years. Adult: Replacement of endogenous GH in adults with GH deficiency		9
Zorbtive® (somatropin) Subcutaneous injection	-Treatment of short bowel syndrome in adult patients receiving specialized nutritional support		3

CLINICAL RATIONALE

Growth Hormone Deficiency in Children and Adults	Growth hormone deficiency (GHD) can be divided into congenital and acquired forms. The single most important clinical manifestation of GHD is growth failure, and careful documentation of height velocity is critical to making the correct diagnosis. Patients with congenital GHD have only a slightly reduced birth length and may not immediately show growth failure. Neonatal morbidity may include hypoglycemia. Children with acquired GHD present with severe growth failure, delayed bone age, and increased weight:height ratios. Causes of acquired GHD include intracranial tumors involving the hypothalamic-pituitary region, cranial irradiation, and head trauma.(10) Clinical presentation, diagnosis, and treatment of GHD in children and adolescents, as described by the 2016 Pediatric Endocrine Society Guidelines for Growth Hormone and Insulin-Like Growth Factor-1 (IGF-1) Treatment in Children and Adolescents(11), the 2019 Growth Hormone Research Society (GRS) Guidelines for the Diagnosis, Genetics, and Therapy of Short Stature Children(12), and the 2000 Growth Hormone Research Society (GRS) Consensus Guidelines for the Diagnosis and Treatment of Growth Hormone (GH) Deficiency in Childhood and Adolescence(13) is stated as follows:

	• A more comprehensive evaluation is warranted in children with one or more of the following:
	  ○ Height-for-age curve that has deviated downward across two major height percentile curves (e.g., from above the 25th percentile to below the 10th percentile)(10)
	  ○ Age 2-4 years: height velocity (HV) less than 5.5 cm/year (less than 2.2 inches/year)(10)
	  ○ Age 4-6 years: HV less than 5 cm/year (less than 2 inches/year)(10)
	  ○ Age 6 years to puberty:
	  ▪ HV less than 4 cm/year for boys (less than 1.6 inches/year)(10)
	  ▪ HV less than 4.5 cm/year for girls (less than 1.8 inches/year)(10)
	  ○ Decrease in height standard deviation (SD) of more than 0.5 over one year in children over 2 years of age(13)
	  ○ Height velocity more than 2 SD below the mean over one year, or more than 1.5 SD sustained over 2 years(13)
	  ○ Height more than 1.5 SD below the midparental height(12,13)
	  ○ Height greater than 2 SD below the mean for age and sex(12)
	  ○ Severe short stature (e.g., height less than or equal to -2.5 standard deviations [SD], i.e., 0.6th percentile), or less severe short stature combined with growth failure(12,13)
	  ○ Features that raise concerns for hypothalamic-pituitary dysfunction, either congenital or acquired, with decelerating growth, even if the child's height is within the normal range(10,12)
	  ○ Evidence for deficits in other hypothalamic-pituitary hormones, either congenital or acquired(12)
	
	• Once the decision to evaluate a short child has been made, a variety of different tests can be performed. Assessment of pituitary GH production is difficult because GH secretion is pulsatile. Between normal pulses of GH secretion, serum GH levels are often low, below the limits of sensitivity of most conventional assays. Because of these issues, the diagnosis of GHD is made with a combination of clinical assessment and auxology, levels of insulin-like growth factor I (IGF-I) and insulin-like growth factor binding protein 3 (IGFBP-3), and GH stimulation (provocation) tests.(10,12,13)
	• The IGF-I, IGFBP-3, and bone age testing results may be interpreted as follows:

	○ *Moderately or severely reduced*: IGF-I and IGFBP-3 less than -2 SD with delayed bone age; possibility of GHD should be explored by provocative testing in most cases(13) ○ *Somewhat low*: IGF-I and IGFBP-3 between 0 and -2 SD; decision about whether to perform provocative testing depends on other factors(13) ○ *Clearly normal*: IGF-I and IGFBP-3 SD greater than or equal to 0; no further testing required(13) ○ If the IGF-I and IGFBP-3 are discordant, IGF-I takes precedence except for infants and young children, in whom IGFBP-3 should guide the decision about further testing.(12,13) • Provocative (stimulation) GH testing is indicated for most patients to confirm GHD, however, because this testing has limitations, it should not be the sole diagnostic criterion.(11,13) In general, two different tests should be used for provocative GH testing. For those with known pathology of the central nervous system, history of irradiation, other pituitary hormone defects (e.g., multiple pituitary hormone deficiency [MPHD]), or a genetic defect, one test is sufficient.(12,13) • The use of GH provocative testing is not required for diagnosis of GHD in the following conditions: ○ In patients possessing all of the following three conditions: auxological criteria, hypothalamic-pituitary defect (such as major congenital malformation [ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk], tumor or irradiation), and deficiency of at least one additional pituitary hormone(10,11,12) ○ In a newborn with hypoglycemia who does not attain a serum GH concentration above 5 mcg/L and has deficiency of at least one additional pituitary hormone and/or congenital pituitary abnormality (ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk)(10,11,12) ○ Infant or young child with extreme short stature (e.g., height less than -3 SD), normal nutrition, significantly reduced IGF-1 and IGFBP-3 (e.g., less than -2 SD), and delayed bone age(12) ○ In newborns who present with hypoglycemia in the absence of a metabolic disorder, a serum growth hormone level of less than 20 mcg/L suggests GHD. An IGFBP-3 measurement (e.g., less than -2 SD) is of value for the diagnosis of GHD in infancy.(13) ○ When an alternative diagnosis for short stature is evident, such as Turner syndrome, Noonan syndrome, Prader-Willi syndrome

	(PWS), SHOX deficiency, chronic renal insufficiency, or in children born small for gestational age (SGA)(12) • Some guidelines acknowledge that a threshold test result distinguishing "normal" from GHD has not been well established.(11,12) Most pediatric endocrinologists define a "normal" response by a serum GH concentration of greater than 10 mcg/L, but a cutoff of 7.5 mcg/L is often used for modern assays.(12,13) • Treatment of children with GHD is the following: o Weight-based or body-surface-area dosing should be used.(11,12,13) o Measure serum IGF-1 levels to monitor adherence and for dose changes.(11,12,13) o Serum levels of IGF-1 should be measured approximately 4 weeks after beginning GH treatment and/or making a dose adjustment(13) o Routine follow-up (once IGF-1 levels are in target range) of pediatric patients should be conducted on a 3- to 6-month basis(13) o Treatment is appropriate for children with GHD whose epiphyses are open(13) • Treatment is generally continued at least until linear growth decreases to less than 2.0 to 2.5 cm/year.(11) Guidelines for patients transitioning from pediatric to adult care, as described by the 2016 Pediatric Endocrine Society Guidelines for Growth Hormone and Insulin-Like Growth Factor-1 (IGF-1) Treatment in Children and Adolescents(11), the 2000 Growth Hormone Research Society (GRS) Consensus Guidelines for the Diagnosis and Treatment of Growth Hormone (GH) Deficiency in Childhood and Adolescence(13), the 2019 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology Guidelines for Management of Growth Hormone Deficiency in Adults and Patients Transitioning from Pediatric to Adult Care(24), and the 2011 Endocrine Society Clinical Practice Guidelines for Evaluation and Treatment of Adult Growth Hormone Deficiency(25) is stated as follows: • Only a minority of children with childhood-onset GHD will remain deficient as adults and require ongoing GH therapy. The transition period is loosely defined as occurring from mid-to-late teens until 6-7 years after reaching near-adult height.(27) • For patients transitioning from pediatric to adult care: o Because the majority of isolated childhood-onset GHD patients will have normal results when tested as adults, it is important to

	repeat GH stimulation testing to determine if ongoing therapy is required.(11,24,27) ○ Measurement of the serum IGF-1 concentration should be the initial test of the somatotropic axis if re-evaluation of the somatotropic axis is clinically indicated.(11) ○ GH provocative testing should be performed to evaluate the function of the somatotropic axis in the transition period if indicated by a low IGF-I level.(11,24,25) ○ Patients with multiple (≥ 3) pituitary hormone deficiencies regardless of etiology, or GHD with an established causal genetic mutation, or GHD with a specific pituitary/hypothalamic structural defect (except ectopic posterior pituitary), should be diagnosed with persistent GHD.(11,13,24,27) GH treatment should be offered to individuals with persistent GHD in the transition period.(11,24,25,27) Clinical presentation, diagnosis, and treatment of GHD in adults, as described by the 2019 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology Guidelines for Management of Growth Hormone Deficiency in Adults and Patients Transitioning from Pediatric to Adult Care(24), and the 2011 Endocrine Society Clinical Practice Guidelines for Evaluation and Treatment of Adult Growth Hormone Deficiency(25) is stated as follows: • The diagnosis of adult GHD should be based on the combination of documented pituitary or hypothalamic disease, panhypopituitarism, and a subnormal serum IGF-1 concentration (lower than the gender- and age-specific lower limit of normal). GH levels decline with aging, whereas serum IGF-1 levels can be lowered by factors such as malnutrition and various comorbidities (e.g., diabetes, renal and/or hepatic disease). Stimulation (provocative) tests should only be performed based on the clinical context of each patient with a history suggestive of a reasonable clinical suspicion of GHD, and with the intent to initiate GH therapy if the diagnosis is confirmed.(24) • Diagnosis of adult GHD, without the need for stimulation/provocation tests, can be made in the following patient subtypes: ○ Patients with organic hypothalamic-pituitary disease (e.g., suprasellar mass with previous surgery and cranial irradiation) and presence of deficiencies in three or more pituitary axes (multiple pituitary hormone deficiency [MPHD]) together with subnormal serum IGF-1 levels (less than -2 SD)(24,25)

	○ Patients with genetic defects affecting the hypothalamic-pituitary axes(24,25) ○ Patients with hypothalamic-pituitary structural brain defects(24,25) • GH stimulation tests are needed to confirm diagnosis in the following patient subtypes: ○ In patients with less than or equal to 2 pituitary hormone deficiencies, subnormal IGF-1 levels alone are not sufficient to make a diagnosis of adult GHD; one GH stimulation test should be performed to confirm the diagnosis.(24) In transition patients who have completed longitudinal growth: ▪ After at least one month of discontinuation of therapy, patients with childhood-onset GHD and subnormal serum IGF-1 levels should be retested for GHD with provocation tests.(24,25) ▪ Patients with idiopathic childhood-onset GHD with organic hypothalamic-pituitary disease should have at least one stimulation test performed.(24) ▪ In the past, a level of serum GH less than or equal to 5 mcg/L on the insulin tolerance test was considered confirmation of GHD. However, experts increasingly report the disuse of this test and instead the glucagon-stimulation test (GST) and the macimorelin test should be utilized.(24)
Idiopathic Short Stature	Idiopathic short stature (ISS) refers to extreme short stature that does not have a diagnostic explanation. "Short stature" has been defined by the American Association of Clinical Endocrinologists as height more than two standard deviations (SD) below the mean for age and sex. A consensus conference of the International Societies of Pediatric Endocrinology and the Growth Hormone Research Society proposed that children with ISS whose heights are less than -2.0 SDS and who are more than 2.0 SDS below their mid-parental target height or had a predicted height less than -2.0 SDS warrant consideration for treatment.(34) If the initial growth response is good while on GH therapy, (at least 2.5 cm/year above the baseline height velocity after one year of treatment), treatment continues until linear growth decreases to less than 2.0 to 2.5 cm (approximately 1 inch)/year. This decrease usually occurs in late puberty, equating to a bone age of 13 to 13.5 years in girls or 15.5 to 16 years in boys.(16) GH therapy was approved in the United States for children with ISS with height at or less than -2.25 SDS (1.2 percentile) below the mean for age and sex,

	associated with growth rates unlikely to permit attainment of adult height in the normal range (this corresponds to an adult height less than 63 inches for males and less than 59 inches for females), in whom diagnostic work up excluded other causes for short stature that should be observed or treated by other means, and in pediatric patients whose epiphyses are not closed.(33,34) The evaluation should attempt to identify children with growth patterns consistent with constitutional delay of growth and puberty (CDGP) because they are likely to have catch-up growth without GH treatment. Clinical evidence supporting CDGP includes delayed bone age and/or history of delayed growth and puberty in a parent. Moreover, adolescent boys with CDGP and moderate short stature (taller than -2.5 SD) are more appropriately treated with testosterone replacement rather than GH. However, treatment of children with ISS with GH is controversial because of variable efficacy and high costs.(16,17)
Growth Failure in Chronic Kidney Disease	The goal of GH therapy in children with chronic kidney disease (CKD) is normalization of final height. GH therapy should be initiated when the following criteria have been met:(18,19) • All other amenable risk factors for growth impairment have been addressed • There is evidence of growth impairment, defined as HV for age less than -1.88 SD OR a HV for age less than 3rd percentile
Short Bowel Syndrome	Short bowel syndrome (SBS) is a malabsorption disorder caused by either the surgical removal of the small intestine or the loss of its absorptive function due to various diseases. Zorbtive is indicated for the treatment of SBS in adult patients receiving specialized nutritional support.(3) The beneficial effect of growth hormone (GH) as an aid to wean parenteral nutrition (PN) in short bowel syndrome (SBS) is controversial and a considerable amount of skepticism surrounds the long-term benefits. Four randomized placebo controlled studies have been performed using growth hormone to stimulate mucosal growth. In three studies there was no significant increase in absorption but one showed a small improvement in nutrient absorption.(31) A phase 3, prospective, randomized, placebo-controlled trial enrolled 41 PN-dependent SBS patients who were studied in an inpatient-like setting for 6 weeks, with 2 weeks of diet and medication optimization and PN stabilization followed by a 4-week treatment period. Patients were randomized into 3 groups: recombinant human growth hormone plus glutamine, growth hormone without glutamine, and placebo plus glutamine. A significant reduction was seen in PN requirements in both groups treated with growth hormone at the end of the 4-week treatment period. PN reduction remained significantly reduced

	during a 12-week observation period only in the group treated with growth hormone plus glutamine.(32)
Growth Failure in Children Born Small for Gestational Age	Low birth weight remains a major cause of morbidity and mortality in early infancy and childhood throughout the world. The International Societies of Pediatric Endocrinology and the Growth Hormone Research Society (GRS) 2007 Consensus Statement Guidelines on the Management of the Child Born Small for Gestational Age (SGA) recommend that SGA should be defined as a birth weight and/or birth length less than -2 SD below the population average. Approximately 90% of term SGA infants display sufficient catch-up growth to attain a height above -2 SD by the age of 2 years, whereas 10 percent remain short throughout childhood and adolescence.(20, 21) A child who reaches 24 months of age and fails to manifest catch-up growth (i.e., height remains less than 2 SD below the mean for age and gender) meets the indication to receive GH therapy.(23)
HIV Patients with Wasting or Cachexia	HIV/AIDS wasting syndrome is defined by the Centers for Disease Control and Prevention (CDC) as an involuntary weight loss of greater than 10% of body weight. The incidence of wasting has declined since the introduction of anti-retroviral therapy (ART), but many patients still meet the criteria for serious weight loss and wasting. Tissue wasting responds rapidly to ART, and the primary therapy for HIV wasting is ART.(28,30) The diagnosis of HIV wasting requires one of the following:(29) • 10% unintentional weight loss over 12 months • 7.5% unintentional weight loss over 6 months • Greater than 5% unintentional weight loss over 4 months • 5% body cell mass (BCM) loss within 6 months • Body mass index (BMI) less than 20 kg/m^2 • In men: BCM less than 35% of total body weight and BMI less than 27 kg/m^2 • In women: BCM less than 23% of total body weight and BMI less than 27 kg/m^2
Growth Hormone Statute	U.S. Code Title 21 Chapter 21 Chapter § 333(e) states: Prohibited distribution of human growth hormone (1) Except as provided in paragraph (2), whoever knowingly distributes, or possesses with intent to distribute, human growth hormone for any use in humans other than the treatment of a disease or other recognized medical condition, where such use has been authorized by the Secretary of Health and Human Services under section 355 of this title and pursuant to the order of a physician, is guilty of an offense punishable by not more than 5 years in prison, such fines as are authorized by title 18, or both. (2) Whoever commits any offense set forth in paragraph (1) and such offense involves an individual under 18 years of age is punishable by not more than 10

	years imprisonment, such fines as are authorized by title 18, or both. (3) Any conviction for a violation of paragraphs (1) and (2) of this subsection shall be considered a felony violation of the Controlled Substances Act [21 U.S.C. 801 et seq.] for the purposes of forfeiture under section 413 of such Act [21 U.S.C. 853]. (4) As used in this subsection the term ''human growth hormone'' means somatrem, somatropin, or an analogue of either of them. (5) The Drug Enforcement Administration is authorized to investigate offenses punishable by this subsection.(35)
Efficacy	Recombinant growth hormone products are considered clinically identical, with no evidence that one commercial product is different or more advantageous than another, apart from differences in how the GH product is stored, dosed, and administered by device. Therefore, one commercial GH product is not recommended over another because there are no prospective head-to-head trials comparing the clinical efficacy of one commercial product with another.(24)
Safety	Genotropin, Humatrope, Norditropin, Nutropin AQ, Omnitrope, Saizen, ZOMACTON have the following contraindications:(1,4-9) • Acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure • Children with Prader-Willi syndrome who are severely obese, have a history of upper airway obstruction or sleep apnea, or have severe respiratory impairment • Active malignancy • Active proliferative or severe non-proliferative diabetic retinopathy • Children with closed epiphyses • Hypersensitivity to somatropin or diluents/excipients Ngenla has the following contraindications:(38) • Acute critical illness • Hypersensitivity to somatrogon-ghla or excipients • Closed epiphyses • Active malignancy • Active proliferative or severe non-proliferative diabetic retinopathy • Prader-Willi syndrome who are severely obese or have severe respiratory impairment Serostim has the following contraindications:(2)

	• Acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or acute respiratory failure • Active malignancy • Active proliferative or severe non-proliferative diabetic retinopathy • Hypersensitivity to somatropin or diluent Skytrofa has the following contraindications:(36) • Acute critical illness • Hypersensitivity to somatropin or any excipients in Skytrofa • Children with close epiphyses • Active malignancy • Active proliferative or severe non-proliferative diabetic retinopathy • Children with Prader-Willi syndrome who are severely obese or have severe respiratory impairment due to risk of sudden death Sogroya has the following contraindications:(37) • Acute critical illness • Active malignancy • Hypersensitivity to somapacitan-beco or excipients • Active proliferative or severe non-proliferative diabetic retinopathy • Closed epiphyses in children used for longitudinal growth promotion • Children with Prader-Willi syndrome who are severely obese or have severe respiratory impairment due to risk of sudden death Zorbtive has the following contraindications:(3) • Acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or acute respiratory failure • Active neoplasia • Known hypersensitivity to growth hormone

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Number	Reference
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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td>Adults: Long and Short Acting Growth Hormone with Preferred Exception</td><td>
TARGET AGENT(S)
<table>
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Omnitrope (somatropin)</td><td>Humatrope (somatropin)
Norditropin FlexPro (somatropin)
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Sogroya (somapacitan-beco)</td></tr>
</table>
Adults – Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient is an adult (as defined by the prescriber) AND
2. The patient has ONE of the following diagnoses:
A. The patient has a diagnosis of AIDS wasting/cachexia AND ALL of the following:
1. The requested agent is a short-acting growth hormone (GH) AND
2. The patient is currently treated with antiretroviral therapy AND
3. The patient will continue antiretroviral therapy in combination with the requested agent AND
4. BOTH of the following:
A. ONE of the following:
1. The patient has had weight loss that meets ONE of the following:
A. Unintentional weight loss greater than 10% over 12 months OR
B. Unintentional weight loss greater than 7.5% over 6 months OR
2. The patient has a body cell mass (BCM) loss greater than or equal to 5% within 6 months OR
</td></tr>
</table>

Module	Clinical Criteria for Approval
	3. The patient's sex is male and has a BCM less than 35% of total body weight and body mass index (BMI) less than 27 kg/m^2 **OR** 4. The patient's sex is female and has a BCM less than 23% of total body weight and BMI less than 27 kg/m^2 **OR** 5. There is support that the patient's BCM less than 35% or less than 23% (based on sex) and BMI less than 27 kg/m^2 are medically appropriate for diagnosing AIDS wasting/cachexia for the patient's sex **OR** 6. The patient's BMI is less than 20 kg/m^2 **AND** B. All other causes of weight loss have been ruled out **OR** B. The patient has a diagnosis of short bowel syndrome (SBS) AND BOTH of the following: 1. The requested agent is a short-acting GH **AND** 2. The patient is receiving specialized nutritional support **OR** C. The patient has a diagnosis of growth hormone deficiency (GHD) or growth failure due to inadequate secretion of endogenous growth hormone AND ONE of the following: 1. The patient had a diagnosis of childhood-onset growth hormone deficiency AND has failed at least one growth hormone (GH) stimulation test as an adult **OR** 2. The patient has a low insulin-like growth factor-1 (IGF-1) level AND ONE of the following: A. Organic hypothalamic-pituitary disease **OR** B. Pituitary structural lesion or trauma **OR** C. The patient has panhypopituitarism or multiple (greater than or equal to 3) pituitary hormone deficiency **OR** 3. The patient has an established causal genetic mutation OR hypothalamic-pituitary structural defect other than ectopic posterior pituitary **OR** 4. The patient has failed at least two growth hormone (GH) stimulation tests as an adult **OR** 5. The patient has failed at least one GH stimulation test as an adult AND the patient has an organic pituitary disease **OR** D. The patient has another FDA labeled indication for the requested agent and route of administration **OR** E. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 3. The request is for a long-acting GH agent AND if the patient has an FDA labeled indication, then ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. The requested quantity (dose) is within FDA labeled dosing (or supported in compendia) for the requested indication **AND** 7. ONE of the following: A. The request is for a short-acting GH agent AND if the client has preferred agent(s), then ONE of the following: 1. BOTH of the following: A. The request is for a preferred agent **AND** B. The preferred agent is supported in FDA labeling for the requested indication **OR** 2. If the request is for a nonpreferred agent, then BOTH of the following: A. The nonpreferred agent is supported in FDA labeling for the requested indication **AND** B. ONE of the following: 1. The preferred agent(s) are NOT supported in FDA labeling for the requested indication **OR** 2. ONE of the following: A. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to a preferred agent that is not expected to occur with the requested nonpreferred agent (medical record required) **OR** B. There is support for the efficacy of the requested nonpreferred agent over ALL preferred agent(s) for the intended diagnosis (medical record required) **OR** B. The request is for a long-acting GH agent AND if the client has preferred agent(s), then ALL of the following: 1. The requested agent is FDA labeled for the requested indication **AND** 2. ONE of the following: A. The preferred short-acting GH agent(s) are NOT FDA labeled for the requested indication **OR** B. The patient has received at least 12 months of therapy with a preferred short-acting GH agent **OR**

<table>
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C. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to a preferred short-acting GH agent that is not expected to occur with the requested agent (medical record required) AND
3. ONE of the following:
A. The requested agent is a preferred agent OR
B. The preferred agent(s) are NOT FDA labeled for the requested indication OR
C. The patient has received at least 12 months of therapy with a preferred long-acting GH agent OR
D. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to a preferred long-acting GH agent that is not expected to occur with the requested nonpreferred agent (medical record required)

Compendia Allowed: AHFS or DrugDex 1 or 2a level of evidence

Length of Approval:

<table>
<tr><td>SBS</td><td>4 weeks</td></tr>
<tr><td>AIDS wasting/cachexia</td><td>12 weeks</td></tr>
<tr><td>All other indications</td><td>12 months</td></tr>
</table>

Adults – Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been approved for therapy with GH previously through the plan’s prior authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] AND
2. The patient is an adult (as defined by the prescriber) AND
3. ONE of the following:
A. The request is for a short-acting GH agent AND if the client has preferred agent(s), then ONE of the following:
</td></tr>
</table>

Module	Clinical Criteria for Approval
	1. BOTH of the following: A. The request is for a preferred agent **AND** B. The preferred agent is supported in FDA labeling for the requested indication **OR** 2. If the request is for a nonpreferred agent, then BOTH of the following: A. The nonpreferred agent is supported in FDA labeling for the requested indication **AND** B. ONE of the following: 1. The preferred agent(s) are NOT supported in FDA labeling for the requested indication **OR** 2. ONE of the following: A. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to a preferred agent that is not expected to occur with the requested nonpreferred agent (medical record required) **OR** B. There is support for the efficacy of the requested nonpreferred agent over ALL preferred agent(s) for the intended diagnosis (medical record required) **OR** B. The request is for a long-acting GH agent AND if the client has preferred agent(s), then ALL of the following: 1. The requested agent is FDA labeled for the requested indication **AND** 2. ONE of the following: A. The preferred short-acting agent(s) are NOT FDA labeled for the requested indication **OR** B. The patient has received at least 12 months of therapy with a preferred short-acting GH agent **OR** C. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to a preferred short-acting GH that is not expected to occur with the requested agent (medical record required) **AND** 3. ONE of the following: A. The requested agent is a preferred agent **OR** B. The preferred agent(s) are NOT FDA labeled for the requested indication C. The patient has received at least 12 months of therapy with a preferred long-acting GH agent **OR** D. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to a preferred long-acting GH agent that is not expected to occur with the requested nonpreferred agent (medical record required) **AND**

<table>
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<tr><td></td><td>
4. ONE of the following:
A. The patient has a diagnosis of short bowel syndrome (SBS) AND has had clinical benefit with the requested agent OR
B. The patient has a diagnosis of AIDS wasting/cachexia AND ALL of the following:
1. The patient is currently treated with antiretroviral therapy AND
2. The patient will continue antiretroviral therapy in combination with the requested agent AND
3. The patient has had clinical benefit with the requested agent (i.e., an increase in weight or weight stabilization) OR
C. The patient has growth hormone deficiency (GHD) or growth failure due to inadequate secretion of endogenous growth hormone AND BOTH of the following:
1. The patient's IGF-I level has been evaluated to confirm the appropriateness of the current dose AND
2. The patient has had clinical benefit with the requested agent (i.e., body composition, hip-to-waist ratio, cardiovascular health, bone mineral density, serum cholesterol, physical strength, or quality of life) OR
D. The patient has a diagnosis other than SBS, AIDS wasting/cachexia, GHD, or growth failure due to inadequate secretion of endogenous growth hormone AND has had clinical benefit with the requested agent AND
5. The patient does NOT have any FDA labeled contraindications to the requested agent AND
6. The prescriber is a specialist in the area of the patient’s diagnosis (e.g., endocrinologist) or has consulted with a specialist in the area of the patient’s diagnosis AND
7. The requested quantity (dose) is within FDA labeled dosing (or supported in compendia) for the requested indication AND
8. The patient is being monitored for adverse effects of GH therapy

Compendia Allowed: AHFS or DrugDex 1 or 2a level of evidence

Length of Approval:

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<tr><td>Children: Long-</td><td>TARGET AGENT(S)</td></tr>
</table>

<table>
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</table>
Children – Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following
A. The patient has a diagnosis of growth hormone deficiency (GHD) or growth failure due to inadequate secretion of endogenous growth hormone AND ONE of the following:
1. The patient has extreme short stature (e.g., height less than or equal to -3 SD), normal nutrition, significantly reduced IGF-1 and IGFBP-3 (e.g., less than -2 SD), and delayed bone age OR
2. BOTH of the following:
A. The patient has ONE of the following:
1. Height is greater than 2 SD below the mean for age and sex OR
2. Height greater than 1.5 SD below the midparental height OR
3. A decrease in height SD of greater than 0.5 over one year in children greater than 2 years of age OR
4. Height velocity (HV) greater than 2 SD below the mean over one year or greater than 1.5 SD sustained over two years OR
5. Height-for-age curve that has deviated downward across two major height percentile curves (e.g., from above the 25th percentile to below the 10th percentile) OR
6. BOTH of the following:
A. The patient’s age is 2-4 years AND
B. The patient has a HV less than 5.5 cm/year (less than 2.2 inches/year) OR
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</table>

Module	Clinical Criteria for Approval
	7. BOTH of the following: A. The patient's age is 4-6 years **AND** B. The patient has a HV less than 5 cm/year (less than 2 inches/year) **OR** 8. The patient's age is 6 years to puberty AND ONE of the following: A. The patient's sex is male and HV is less than 4 cm/year (less than 1.6 inches/year) **OR** B. The patient's sex is female and HV is less than 4.5 cm/year (less than 1.8 inches/year) **AND** B. ONE of the following: 1. The patient has failed at least 2 growth hormone (GH) stimulation tests (e.g., peak GH value of less than 10 mcg/L after stimulation, or otherwise considered abnormal as determined by testing lab) **OR** 2. The patient has failed at least 1 GH stimulation test (e.g., peak GH value of less than 10 mcg/L after stimulation, or otherwise considered abnormal as determined by testing lab) AND ONE of the following: A. Pathology of the central nervous system **OR** B. History of irradiation **OR** C. Other pituitary hormone defects (e.g., multiple pituitary hormone deficiency [MPHD]) **OR** D. A genetic defect **OR** 3. The patient has a pituitary abnormality and a known deficit of at least one other pituitary hormone **OR** B. The patient has another FDA labeled indication for the requested agent and route of administration **OR** C. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. The patient is a child (as defined by the prescriber) **AND** 3. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 4. If the client has preferred agent(s), then BOTH of the following: A. The requested agent is FDA labeled for the requested indication **AND** B. ONE of the following:

Module	Clinical Criteria for Approval
	1. The preferred short-acting GH agent(s) are NOT FDA labeled for the requested indication **OR** 2. The patient has received at least 12 months of therapy with a preferred short-acting GH agent **OR** 3. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to a preferred short-acting GH agent that is not expected to occur with the requested agent (medical record required) **AND** C. ONE of the following: 1. The requested agent is a preferred agent **OR** 2. The preferred agent(s) are NOT FDA labeled for the requested indication **OR** 3. The patient has received at least 12 months of therapy with a preferred long-acting GH agent **OR** 4. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to a preferred long-acting GH agent that is not expected to occur with the requested nonpreferred agent (medical record required) **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or has consulted with a specialist in the area of the patient's diagnosis **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 7. The requested quantity (dose) is within FDA labeled dosing (or supported in compendia) for the requested indication **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months **Children – Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for therapy with GH through the plan's prior authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient is a child (as defined by the prescriber) **AND** 3. If the client has preferred agent(s), then ALL of the following: A. The requested agent is FDA labeled for the requested indication **AND** B. ONE of the following: 1. The preferred short-acting GH agent(s) are NOT FDA labeled for the requested indication **OR**

Module	Clinical Criteria for Approval
	2. The patient has received at least 12 months of therapy with a preferred short-acting GH agent **OR** 3. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to a preferred short-acting GH agent that is not expected to occur with the requested agent (medical record required) **AND** C. ONE of the following: 1. The requested agent is a preferred GH agent **OR** 2. The preferred GH agent(s) are NOT FDA labeled for the requested indication **OR** 3. The patient has received at least 12 months of therapy with a preferred long-acting GH agent **OR** 4. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to a preferred long-acting GH agent that is not expected to occur with the requested nonpreferred agent (medical record required) **AND** 4. ONE of the following: A. The patient has a diagnosis of growth hormone deficiency (GHD) or growth failure due to inadequate secretion of endogenous growth hormone AND BOTH of the following: 1. The patient does NOT have closed epiphyses **AND** 2. The patient's height has increased greater than or equal to 2 cm over the previous year with GH therapy **OR** B. The patient has a diagnosis other than GHD or growth failure due to inadequate secretion of endogenous growth hormone AND has had clinical benefit with the requested agent **AND** 5. The patient is being monitored for adverse effects of GH therapy **AND** 6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or has consulted with a specialist in the area of the patient's diagnosis **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 8. The requested quantity (dose) is within FDA labeled dosing (or supported in compendia) for the requested indication **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months
Children: Short-Acting Growth Hormone	**TARGET AGENT(S)**

<table>
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Serostim (somatropin)
Zomacton (somatropin)
Zorbtive (somatropin)</td></tr>
</table>
Children – Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient is a child (as defined by the prescriber) AND
2. The patient has ONE of the following diagnoses:
A. ALL of the following:
1. The patient is a newborn (less than or equal to 4 months of age) with hypoglycemia AND
2. The patient has a serum growth hormone (GH) concentration less than or equal to 5 mcg/L AND
3. ONE of the following:
A. Congenital pituitary abnormality (e.g., ectopic posterior pituitary and pituitary hypoplasia with abnormal stalk) OR
B. Deficiency of at least one additional pituitary hormone OR
B. ALL of the following:
1. The patient is a newborn (less than or equal to 4 months of age) with hypoglycemia AND
2. The patient has a growth hormone (GH) concentration less than 20 mcg/L AND
3. The patient does not have a known metabolic disorder AND
4. The patient has a reduced IGFBP-3 level (e.g., less than -2 SD) OR
C. The patient has a diagnosis of Turner syndrome OR
D. The patient has a diagnosis of Noonan syndrome OR
E. The patient has a diagnosis of Prader-Willi syndrome OR
F. The patient has a diagnosis of SHOX gene deficiency OR
G. The patient has a diagnosis of short bowel syndrome (SBS) AND is receiving specialized nutritional support AND ONE of the following:
1. The patient’s age is within FDA labeling for the requested indication for the requested agent OR
</td></tr>
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Module	Clinical Criteria for Approval
	2. There is support for using the requested agent for the patient's age for the requested indication **OR** H. The patient has a diagnosis of panhypopituitarism or has deficiencies in at least 3 or more pituitary axes AND serum IGF-I levels below the age- and sex-appropriate reference range when off GH therapy **OR** I. The patient has a diagnosis of chronic renal insufficiency and BOTH of the following: 1. The patient's height velocity (HV) for age is less than -1.88 standard deviations (SD) OR HV for age is less than the third percentile **AND** 2. Other etiologies for growth impairment have been addressed **OR** J. The patient has a diagnosis of small for gestational age (SGA) and ALL of the following: 1. The patient is 2 years of age or older **AND** 2. The patient has a documented birth weight and/or birth length that is 2 or more standard deviations (SD) below the mean for gestational age **AND** 3. At 24 months of age, the patient failed to manifest catch-up growth evidenced by a height that remains 2 or more standard deviations (SD) below the mean for age and sex **OR** K. The patient has a diagnosis of idiopathic short stature (ISS) AND ALL of the following: 1. The patient has a height less than or equal to -2.25 SD below the corresponding mean height for age and sex **AND** 2. The patient has open epiphyses **AND** 3. ONE of the following: A. The patient has a predicted adult height that is below the normal range AND ONE of the following: 1. The patient's sex is male and predicted adult height is less than 63 inches **OR** 2. The patient's sex is female and predicted adult height is less than 59 inches **OR** B. The patient is greater than 2 SD below their mid-parental target height **AND** 4. BOTH of the following: A. The patient has been evaluated for constitutional delay of growth and puberty (CDGP) **AND** B. The patient does NOT have a diagnosis of CDGP **OR** L. The patient has a diagnosis of growth hormone deficiency (GHD) or growth failure due to inadequate secretion of endogenous growth hormone AND ONE of the following:

Module	Clinical Criteria for Approval
	1. The patient has extreme short stature (e.g., height less than or equal to -3 SD), normal nutrition, significantly reduced IGF-1 and IGFBP-3 (e.g., less than -2 SD), and delayed bone age **OR** 2. BOTH of the following: A. The patient has ONE of the following: 1. Height greater than 2 SD below the mean for age and sex **OR** 2. Height greater than 1.5 SD below the midparental height **OR** 3. A decrease in height SD of greater than 0.5 over one year in children greater than 2 years of age **OR** 4. Height velocity (HV) greater than 2 SD below the mean over one year or greater than 1.5 SD sustained over two years **OR** 5. Height-for-age curve that has deviated downward across two major height percentile curves (e.g., from above the 25th percentile to below the 10th percentile) **OR** 6. BOTH of the following: A. The patient's age is 2-4 years **AND** B. The patient has a HV less than 5.5 cm/year (less than 2.2 inches/year) **OR** 7. BOTH of the following: A. The patient's age is 4-6 years **AND** B. The patient has a HV less than 5 cm/year (less than 2 inches/year) **OR** 8. The patient's age is 6 years to puberty AND ONE of the following: A. The patient's sex is male and HV is less than 4 cm/year (less than 1.6 inches/year) **OR** B. The patient's sex is female and HV is less than 4.5 cm/year (less than 1.8 inches/year) **AND** B. ONE of the following: 1. The patient has failed at least 2 GH stimulation tests (e.g., peak GH value of less than 10 mcg/L after stimulation, or otherwise considered abnormal as determined by testing lab) **OR** 2. The patient has failed at least 1 GH stimulation test (e.g., peak GH value of less than 10 mcg/L after stimulation, or otherwise considered abnormal as determined by testing lab) AND ONE of the following: A. Pathology of the central nervous system **OR** B. History of irradiation **OR**

Module	Clinical Criteria for Approval
	C. Other pituitary hormone defects (e.g., multiple pituitary hormone deficiency [MPHD]) **OR** D. A genetic defect **OR** 3. The patient has a pituitary abnormality and a known deficit of at least one other pituitary hormone **AND** M. The patient has another FDA labeled indication for the requested agent and route of administration **OR** N. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The requested quantity (dose) is within FDA labeled dosing (or supported in compendia) for the requested indication **AND** 6. If the client has preferred agent(s), then ONE of the following: A. BOTH of the following: 1. The request is for a preferred agent **AND** 2. The preferred agent(s) are supported in FDA labeling for the requested indication **OR** B. The request is for a nonpreferred agent and BOTH of the following: 1. The nonpreferred agent is supported in FDA labeling for the requested indication **AND** 2. ONE of the following: A. The preferred agent(s) are NOT supported in FDA labeling for the requested indication **OR** B. ONE of the following: 1. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to a preferred agent that is not expected to occur with the requested nonpreferred agent (medical record required) **OR** 2. There is support for the efficacy of the requested nonpreferred agent over ALL preferred agent(s) for the intended diagnosis (medical record required) **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 4 weeks for SBS 12 months for all other indications

Module	Clinical Criteria for Approval
	Children – Renewal Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for therapy with GH through the plan's prior authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient is a child (as defined by the prescriber) **AND** 3. If the client has preferred agent(s), then ONE of the following: A. BOTH of the following: 1. The request is for a preferred agent **AND** 2. The preferred agent(s) are supported in FDA labeling for the requested indication **OR** B. The request is for a nonpreferred agent and BOTH of the following: 1. The nonpreferred agent is supported in FDA labeling for the requested indication **AND** 2. ONE of the following: A. The preferred agent(s) are NOT supported in FDA labeling for the requested indication **OR** B. ONE of the following: 1. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to a preferred agent that is not expected to occur with the requested nonpreferred agent (medical record required) **OR** 2. There is support for the efficacy of the requested nonpreferred agent over ALL preferred agent(s) for the intended diagnosis (medical record required) **AND** 4. ONE of the following: A. The patient has a diagnosis of short bowel syndrome (SBS) AND has had clinical benefit with the requested agent AND ONE of the following: 1. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** 2. There is support for the requested agent for the patient's age for the requested indication **OR** B. The patient has a diagnosis of ISS and BOTH of the following: 1. Height has increased greater than or equal to 2 cm over the previous year with GH therapy **AND**

Module	Clinical Criteria for Approval
	2. Bone age is less than 16 years in patients with a sex of male and 15 years in patients with a sex of female AND the patient has open epiphyses **OR** C. The patient has a diagnosis of growth hormone deficiency (GHD), growth failure due to inadequate secretion of endogenous growth hormone, short stature disorder (i.e., Noonan's syndrome, SHOX deficiency, Turner syndrome, small for gestational age), or renal function impairment with growth failure AND BOTH of the following: 1. The patient does NOT have closed epiphyses **AND** 2. The patient's height has increased greater than or equal to 2 cm over the previous year with GH therapy **OR** D. The patient has a diagnosis of Prader-Willi syndrome AND has had clinical benefit with the requested agent **OR** E. The patient has a diagnosis other than SBS, ISS, GHD, growth failure due to inadequate secretion of endogenous growth hormone, short stature disorder (i.e., Noonan's syndrome, SHOX deficiency, Turner syndrome, small for gestational age), or renal function impairment with growth failure, and Prader-Willi AND has had clinical benefit with the requested agent **AND** 5. The patient is being monitored for adverse effects of GH **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 7. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or has consulted with a specialist in the area of the patient's diagnosis **AND** 8. The requested quantity (dose) is within FDA labeled dosing (or supported in compendia) for the requested indication **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 4 weeks for SBS 12 months for all other indications

Hyperpolarization-Activated Cyclic Nucleotide-Gated (HCN) Channel Blocker (Corlanor)

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Corlanor® (ivabradine) Tablet* Oral Solution	Reduce the risk of hospitalization for worsening heart failure in adult patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction less than or equal to 35%, who are in sinus rhythm with resting heart rate greater than or equal to 70 beats per minute and either are on maximally tolerated doses of beta blockers or have a contraindication to beta-blocker use. Treatment of stable symptomatic heart failure due to dilated cardiomyopathy (DCM) in pediatric patients aged 6 months and older, who are in sinus rhythm with an elevated heart rate.	*generic available	1

CLINICAL RATIONALE

Heart Failure	Heart failure (HF) is a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood. The American Heart Association/American College of Cardiology (AHA/ACC) stages of heart failure emphasize the development and progression of disease, and advanced stages and progression are associated with reduced survival. The New York Heart Association (NYHA) classification is used to characterize symptoms and functional capacity of patients with symptomatic (NYHA Class II-IV) HF or advanced HF. In HF, NYHA functional class I includes patients with no limitations in physical activity resulting from their HF. NYHA class II includes patients who are comfortable at rest but have slight symptoms resulting from HF (dyspnea, fatigue, lightheadedness) with ordinary activity. NYHA class III includes patients who are comfortable at rest but have symptoms of HF with less than ordinary activity. NYHA class IV includes patients who are unable to carry out any physical activity without symptoms and have symptoms at rest. It is a subjective assessment by a clinician and can change over time. Although reproducibility and validity can be limited, the NYHA functional classification is an independent predictor of mortality, and it is widely

used in clinical practice to determine the eligibility of patients for treatment strategies. Because of the complexity of HF management and coordination of other health and social services required, HF care is ideally provided by multidisciplinary teams that include cardiologists, nurses, and pharmacists who specialize in HF as well as dieticians, mental health clinicians, social workers, primary care clinicians, and additional specialists.(3)

Left ventricular ejection fraction (LVEF) is considered important in the classification of patients with HF because of differing prognosis and response to treatments and because most clinical trials select patients based on ejection fraction (EF). The classification of HF by LVEF is as follows:(3)

Type of HF According to LVEF	LVEF Criteria
HFrEF (HF with reduced EF)	Less than or equal to 40%
HFimpEF (HF with improved EF)	Previous LVEF less than or equal to 40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	41-49% Evidence of spontaneous or provokable increased LV filling pressures
HFpEF (HF with preserved EF)	Greater than or equal to 50% Evidence of spontaneous or provokable increased LV filling pressures

The ACCF/AHA/HFSA (American College of Cardiology/Heart Failure Society of America) 2022 Guideline for the Management of Heart Failure states that ivabradine can be beneficial to reduce HF hospitalizations and cardiovascular death for patients with symptomatic (NYHA class II-III) stable chronic heart failure with reduced ejection fraction (HFrEF) (LVEF less than or equal to 35%) who are receiving guideline directed medical therapy (GDMT), including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest.(3)

Treatment recommendations for HFrEF (LVEF less than or equal to 40%) for

	stages C (Structural heart disease with current or previous symptoms of HF) and D (Marked HF symptoms that interfere with daily life and with recurrent hospitalizations despite attempts to optimize GDMT) progress from step 1 to step 6 and are based on several individual patient factors. Step 1 medications may be started simultaneously at initial (low) doses recommended for HFrEF. Alternatively, these medications may be started sequentially, with sequence guided by clinical or other factors, without need to achieve target dosing before initiating next medication while increasing to target as tolerated. Step 1 medications with a class of recommendation (COR) of 1 (strong) are given to diuretics as needed; sodium-glucose cotransporter 2 inhibitor (SGLT2i); beta blocker; mineralocorticoid receptor antagonist [MRA]; angiotensin receptor-neprilysin inhibitor [ARNi] in NYHA II-III, angiotensin-converting enzyme inhibitor [ACEi] or angiotensin receptor blocker [ARB] in NYHA II-IV).(3)
DCM	Dilated cardiomyopathy (DCM) is a clinical diagnosis characterized by left ventricular or biventricular dilation and impaired contraction that is not explained by abnormal loading conditions (for example, hypertension and valvular heart disease) or coronary artery disease. Mutations in several genes can cause DCM, including genes encoding structural components of the sarcomere and desmosome. Nongenetic forms of DCM can result from different etiologies, including inflammation of the myocardium due to an infection (mostly viral); exposure to drugs, toxins or allergens; and systemic endocrine or autoimmune diseases. The heterogeneous etiology and clinical presentation of DCM make a correct and timely diagnosis challenging. Echocardiography and other imaging techniques are required to assess ventricular dysfunction and adverse myocardial remodeling. Immunological and histological analyses of an endomyocardial biopsy sample are indicated when inflammation or infection is suspected. As DCM eventually leads to impaired contractility, standard approaches to prevent or treat heart failure are the first-line treatment for patients with DCM. Cardiac resynchronization therapy and implantable cardioverter–defibrillators may be required to prevent life-threatening arrhythmias.(4)
Efficacy	Ivabradine is a hyperpolarization-activated cyclic nucleotide-gated channel blocker that reduces the spontaneous pacemaker activity of the cardiac sinus node by selectively inhibiting the I current, resulting in heart rate reduction with no effect on ventricular repolarization and no effects on myocardial contractility.(1) It gained its indication for heart failure in adult patients via the systolic heart failure treatment with the If inhibitor ivabradine trial (SHIFT). This was a randomized, double-blind trial comparing Corlanor and placebo in 6558 patients

	with stable NYHA class II to IV heart failure, left ventricular ejection fraction less than or equal to 35%, and resting heart rate greater than or equal to 70 bpm. Patients had to have been clinically stable for at least 4 weeks on an optimized and stable clinical regimen, which included maximally tolerated doses of beta blockers and, in most cases, ACE inhibitors or ARBs, spironolactone, and diuretics, with fluid retention and symptoms of congestion minimized. Patients had to have been hospitalized for heart failure within 12 months prior to study entry. SHIFT demonstrated that Corlanor reduced the risk of the combined endpoint of hospitalization for worsening heart failure or cardiovascular death based on a time-to-event analysis.(1) Because Corlanor was effective in improving outcomes in patients with dilated cardiomyopathy (DCM) in SHIFT, the effect on heart rate was considered a reasonable basis to infer clinical benefits in pediatric patients with DCM. Thus, Corlanor was evaluated for its effect on heart rate in a multi-center, randomized, double-blind, placebo-controlled trial in children with symptomatic DCM. The study collected data from 116 patients 6 months to less than 18 years old with DCM in sinus rhythm, NYHA/Ross class II to IV heart failure, and left ventricular ejection fraction less than or equal to 45%. A statistically significant reduction in heart rate was observed with Corlanor compared to placebo at the end of the titration period (-23 plus or minus 11 bpm vs. -2 plus or minus 12 bpm respectively).(1)
Safety	Ivabradine is contraindicated in patients with:(1) • Acute decompensated heart failure • Clinically significant hypotension • Sick sinus syndrome, sinoatrial block, or 3rd degree AV block, unless a functioning demand pacemaker is present • Clinically significant bradycardia • Severe hepatic impairment • Pacemaker dependence (heart rate maintained exclusively by the pacemaker) • Concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors

REFERENCES

Number	Reference
1	Corlanor prescribing information. Amgen Inc. August 2021.
2	Reference no longer used
3	Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(18). doi:10.1161/cir.0000000000001063
4	Schultheiss HP, Fairweather D, Caforio ALP, et al. Dilated cardiomyopathy. Nature Reviews Disease Primers. 2019;5(1). doi:10.1038/s41572-019-0084-1

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of approval:** up to 12 months

Hemlibra (emicizumab-kxwh)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Hemlibra® (emicizumab-Kxwh) Injection for subcutaneous use	• Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with Hemophilia A (congenital factor VIII deficiency) with or without factor VIII inhibitors		1

CLINICAL RATIONALE

Hemophilia A	Hemophilia A, also called Factor VIII (FVIII) deficiency or classic hemophilia, is a genetic disorder caused by missing or defective Factor VIII (FVIII), a clotting protein. Although it is passed down from mothers to children, about 1/3 of cases found have no previous family history.(6) Treatment for hemophilia A is dependent on several factors and there is not a universal therapy that will work for all patients. Clinically the hallmark of bleeding in hemophilia is bleeding into the joints, muscles, and soft tissues. The severity and the risk of that bleeding can be correlated to the residual factor activity that can be measured in the blood. Patients with severe disease have less than 1% residual activity, and often have zero. These are the patients who are at risk for spontaneous as well as traumatic bleeding. Having over 5% residual amount makes bleeding into the joints very unusual (although not inconceivable), and most bleeding is triggered only by trauma. Residual activity of 1-5% appears for the most part to prevent spontaneous bleeding, but patients can still be at risk for joint bleeds with even relatively minor trauma.(8) The main goal of any therapy is to completely prevent bleeding. The current World Hemophilia Federation Guidelines for the Management of Hemophilia state:(3)

	• Both virus-inactivated plasma-derived and recombinant clotting factor concentrates (CFCs), as well as other hemostasis products when appropriate can be used for treatment of bleeding and prophylaxis in people with hemophilia • Prophylaxis is the standard of care for people with severe hemophilia, and for some people with moderate hemophilia or for those with a severe bleeding phenotype and/or a high risk of spontaneous life-threatening bleeding • Episodic CFC replacement should not be considered a long-term option for the management of hemophilia as it does not alter its natural history of spontaneous bleeding and related complications • Emerging therapies in development with alternative modes of delivery (e.g., subcutaneous injection) and novel targets may overcome the limitations of standard CFC replacement therapy (i.e., need for intravenous administration, short half-life, risk of inhibitor formation) • The development of gene therapies for hemophilia has advanced significantly, with product registration likely in the near future • Gene therapy should make it possible for some people with hemophilia to aspire to and attain much better health outcomes and quality of life than that attainable with currently available hemophilia therapies • Given the ongoing advances transforming the hemophilia treatment landscape, it is important to establish systems to constantly monitor developments in emerging and gene therapies for hemophilia and make them available as soon as possible following approval by regulatory authorities Approximately 1 in 5 people with hemophilia A will develop an antibody – called an inhibitor – to the clotting factor concentrate(s) used to treat or prevent their bleeding episodes. Developing an inhibitor is one of the most serious and costly medical complications of a bleeding disorder because it becomes more difficult to treat bleeds. Inhibitors most often appear in the first 50 exposure days of clotting factor concentrates.(7-8) The National Hemophilia Foundation classifies inhibitors as low responding and high responding in addition to low titer (less than 5 BU) and high titer (greater than or equal to 5 BU). In low responding inhibitors when the patient receives Factor VIII the inhibitor titer does not rise. These patients can be treated with higher doses of the CFC. If the inhibitor titer increases with CFC it is considered high- responding. For high responding inhibitors, the situation becomes much more complicated as even large doses of infused CFC are often rendered ineffectual by the sheer potency of the antibody response.(4)

	In the cases of high-responding inhibitors treatment is based on several components including the type of hemophilia and the nature of the bleed. During a life or limb-threatening bleeding episode, physicians can remove antibodies from the body using plasmapheresis. This is only a temporary solution however as within a few days the body will produce large amounts of new antibodies. For the person with a high responding inhibitor there are therapies that can effectively treat bleeds by circumventing the need to replace FVIII. These agents are commonly referred to as bypassing agents (BPAs) and include activated prothrombin complex concentrate (aPCC) and recombinant activated Factor VII concentrates. Hemlibra, a therapy that does not function by FVIII or Factor IX replacement, is a newer therapy that can be used for these patients.(4) If left unchecked, a persistent inhibitor will present a severe burden on patients and families, as the ongoing physical, emotional, and in many cases financial toll continue to intensify. Healthcare providers will often attempt to proactively stamp out an inhibitor through immune tolerance therapy (ITI). ITI is an approach to inhibitor eradication where the body's immune system begins to tolerate a therapy after daily doses of factor are administered over time. The majority of people who undergo ITI therapy will see an improvement within 12 months, but more difficult cases can take two years or longer.(9) There is a general consensus that failure of ITI is the inability to achieve successful tolerance within 2-3 years of initiation of an ITI regimen.(3) The World Hemophilia Federation similarly recommends that treatment of patients with inhibitors depends on several components including the titer of the inhibitor, records of clinical response to product, and site and nature of the bleed. Patients with a low responding inhibitor or those with a high responding inhibitor but low titer may be treated with factor product at a much higher dose. With an inhibitor level greater than or equal to 5 BU, the likelihood that specific factor replacement will be effective in overwhelming the inhibitor without ultra-high dose continuous infusion therapy and alternative agents, include bypassing agents such as recombinant factor VIIa and activated prothrombin complex concentrate (aPCC) is extremely low.(3) Emicizumab-kxwh is a recombinant, humanized, bispecific immunoglobulin G4 monoclonal antibody that substitutes for part of the cofactor function of activated factor VIII (FVIII) by bridging activated factor IX and Factor X. Emicizumab-kxwh is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults and children of all ages, newborn and older, with hemophilia A with and without Factor VIII inhibitors. There is

	significant reduction in annualized bleeding rates at all doses for all age groups, with or without inhibitors.(10) The Future of Immunotolerance Treatment (FIT) Expert group was established to determine and recommend the best management options for patients with hemophilia A and inhibitors. This group concluded that despite the considerable success of emicizumab in the management of inhibitor patients, eradicating inhibitors is important. The availability of emicizumab and other non-factor therapies in the future might impact greatly on how ITI is undertaken. Theoretically, concomitant use of emicizumab and FVIII might allow emicizumab to effectively prevent bleeding with lower dose ITI regimens. But as there are no published data regarding the concomitant use of emicizumab and FVIII for ITI, the FIT Expert group encourages the undertaking of properly conducted prospective studies to explore these approaches further.(13) The FIT Expert group stratified patients into the following four groups based on historical pre-ITI peak titer to predict the potential success with ITI treatment:(13) • Patients with titer less than 25 BU have a very good prognosis • Patients with titer 25 to less than 200 BU have a good prognosis • Patients with titer 200 to less than 1000 BU have a poor prognosis • Patients with titer greater than or equal to 1000 BU have a very poor prognosis Factor VIII and emicizumab-kxwh are fundamentally different proteins and are regulated differently. These differences should also be a part of the discussion on treatment.(10) Some of the differences of Factor VIII and emicizumab are:(10) • FVIIIa has multiple sites of interaction with FIXa, FX and the phospholipid surface, emicizumab has a single site • FVIII needs to be activated (thrombin mediated), emicizumab does not • FVIII binds to VWF, emicizumab does not • FVIII binds to phospholipid surface, emicizumab does not - greater FVIII binding limits movement of the FX-activating complex more than emicizumab • FVIIIa binds to surface on activated platelet, emicizumab most likely does not • FVIII has a much higher binding affinity than emicizumab • FVIIIa enhances FXa generation approximately 10 fold over emicizumab

	• Emicizumab can bind both activated and non-activated forms of FIX and FX Based on the clinical trial data, The Medical and Scientific Advisory Council (MASAC) recommends the following for emicizumab therapy:(10) • Any person with hemophilia A with an inhibitor who has spontaneous or traumatic bleeding episodes, whether treated with episodic or prophylactic BPA, should be considered for emicizumab prophylaxis as first-line of therapy • Patients on BPA prophylaxis with few bleeding episodes could consider switching from BPA prophylaxis to emicizumab prophylaxis based on overall cost-effectiveness and simpler administration • Infants should be considered for prophylaxis with emicizumab at any time after birth given the increased risk of intracranial hemorrhage prior to initiation of FVIII prophylaxis • Prescribers should discuss use of emicizumab prophylactic therapy in patients with hemophilia A without inhibitors. Discussion should include an assessment of the risks and benefits of emicizumab compared to their existing therapy • For patients without inhibitors, FVIII prophylaxis continuation during the week after initiation of emicizumab is a common and reasonable approach. However, given that steady-state levels of emicizumab are not achieved until after four weekly doses of 3 mg/kg, it may be reasonable to continue FVIII prophylaxis in select individuals based on their bleeding history and physical activity level, until they are ready to start maintenance dosing The World Federation of Hemophilia Guidelines state that CFCs are the treatment of choice for people with hemophilia as they are very safe and effective for treating and preventing bleeds. These guidelines do have further clarification on emicizumab use. The guidelines state that patients with hemophilia with inhibitors emicizumab should be used for regular prophylaxis and patients with hemophilia A with no inhibitors emicizumab can be used for regular prophylaxis.(3) In 2020 The Institute for Clinical and Economic Review (ICER) reviewed prophylaxis with FVIII products and prophylaxis with emicizumab for patients without inhibitors. Their conclusions were there is high certainty that there is at least a comparable benefit of emicizumab compared with Factor VIII prophylaxis at the doses now typically used in the US and a moderate certainty of a small or

	substantial net health benefit. ICER rated emicizumab as comparable or better (C++) compared with FVIII prophylaxis.(11) In 2018 ICER reviewed emicizumab treatment for hemophilia patients with inhibitors. The conclusions of this report are for people ages 12 and older with hemophilia A with inhibitors who will not be treated with ITI or for whom ITI has been unsuccessful, the have high certainty that emicizumab provides a substantial net health benefit ("A") compared with no prophylaxis. Given the results of the trials and the reduced burden with emicizumab, for children younger than 12 they have high certainty that emicizumab provides at least a small net health benefit ("B+") compared with no prophylaxis, and in adults and children they have high certainty that emicizumab provides at least a small net health benefit ("B+") compared with prophylaxis with BPAs.(5) There is limited data on the concomitant use of emicizumab prophylaxis during ITI. There is a case series of children with hemophilia A and inhibitors who underwent ITI in combination with emicizumab prophylaxis (Atlanta Protocol), and a larger clinical trial of this protocol is underway [MOTIVATE study (NCT04023019)].(10) The MOTIVATE study is a non-interventional, multicenter, observational, international study in male persons with hemophilia A who have developed inhibitors to any replacement coagulation Factor VIII (FVIII product). The purpose of the study is to capture different approaches in the management and to evaluate the efficacy and safety of immune tolerance induction, including the combination of FVIII and emicizumab. Patients will be assigned to 1 of 3 groups based on the treatments they receive and may switch to another group if their treatment is changed. The 3 groups are:(12) • ITI with Nuwiq, Octanate, or Wilate • ITI with Nuwiq, Octanate, or Wilate with emicizumab • Prophylaxis with emicizumab, aPCC, or recombinant FVIIIa without immune tolerance induction MASAC recommends that the pros and cons of the various approaches for patients with hemophilia A and inhibitors be part of a patient/clinician shared decision-making and ITI should remain an option for their care. MASAC also recommends that long term follow up and interventional trials that include the concomitant use of emicizumab with ITI should be encouraged. If ITI with concomitant emicizumab prophylaxis will be pursued MASAC provides the following recommendations:(10) • No more than 50-100 IU/kg per dose of CFCs be administered unless observation will occur within a clinical trial. This relates to the

	uncertainty as to any potential incremental risk of an elevated FVIII level, even transiently, in patients on emicizumab who may need treatment with a BPA for breakthrough bleeding during ITI • Data on the use of emicizumab prophylaxis with ITI should be conducted under a clinical trial or as part of existing databases collecting data on the natural history of emicizumab use within the US The World Federation of Hemophilia states that the availability of non-factor replacement therapies (e.g., emicizumab) that are effective in bleed prevention in patients with FVIII inhibitors has raised questions about whether such agents should be used before, during, after, or in place of ITI. This remains controversial, however, as there are insufficient data to resolve this question.(3)
Efficacy	Hemlibra (emicizumab-kxwh) is a humanized monoclonal modified immunoglobulin G4(IgG4) antibody with a bispecific antibody structure binding factor IXa and factor X. Emicizumab-kxwh is produced in genetically engineered mammalian (Chinese hamster ovary) cells.(1) Emicizumab bridges activated factor IX and factor X to restore the function of activated factor VIII.(1) The efficacy of Hemlibra for routine prophylaxis in patients with hemophilia A with FVIII inhibitors was evaluated in three clinical trials (adult and adolescent studies [HAVEN 1 and HAVEN 4] and a pediatric study [HAVEN 2]). The HAVEN 4 study included patients with and without inhibitors.(1) The HAVEN 1 study was a randomized phase 3, multicenter, open label trial that enrolled 109 adult and adolescent males (ages 12-75 and weighing greater than 40kg) with hemophilia A with FVIII inhibitors who previously received either episodic (on-demand) or prophylactic treatment with bypassing agents (rFVIIa and/or aPCC). The patients were randomized into 4 arms. Patients who received on-demand treatment with bypassing agents prior to the study entry were randomized 2:1 into arms A and B respectively. Arm A patients received prophylactic emicizumab. The active comparator arm B patients did not receive emicizumab prophylaxis. Arm C was an experimental arm and enrolled patients who received prophylactic bypassing agents prior to the study entry. Arm D was for patients that used on-demand or prophylactic therapy with bypassing agents but were unable to enroll in arms A through C. After at least 24 weeks on-study, the patients in Arm B had the opportunity to switch to emicizumab prophylaxis. All Arms continued to receive episodic bypassing agent therapy to treat breakthrough bleeds.(1)

The primary outcome measure of the HAVEN 1 study was the Annualized Bleed Rate (ABR) for Treated Bleeds (Arms A and B). Secondary outcome measures included ABR for various other bleeds including all Bleeds (treated or untreated), all joint bleeds, targeted joint bleeds and spontaneous bleeds. The ABR for treated bleeds was 2.9 in the emicizumab group vs 23.3 in the no prophylaxis group resulting in 87% reduction in ABR (95%CI p less than 0.0001). Secondary outcomes had similar results (80-92% reduction all with 95%CI and p less than 0.0001).(1)

The HAVEN 2 trial was a non-randomized, single-arm, multicenter, open-label, in pediatric males (ages less than 12, or ages 12-17 weighing less than 40 kg) with hemophilia A with FVIII inhibitors. The patients received emicizumab 3 mg/kg once weekly for the first 4 weeks followed by 1.5 mg/kg once weekly thereafter.(1)

The primary outcome measure was efficacy of weekly emicizumab prophylaxis, including the efficacy of weekly emicizumab compared with previous episodic (on-demand) and prophylactic bypassing agent, measured by ABR. An interim analysis of 23 patients was used for FDA approval in this population. The ABR for all treated bleeds was 0.2 (95% CI). The intra-patient analysis comparing emicizumab to previous therapy showed a 99% reduction in bleed rate (previous ABR while on bypassing agents was 17.2 and 0.2 after emicizumab prophylaxis) in the 13 patients in this group. Since the time from FDA approval to now, this study has expanded and currently has 3 arms. Arm A consists of patients using 1.5 mg/kg every week. Arm B consists of patients using 3 mg/kg every 2 weeks. Arm C consists of patients using 6mg/kg every 4 weeks.(1)

The HAVEN 4 study was a single-arm, multicenter, open-label, clinical trial in 41 adult and adolescent males with hemophilia A with or without Factor VIII inhibitors who previously received wither episodic (on demand) or prophylactic treatment with Factor VIII or with bypassing agents. Efficacy was evaluated in a subgroup of 36 patients with hemophilia A without Factor VIII inhibitors based on the bleed rate for bleeds requiring treatment with coagulation factors. The study also evaluated the efficacy of Hemlibra prophylaxis on all bleeds, treated spontaneous bleeds, treated joint bleeds, and treated target joint bleeds. The results are shown in the table below.(1)

Intra-Patient Comparison of Annualized Bleed Rate with Hemlibra Prophylaxis versus previous FVIII Prophylaxis

Endpoint	Hemlibra	Previous FVIII Prophylaxis (N=48)

	1.5 mg/kg once every week (N=48)	
Median Observation Period (weeks)	33.7	30.1
Treated Bleeds		
ABR (95% CI)[a]	1.5 (1, 2.3)	4.8 (3.2,7.1)
% reduction (95% CI) p-value	68% (48.6%,80.5%) less than 0.0001	
% patients with 0 bleeds (95% CI)	54.2 (39.2,68.6)	39.6 (25.8,54.7)
Median ABR (IQR)	0 (0,2.1)	1.8 (0,7.6)

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile
a - Based on negative binomial regression model

The efficacy of Hemlibra for routine prophylaxis in patients with hemophilia A without Factor VIII inhibitors was evaluated in two clinical trials (adult and adolescent studies [HAVEN 3 and HAVEN 4]). The HAVEN 4 trial included patients with and without inhibitors (see results above).(1)

The HAVEN 3 trial was a randomized, multicenter, open-label, clinical trial in 152 adult and adolescent males with hemophilia A without Factor VIII inhibitors, who previously received either episodic (on demand) or prophylactic treatment with Factor VIII. Efficacy was evaluated after a minimum of 24 weeks of follow-up based on the bleed rate for bleeds requiring treatment with coagulation factors. The results are shown in the table below.(1)

Annualized Bleed Rate with Hemlibra Prophylaxis vs No Prophylaxis in Patients greater than or equal to 12 years of Age without Factor VIII Inhibitors

Endpoint	**Hemlibra** **1.5 mg/kg once every week (N = 36)**	**Hemlibra** **3 mg/kg once every two weeks (N = 35)**	**No Prophylaxis** **(N = 18)**
Treated Bleeds			
ABR (95% CI)[a]	1.5 (0.9,2.5)	1.3 (0.8,2.3)	38.2 (22.9, 63.8)

% reduction (95% CI) p-value	96% (92.5%,98%) less than 0.0001	97% (93.4, 98.3%) less than 0.0001	-
% of patients with 0 bleeds (95% CI)	55.6 (38.1, 72.1)	60 (42.1, 76.1)	0 (0,18.5)
Median ABR (IQR)	0 (0,2.5)	0 (0,1.9)	40.4 (25.3,56.7)
All Bleeds			
ABR (95% CI)[a]	2.5 (1.6,3.9)	2.6 (1.6,4.3)	47.6 (28.5, 79.6)
%reduction (95%CI) p-value	95% (90.1%,97%) less than 0.0001	94% (89.7%,97%) less than 0.0001	-
% of patients with 0 bleeds (95%CI)	50 (32.9,67.1)	40 (23.9,57.9)	0 (0,18.5)
Median ABR (IQR)	0.6 (0,3.9)	1.6 (0,4)	46.9 (26.1,73.9)
Treated Spontaneous Bleeds			
ABR (95% CI)[a]	1.0 (0.5,1.9)	0.3 (0.1,0.8)	15.6 (7.6,31.9)
% reduction (95% CI) p-value	94% (84.9%,97.5%) less than 0.0001	98% (94.4%,99.4%) less than 0.0001	-
% patients with 0 bleeds (95% CI)	66.7 (49.0,81.4)	88.6 (73.3,96.8)	22.2 (6.4,47.6)
Median ABR (IQR)	0 (0,1.3)	0 (0,0)	10.8 (2.1,26)
Treated Joint Bleeds			
ABR (95% CI)[a]	0.6 (0.3,1.4)	0.7 (0.3,1.6)	13 (5.2,32.3)
% reduction (95%CI) p-value	95% (85.7%,98.4%) less than 0.0001	95% (85.3%,98.2%) less than 0.0001	-

<table>
<tr><td></td><td>
<table>
<tr><td>% patients with 0 bleeds (95% CI)</td><td>69.4 (51.9,83.7)</td><td>77.1 (59.9,89.6)</td><td>27.8 (9.7,53.5)</td></tr>
<tr><td>Median ABR (IQR)</td><td>0 (0,1.4)</td><td>0 (0,0)</td><td>12.8 (0,39.1)</td></tr>
</table>

ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile
a - Based on negative binomial regression model

The efficacy of Hemlibra prophylaxis in reducing the number of all bleeds, spontaneous bleeds, joint bleeds, and target joint bleeds. In patients of previous prophylactic factor VIII therapy Hemlibra efficacy was compared to prophylactic factor VIII therapy efficacy. The annualized bleed rate was 1.5 in the Hemlibra treated patients vs 4.8 in these patients previously treated with Factor VIII prophylaxis (95% CI) which was a 68% reduction (95% CI, p less than 0.0001).(1)</td></tr>
<tr><td>Safety</td><td>

Due to the increased coagulation potential with emicizumab, if the patient is using a bypassing agent as prophylactic use, it is recommended to discontinue prophylactic use of bypassing agents the day before starting emicizumab. On-demand use of bypassing agents can be continued with caution based on boxed warning.(1)
Hemlibra has no limitations of use but the prescribing information contains a boxed warning concerning thrombotic microangiopathy and thromboembolism when given with activated prothrombin complex concentrate (aPCC). If these agents must be used together, the patient should be monitored for the development of thrombotic microangiopathy and/or thromboembolism. If one of these events occurs, aPCC therapy should be discontinued and Hemlibra therapy should be interrupted and the event managed as clinically indicated. Consider the benefits and risks of resuming Hemlibra prophylaxis following complete resolution of the event on a case-by-case basis.(1)
Do not use different vials of different concentrations of Hemlibra when combining vials to administer prescribed dose. The 60 mg, 105 mg, and/or 150 mg vials are the same concentration (150 mg/mL) and may be combined for dosing. The 30 mg vials (30 mg/mL) should not be combined in a single injection with the 60 mg, 105 mg, and 150 mg vials.(1)
Hemlibra has no FDA labeled contraindications.(1)

</td></tr>
</table>

REFERENCES

Number	Reference
1	Hemlibra prescribing information. Genentech Inc. January 2024.
2	Reference no longer used.
3	Srivastave A, Santagostino E, Dougall A, et al. World Federation of Hemophilia Guidelines for the Management of Hemophilia. 3rd edition. August 2020.
4	National Hemophilia Foundation. Bleeding Disorders A-Z Overview Inhibitors Treatment for Inhibitors. Accessed at: https://www.hemophilia.org/bleeding-disorders-a-z/overview/inhibitors/treatment-for-inhibitors
5	Institute for Clinical and Economic Review. Emicizumab for Hemophilia A with Inhibitors: Effectiveness and Value. April 2018.
6	National Hemophilia Foundation. Bleeding Disorders A-Z/ Types/ Hemophilia A. Accessed at: https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-a.
7	CDC Centers for Disease Control and Prevention. Inhibitors and Hemophilia. Accessed at: https://www.cdc.gov/ncbddd/hemophilia/inhibitors.html.
8	National Hemophilia Foundation. One Size Does Not Fit All: Individualized Therapy. Dr Steven Pipe. February 2017. Accessed at: https://www.hemophilia.org/educational-programs/education/online-education/one-size-does-not-fit-all-individualized-therapy.
9	National Hemophilia Foundation. Bleeding Disorders A-Z/ Overview/ Inhibitors/ Immune Tolerance. Accessed at: https://www.hemophilia.org/bleeding-disorders-a-z/overview/inhibitors/immune-tolerance.
10	Medical and Scientific Advisory Council (MASAC) MASAC Document 268 – Recommendation on the Use and Management of Emicizumab-kxwh (Hemlibra®) for Hemophilia A with and without Inhibitors. April 2022.
11	Institute for Clinical and Economic Review. Valoctocogene Roxaparvovec and Emicizumab for Hemophilia A without Inhibitors: Effectiveness and Value. November 2020.

Number	Reference
12	Clinicaltrials.gov. NCT04023019. Treatment of Hemophilia A Patients With FVIII Inhibitors (MOTIVATE). Accessed at: https://clinicaltrials.gov/ct2/show/NCT04023019?term=NCT04023019&draw=2&rank=1.
13	Carcao M, Escuriola-Ettingshausen C, Santagostino E, et al. The changing face of immune tolerance induction in haemophilia A with the advent of emicizumab. Haemophilia Volume 25, Issue 4. April 2019.
14	Reference no longer used

ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
85105030202007	Hemlibra	emicizumab-kxwh subcutaneous soln	12 MG/0.4 ML	Determined by patient weight and dosing interval* *See Hemlibra weight based approvable quantities chart for guidance			
85105030202060	Hemlibra	emicizumab-kxwh subcutaneous soln	300 MG/2ML	Determined by patient weight and dosing interval* *See Hemlibra weight based approvable quantities chart for guidance			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
85105030202030	Hemlibra	Emicizumab-kxwh Subcutaneous Soln 105 MG/0.7ML (150 MG/ML)	105 MG/0.7 ML	Determined by patient weight and dosing interval* *See Hemlibra weight based approvable quantities chart for guidance			
85105030202040	Hemlibra	Emicizumab-kxwh Subcutaneous Soln 150 MG/ML	150 MG/ML	Determined by patient weight and dosing interval* *See Hemlibra weight based approvable quantities chart for guidance			
85105030202010	Hemlibra	Emicizumab-kxwh Subcutaneous Soln 30 MG/ML	30 MG/ML	Determined by patient weight and dosing interval* *See Hemlibra weight based approvable quantities chart for guidance			
85105030202020	Hemlibra	Emicizumab-kxwh Subcutaneous Soln 60 MG/0.4ML (150 MG/ML)	60 MG/0.4 ML	Determined by patient weight and dosing interval* *See Hemlibra weight based approvable quantities chart for guidance			

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
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Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Agents Eligible for Continuation of Therapy
Hemlibra (emicizumab-kxwh)

      1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR**
      2. The prescriber states the patient has been treated with the requested agent within the past 90 days (starting on samples is not approvable) AND is at risk if therapy is changed **OR**

   B. The patient has a diagnosis of hemophilia A with or without inhibitors **AND**
2. The requested agent will be used as prophylaxis to prevent or reduce the frequency of bleeding episodes **AND**
3. The prescriber is a specialist in the area of the patient's diagnosis [e.g., prescriber working in a hemophilia treatment center (HTC), hematologist with hemophilia experience] or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**
4. The patient will NOT be using the requested agent in combination with any of the following while on maintenance dosing with the requested agent:
   A. Prophylaxis with a Factor VIIa product (e.g., NovoSeven RT) **OR**
   B. Prophylaxis with a Factor VIII product (e.g., Advate, Adynovate, Eloctate, Nuwiq, Recombinate, Xyntha) **OR**
   C. Prophylaxis with a bypassing agent (e.g., Feiba, NovoSeven) **OR**
   D. Immune tolerance therapy (ITT) (immune tolerance induction [ITI]) **AND**
5. If the patient is receiving Feiba [activated prothrombin complex concentrate (aPCC)] for breakthrough bleeds, BOTH of the following:
   A. The patient will be monitored for thrombotic microangiopathy and thromboembolism **AND**
   B. The prescriber has counseled the patient on the maximum dosages of Feiba to be used (i.e., no more than 100 u/kg/24 hours) **AND**
6. The patient does NOT have any FDA labeled contraindications to the requested agent **AND**

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</table>

Module	Clinical Criteria for Approval
	7. The requested quantity (dose) is within the FDA labeled dosing based on the patient's weight and dosing interval **Length of Approval:** 1 month for induction therapy 12 months for maintenance therapy (or remainder of 12 months if requesting induction therapy and maintenance therapy) NOTE: If Quantity Limit applies, please see Quantity Limit criteria **Renewal Evaluation** **Target Agent(s**) will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process (Note: patients not previously approved for the requested agent will require initial evaluation review) **AND** 2. ONE of the following: A. The patient has had improvements or stabilization with the requested agent as indicated by the number of breakthrough bleeds as reported in the treatment log and/or chart notes (medical records including treatment log and/or chart notes required) **OR** B. There is support for the continued use of the requested agent (medical record required) **AND** 3. If the patient is receiving Feiba [activated prothrombin complex concentrate (aPCC)] for breakthrough bleeds, the patient will be monitored for thrombotic microangiopathy and thromboembolism **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis [e.g., prescriber working in a hemophilia treatment center (HTC), hematologist with hemophilia experience] or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient will NOT be using the requested agent in combination with any of the following: A. Prophylaxis with a Factor VIIa product (e.g., NovoSeven RT) **OR** B. Prophylaxis with a Factor VIII product (e.g., Advate, Adynovate, Eloctate, Nuwiq, Recombinate, Xyntha) **OR** C. Prophylaxis with a bypassing agent (e.g., Feiba, NovoSeven) OR D. Immune tolerance therapy (ITT) (immune tolerance induction [ITI]) **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 7. The requested quantity (dose) is within the FDA labeled dosing based on the patient's weight and dosing interval **Length of Approval:** 12 months

Module	Clinical Criteria for Approval
	NOTE: If Quantity Limit applies, please see Quantity Limit criteria

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Quantity Limit for Target Agent(s)** will be approved when ONE of the following is met: 1. The patient is requesting induction therapy only **OR** 2. The patient is requesting induction therapy and maintenance therapy and the requested quantity (dose) for maintenance therapy does not exceed the program quantity limit (see Hemlibra Weight-Based Approvable Quantities chart) **OR** 3. The patient is requesting maintenance therapy only and the requested quantity (dose) does not exceed the program quantity limit (see the Hemlibra Weight-Based Approvable Quantities chart) **Length of Approval:** up to 12 months **Renewal Evaluation** **Quantity Limit for the Target Agent(s)** will be approved when the requested quantity (dose) for maintenance therapy does not exceed the program quantity limit (see the Hemlibra Weight-Based Approvable Quantities chart) **Length of Approval:** up to 12 months **Hemlibra Weight-Based Approvable Quantities (maintenance dosing)**

Weight (kg)	Dosing Schedule	12 mg/0.4 mL vials	30 mg/1 mL vials	60 mg/0.4 mL vials	105 mg/0.7 mL vials	150 mg/1 mL vials	300 mg/2 mL vial
less than or	1.5 mg/kg	1.6 mL (4	0	0	0	0	0

Module	Clinical Criteria for Approval							
	equal to 5 kg	every week	vials)/28 days					
	less than or equal to 5 kg	3 mg/kg every 2 weeks	0	2 mL (2 vials)/28 days	0	0	0	0
	less than or equal to 5 kg	6 mg/kg every 4 weeks	0	1 mL (1 vial)/28 days	0	0	0	0
	greater than 5 and less than or equal to 10 kg	1.5 mg/kg every week	0	4 mL (4 vials)/28 days	0	0	0	0
	greater than 5 and less than or equal to 10 kg	3 mg/kg every 2 weeks	0	2 mL (2 vials)/28 days	0	0	0	0
	greater than 5 and less than or equal	6 mg/kg every 4 weeks	0	0	0.4 mL (1 vial)/28 days	0	0	0

Module	Clinical Criteria for Approval							
	to 10 kg							
	greater than 10 and less than or equal to 15 kg	1.5 mg/kg every week	0	4 mL (4 vials)/28 days	0	0	0	0
	greater than 10 and less than or equal to 15 kg	3 mg/kg every 2 weeks	0	0	0.8 mL (2 vials)/28 days	0	0	0
	greater than 10 and less than or equal to 15 kg	6 mg/kg every 4 weeks	0	1 mL (1 vial)/28 days	0.4 mL (1 vial)/28 days	0	0	0
	greater than 15 and less than or equal to 20 kg	1.5 mg/kg every week	0	4 mL (4 vials)/28 days	0	0	0	0

Module	Clinical Criteria for Approval							
	greater than 15 and less than or equal to 20 kg	3 mg/kg every 2 weeks	0	0	0.8 mL (2 vials)/28 days	0	0	0
	greater than 15 and less than or equal to 20 kg	6 mg/kg every 4 weeks	0	0	0.8 mL (2 vials)/28 days	0	0	0
	greater than 20 and less than or equal to 25 kg	1.5 mg/kg every week	0	0	1.6 mL (4 vials)/28 days	0	0	0
	greater than 20 and less than or equal to 25 kg	3 mg/kg every 2 weeks	0	2 mL (2 vials)/28 days	0.8 mL (2 vials)/28 days	0	0	0

Module	Clinical Criteria for Approval							
	greater than 20 and less than or equal to 25 kg	6 mg/kg every 4 weeks	0	0	0	0	1 mL (1 vial)/28 days	0
	greater than 25 and less than or equal to 30 kg	1.5 mg/kg once every week	0	0	1.6 mL (4 vials)/28 days	0	0	0
	greater than 25 and less than or equal to 30 kg	3 mg/kg every 2 weeks	0	2 mL (2 vials)/28 days	0.8 mL (2 vials)/28 days	0	0	0
	greater than 25 and less than or equal to 30 kg	6 mg/kg every 4 weeks	0	0	1.2 mL (3 vials)/28 days	0	0	0
	greater than 30 and	1.5 mg/kg once	0	0	1.6 mL (4 vials)/28 days	0	0	0

Module	Clinical Criteria for Approval							
	less than or equal to 35 kg	every week						
	greater than 30 and less than or equal to 35 kg	3mg/kg every 2 weeks	0	0	0	1.4 mL (2 vials)/28 days	0	0
	greater than 30 and less than or equal to 35 kg	6 mg/kg every 4 weeks	0	0	0	1.4 mL (2 vials)/28 days	0	0
	greater than 35 and less than or equal to 40 kg	1.5 mg/kg once every week	0	0	1.6 mL (4 vials)/28 days	0	0	0
	greater than 35 and less than or equal	3 mg/kg every 2 weeks	0	0	1.6 mL (4 vials)/28 days	0	0	0

Module	Clinical Criteria for Approval							
	to 40 kg							
	greater than 35 and less than or equal to 40 kg	6 mg/kg every 4 weeks	0	0	1.6 mL (4 vials)/28 days	0	0	0
	greater than 40 and less than or equal to 45 kg	1.5 mg/kg once every week	0	4 mL (4 vials)/28 days	1.6 mL (4 vials)/28 days	0	0	0
	greater than 40 and less than or equal to 45 kg	3 mg/kg every 2 weeks	0	2 mL (2 vials)/28 days	0	1.4 mL (2 vials)/28 days	0	0
	greater than 40 and less than or equal to 45 kg	6 mg/kg every 4 weeks	0	0	0.8 mL (2 vials)/28 days	0	1 mL (1 vial)/28 days	0

Module	Clinical Criteria for Approval							
	greater than 45 and less than or equal to 50 kg	1.5 mg/kg once every week	0	4 mL (4 vials)/28 days	1.6 mL (4 vials)/28 days	0	0	0
	greater than 45 and less than or equal to 50 kg	3 mg/kg every 2 weeks	0	0	0	0	2 mL (2 vials)/28 days	0
	greater than 45 and less than or equal to 50 kg	6 mg/kg every 4 weeks	0	0	0	0	0	2 mL (1 vial)/28 days
	greater than 50 and less than or equal to 55 kg	1.5 mg/kg once every week	0	4 mL (4 vials)/28 days	1.6 mL (4 vials)/28 days	0	0	0

Module	Clinical Criteria for Approval							
	greater than 50 and less than or equal to 55 kg	3 mg/kg every 2 weeks	0	0	0.8 mL (2 vials)/28 days	1.4 mL (2 vials)/28 days	0	0
	greater than 50 and less than or equal to 55 kg	6 mg/kg every 4 weeks	0	0	0.8 mL (2 vials)/28 days	1.4 mL (2 vials)/28 days	0	0
	greater than 55 and less than or equal to 60 kg	1.5 mg/kg once every week	0	4 mL (4 vials)/28 days	1.6 mL (4 vials)/28 days	0	0	0
	greater than 55 and less than or equal to 60 kg	3 mg/kg every 2 weeks	0	0	2.4 mL (6 vials)/28 days	0	0	0

Module	Clinical Criteria for Approval							
	greater than 55 and less than or equal to 60 kg	6 mg/kg every 4 weeks	0	0	0.4 mL (1 vial)/28 days	0	0	2 mL (1 vial/28 days)
	greater than 60 and less than or equal to 65 kg	1.5 mg/kg once every week	0	0	0	2.8 mL (4 vials)/28 days	0	0
	greater than 60 and less than or equal to 65 kg	3 mg/kg every 2 weeks	0	2 mL (2 vials)/28 days	0.8 mL (2 vials)/28 days	1.4 mL (2 vials)/28 days	0	0
	greater than 60 and less than or equal to 65 kg	6 mg/kg every 4 weeks	0	0	1.6 mL (4 vials)/28 days	0	1 mL (1 vial)/28 days	0
	greater than 65 and	1.5 mg/kg once	0	0	0	2.8 mL (4	0	0

Module	Clinical Criteria for Approval							
	less than or equal to 70 kg	every week				vials)/28 days		
	greater than 65 and less than or equal to 70 kg	3 mg/kg every 2 weeks	0	0	0	2.8 mL (4 vials)/28 days	0	0
	greater than 65 and less than or equal to 70 kg	6 mg/kg every 4 weeks	0	0	0.8 mL (2 vials)/28 days	0	0	2 mL (1 vial)/28 days
	greater than 70 and less than or equal to 75 kg	1.5 mg/kg once every week	0	0	3.2 mL (8 vials)/28 days	0	0	0
	greater than 70 and less than or equal	3 mg/kg every 2 weeks	0	0	1.6mL (4 vials)/28 days	1.4 mL (2 vials)/28 days	0	0

Module	Clinical Criteria for Approval							
	to 75 kg							
	greater than 70 and less than or equal to 75 kg	6 mg/kg every 4 weeks	0	0	0	0	3 mL (3 vials)/28 days	0
	greater than 75 and less than or equal to 80 kg	1.5 mg/kg once every week	0	0	3.2 mL (8 vials)/28 days	0	0	0
	greater than 75 and less than or equal to 80 kg	3 mg/kg every 2 weeks	0	0	3.2 mL (8 vials)/28 days	0	0	0
	greater than 75 and less than or equal to 80 kg	6 mg/kg every 4 weeks	0	0	0.4 mL (1 vial)/28 days	2.8 mL (4 vials)/28 days	0	0

Module	Clinical Criteria for Approval							
	greater than 80 and less than or equal to 85 kg	1.5 mg/kg once every week	0	4 mL (4 vials)/28 days	0	2.8 mL (4 vials)/28 days	0	0
	greater than 80 and less than or equal to 85 kg	3 mg/kg every 2 weeks	0	0	0	1.4 mL (2 vials)/28 days	2 mL (2 vials)/28 days	0
	greater than 80 and less than or equal to 85 kg	6 mg/kg every 4 weeks	0	0	0.4 mL (1 vial)/28 days	0	3 mL (3 vials)/28 days	0
	greater than 85 and less than or equal to 90 kg	1.5 mg/kg once every week	0	4 mL (4 vials)/28 days	0	2.8 mL (4 vials)/28 days	0	0

Module	Clinical Criteria for Approval							
	greater than 85 and less than or equal to 90 kg	3 mg/kg every 2 weeks	0	0	1.6 mL (4 vials)/28 days	0	2 mL (2 vials)/28 days	0
	greater than 85 and less than or equal to 90 kg	6 mg/kg every 4 weeks	0	0	0.8 mL (2 vials)/28 days	2.8 mL (4 vials)/28 days	0	0
	greater than 90 and less than or equal to 95 kg	1.5 mg/kg once every week	0	0	0	0	4 mL (4 vials)/28 days	0
	greater than 90 and less than or equal to 95 kg	3 mg/kg every 2 weeks	0	0	2.4 mL (6 vials)/28 days	1.4 mL (2 vials)/28 days	0	0

Module	Clinical Criteria for Approval							
	greater than 90 and less than or equal to 95 kg	6 mg/kg every 4 weeks	0	0	0	2.8 mL (4 vials)/28 days	1 mL (1 vial)/28 days	0
	greater than 95 and less than or equal to 100 kg	1.5 mg/kg once every week	0	0	0	0	4 mL (4 vials)/28 days	0
	greater than 95 and less than or equal to 100 kg	3 mg/kg every 2 weeks	0	0	0	0	0	4 mL (2 vials)/28 days
	greater than 95 and less than or equal to 100 kg	6 mg/kg every 4 weeks	0	0	0	0	0	4 mL (2 vials)/28 days

Module	Clinical Criteria for Approval							
	greater than 100 and less than or equal to105 kg	1.5 mg/kg once every week	0	0	1.6 mL (4 vials)/28 days	2.8 mL (4 vials)/28 days	0	0
	greater than 100 and less than or equal to 105 kg	3 mg/kg every 2 weeks	0	0	0	4.2 mL (6 vials)/28 days	0	0
	greater than 100 and less than or equal to 105 kg	6 mg/kg every 4 weeks	0	0	0	4.2 mL (6 vials)/28 days	0	0
	greater than 105 and less than or equal	1.5 mg/kg once every week	0	0	1.6 mL (4 vials)/28 days	2.8 mL (4 vials)/28 days	0	0

Module	Clinical Criteria for Approval							
	to 110 kg							
	greater than 105 and less than or equal to 110 kg	3 mg/kg every 2 weeks	0	0	1.6 mL (4 vials)/28 days	2.8 mL (4 vials)/28 days	0	0
	greater than 105 and less than or equal to 110 kg	6 mg/kg every 4 weeks	0	0	0.4 mL (1 vial)/28 days	0	0	4 mL (2 vials/28 days)
	greater than 110 and less than or equal to 115 kg	1.5 mg/kg once every week	0	0	4.8 mL (12 vials)/28 days	0	0	0
	greater than 110 and less than or	3 mg/kg every 2 weeks	0	0	3.2 mL (8 vials)/28 days	1.4 mL (2 vials)/28 days	0	0

Module	Clinical Criteria for Approval							
	equal to 115 kg							
	greater than 110 and less than or equal to 115 kg	6 mg/kg every 4 weeks	0	0	0.4 mL (1 vial)/28 days	4.2 mL (6 vials)/28 days	0	0
	greater than 115 and less than or equal to 120 kg	1.5 mg/kg once every week	0	0	4.8 mL (12 vials)/28 days	0	0	0
	greater than 115 and ≤less than or equal to120 kg	3 mg/kg every 2 weeks	0	0	0.8 mL (2 vials)/28 days	0	0	4 mL (2 vials)/28 days
	greater than 115 and less	6 mg/kg every 4 weeks	0	0	0.8 mL (2 vials)/28 days	0	0	4 mL (2 vials)/28 days

Module	Clinical Criteria for Approval							
	than or equal to 120 kg							
	greater than 120 and less than or equal to 125 kg	1.5 mg/kg once every week	0	4 mL (4 vials)/28 days	1.6 mL (4 vials)/28 days	2.8 mL (4 vials)/28 days	0	0
	greater than 120 and less than or equal to 125 kg	3 mg/kg every 2 weeks	0	0	0.8 mL (2 vials)/28 days	4.2 mL (6 vials)/28 days	0	0
	greater than 120 and less than or equal to 125 kg	6 mg/kg every 4 weeks	0	0	0	0	5 mL (5 vials)/28 days	0
	greater than 125 and	1.5 mg/kg once	0	4 mL (4 vials)/28 days	1.6 mL (4 vials)/28 days	2.8 mL (4	0	0

Module	Clinical Criteria for Approval							
	less than or equal to130 kg	every week				vials)/28 days		
	greater than 125 and less than or equal to 130 kg	3 mg/kg every 2 weeks	0	0	3.2 mL (8 vials)/28 days	0	2 mL (2 vials)/28 days	0
	greater than 125 and less than or equal to 130 kg	6 mg/kg every 4 weeks	0	0	1.2 mL (3 vials)/28 days	0	0	4 mL (2 vials)/28 days
	greater than 130 and less than or equal to 135 kg	1.5 mg/kg once every week	0	0	0	5.6 mL (8 vials)/28 days	0	0

Module	Clinical Criteria for Approval							
	greater than 130 and less than or equal to 135 kg	3 mg/kg every 2 weeks	0	0	0	1.4 mL (2 vials)/28 days	0	4 mL (2 vials)/28 days
	greater than 130 and less than or equal to 135 kg	6 mg/kg every 4 weeks	0	0	0.4 mL (1 vial)/28 days	0	5 mL (5 vials)/28 days	0
	greater than 135 and less than or equal to 140 kg	1.5 mg/kg once every week	0	0	0	5.6 mL (8 vials)/28 days	0	0
	greater than 135 and less than or equal	3 mg/kg every 2 weeks	0	0	1.6 mL (4 vials)/28 days	0	0	4 mL (2 vials)/28 days

Module	Clinical Criteria for Approval							
	to 140 kg							
	greater than 135 and less than or equal to 140 kg	6 mg/kg every 4 weeks	0	0	0	5.6 mL (8 vials)/28 days	0	0
	greater than 140 and less than or equal to 145 kg	1.5 mg/kg once every week	0	0	3.2 mL (8 vials)/28 days	2.8 mL (4 vials)/28 days	0	0
	greater than 140 and less than or equal to 145 kg	3 mg/kg every 2 weeks	0	0	1.6 mL (4 vials)/28 days	4.2 mL (6 vials)/28 days	0	0
	greater than 140 and less than or	6 mg/kg every 4 weeks	0	0	0.8 mL (2 vials)/28 days	0	5 mL (5 vials)/28 days	0

Module	Clinical Criteria for Approval							
	equal to 145 kg							
	greater than 145 and less than or equal to 150 kg	1.5 mg/kg once every week	0	0	3.2 mL (8 vials)/28 days	2.8 mL (4 vials)/28 days	0	0
	greater than 145 and less than or equal to 150 kg	3 mg/kg every 2 weeks	0	0	0	0	6 mL (6 vials)/28 days	0
	greater than 145 and less than or equal to 150 kg	6 mg/kg every 4 weeks	0	0	0	0	0	6 mL (3 vials)/28 days
	greater than 150 and less	1.5 mg/kg once	0	4 mL (4 vials)/28 days	0	5.6 mL (8 vials)/28 days	0	0

Module	Clinical Criteria for Approval							
	than or equal to 155 kg	every week						
	greater than 150 and less than or equal to 155 kg	3 mg/kg every 2 weeks	0	0	0.8 mL (2 vials)/28 days	1.4 mL (2 vials)/28 days	0	4 mL (2 vials)/28 days
	greater than 150 and less than or equal to 155 kg	6 mg/kg every 4 weeks	0	1 mL (1 vial)/28 days	0	0	0	6 mL (3 vials)/28 days
	greater than 155 and less than or equal to 160 kg	1.5 mg/kg once every week	0	4 mL (4 vials)/28 days	0	5.6 mL (8 vials)/28 days	0	0
	greater than 155 and	3 mg/kg every 2 weeks	0	2 mL (2 vials)/28 days	0	0	6 mL (6 vials)/28 days	0

Module	Clinical Criteria for Approval							
	less than or equal to 160 kg							
	greater than 155 and less than or equal to 160 kg	6 mg/kg every 4 weeks	0	0	0.4 mL (1 vial)/28 days	0	0	6 mL (3 vials)/28 days
	greater than 160 and less than or equal to 165 kg	1.5 mg/kg once every week	0	0	0	2.8 mL (4 vials)/28 days	4 mL (4 vials)/28 days	0
	greater than 160 and less than or equal to 165 kg	3 mg/kg every 2 weeks	0	0	2.4 mL (6 vials)/28 days	4.2 mL (6 vials)/28 days	0	0

Module	Clinical Criteria for Approval							
	greater than 160 and less than or equal to 165 kg	6 mg/kg every 4 weeks	0	1 mL (1 vial)/28 days	0	1.4 mL (2 vials)/28 days	5 mL (5 vials)/28 days	0
	greater than 165 and less than or equal to 170 kg	1.5 mg/kg once every week	0	0	0	2.8 mL (4 vials)/28 days	4 mL (4 vials)/28 days	0
	greater than 165 and less than or equal to 170 kg	3 mg/kg every 2 weeks	0	0	0.8 mL (2 vials)/28 days	0	6 mL (6 vials)/28 days	0
	greater than 165 and less than or equal	6 mg/kg every 4 weeks	0	0	0.4 mL (1 vial)/28 days	1.4 mL (2 vials)/28 days	5 mL (5 vials)/28 days	0

Module	Clinical Criteria for Approval							
	to 170 kg							
	greater than 170 and less than or equal to 175 kg	1.5 mg/kg once every week	0	0	2.4 mL (4 vials)/28 days	5.6 mL (8 vials)/28 days	0	0
	greater than 170 and less than or equal to 175 kg	3 mg/kg every 2 weeks	0	0	0.8 mL (2 vials)/28 days	4.2 mL (6 vials)/28 days	2 mL (2 vials)/28 days	0
	greater than 170 and less than or equal to 175 kg	6 mg/kg every 4 weeks	0	0	0	0	7 mL (7 vials)/28 days	0
	greater than 175 and less than or	1.5 mg/kg once every week	0	0	2.4 mL (4 vials)/28 days	5.6 mL (8 vials)/28 days	0	0

Module	Clinical Criteria for Approval							
	equal to 180 kg							
	greater than 175 and less than or equal to 180 kg	3 mg/kg every 2 weeks	0	2 mL (2 vials)/28 days	0	2.8 mL (4 vials)/28 days	0	4 mL (2 vials)/28 days
	greater than 175 and less than or equal to 180 kg	6 mg/kg every 4 weeks	0	1 mL (1 vial)/28 days	0	0	7 mL (7 vials)/28 days	0
	greater than 180 and less than or equal to 185 kg	1.5 mg/kg once every week	0	4 mL (4 vials)/28 days	0	2.8mL (4 vials)/28 days	4 mL (4 vials)/28 days	0
	greater than 180 and less	3 mg/kg every 2 weeks	0	0	0	1.4 mL (2 vials)/28 days	6 mL (6 vials)/28 days	0

Module	Clinical Criteria for Approval							
	than or equal to 185 kg							
	greater than 180 and less than or equal to 185 kg	6 mg/kg every 4 weeks	0	0	0.4 mL (1 vial)/28 days	0	7 mL (7 vials)/28 days	0
	greater than 185 and less than or equal to 190 kg	1.5 mg/kg once every week	0	4 mL (4 vials)/28 days	0	2.8mL (4 vials)/28 days	4 mL (4 vials)/28 days	0
	greater than 185 and less than or equal to 190 kg	3 mg/kg every 2 weeks	0	0	0.8 mL (2 vials)/28 days	2.8 mL (4 vials)/28 days	0	4 mL (2 vials)/28 days
	greater than 185 and	6 mg/kg every 4 weeks	0	1 mL (1 vial)/28 days	0	1.4 mL (2	0	6 mL (3 vials)/28 days

Module	Clinical Criteria for Approval							
	less than or equal to 190 kg					vials)/28 days		
	greater than 190 and less than or equal to 195 kg	1.5 mg/kg once every week	0	0	0	0	0	8 mL (4 vials)/28 days
	greater than 190 and less than or equal to 195 kg	3 mg/kg every 2 weeks	0	2 mL (2 vials)/28 days	0	1.4 mL (2 vials)/28 days	6 mL (6 vials)/28 days	0
	greater than 190 and less than or equal to 195 kg	6 mg/kg every 4 weeks	0	0	0.4 mL (1 vial)/28 days	1.4 mL (2 vials)/28 days	0	6 mL (3 vials)/28 days

Module	Clinical Criteria for Approval							
	greater than 195 and less than or equal to 200 kg	1.5 mg/kg once every week	0	0	0	0	0	8 mL (4 vials)/28 days
	greater than 195 and less than or equal to 200 kg	3 mg/kg every 2 weeks	0	0	0	0	0	8 mL (4 vials)/28 days
	greater than 195 and less than or equal to 200 kg	6 mg/kg every 4 weeks	0	0	0	0	0	8 mL (4 vials)/28 days
	greater than 200 kg	Approve quantity requested if appropriate for patient weight and dosing interval						
	The 12 mg and 30 mg vials are the same concentration (30 mg/mL) and may be combined for dosing							

Module	Clinical Criteria for Approval
	The 60 mg, 105 mg, 150 mg, and/or 300 mg vials are the same concentration (150 mg/mL) and may be combined for dosing
	The 12 mg vials and 30 mg vials (30mg/mL) should NOT be combined in the same injection with the 60 mg, 105 mg, 150 mg, or 300 mg vials and should be given as a separate injection

Hemophilia Factor IX

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
AlphaNine SD® (Coagulation Factor IX [Human]) Powder for reconstitution for intravenous use	• The prevention and control of bleeding in patients with Factor IX deficiency due to hemophilia B. AlphaNine SD contains low, non-therapeutic levels of Factors II, VII, and X, and, therefore, is *not* indicated for the treatment of Factor II, VII or X deficiencies. This product is also *not* indicated for the reversal of coumarin anticoagulant-induced hemorrhage, nor in the treatment of hemophilia A patients with inhibitors to Factor VIII.	Human Plasma-derived Coagulation Factor IX Concentrates	1

Alprolix®
 	
(Coagulation Factor IX [recombinant], Fc Fusion protein)
 	
Powder for solution for intravenous use
	• Adults and children with hemophilia B for:
	  ○ On-demand treatment and control of bleeding episodes
	  ○ Perioperative management of bleeding
	  ○ Routine prophylaxis to reduce the frequency of bleeding episodes
	
	Limitations of Use:
	
	Alprolix is not indicated for induction of immune tolerance in patients with hemophilia B
		Recombinant Factor IX Concentrates	2

BeneFIX®
 	
(Coagulation Factor IX [recombinant])
 	
Powder for reconstitution for intravenous use
	• Adult and children with hemophilia B (congenital factor IX deficiency or Christmas disease) for:
	  ○ On-demand treatment and control of bleeding episodes
	  ○ Peri-operative management of bleeding
		Recombinant Factor IX Concentrates	3

Agent(s)	FDA Indication(s)	Notes	Ref#
	○ Routine prophylaxis to reduce the frequency of bleeding episodes Limitations of Use: BeneFIX is not indicated for induction of immune tolerance in patients with hemophilia B		
Idelvion® (Coagulation Factor IX [recombinant]) Lyophilized powder for solution for intravenous use	• Children and adults with Hemophilia B (congenital Factor IX deficiency) for: ○ On-demand treatment and control of bleeding episodes ○ Perioperative management of bleeding ○ Routine prophylaxis to reduce the frequency of bleeding episodes Limitations of Use: Idelvion is not indicated for immune tolerance induction in patients with Hemophilia B.	Recombinant Factor IX Concentrates	4
Ixinity® (Coagulation Factor IX [recombinant]) Lyophilized powder for solution for intravenous use	• Adults and children greater than or equal to 12 years of age with hemophilia B for: ○ On-demand treatment and control of bleeding episodes ○ Perioperative management ○ Routine prophylaxis to reduce the frequency of bleeding episodes Limitations of Use: Ixinity is not indicated for induction of immune tolerance in patients with hemophilia B.	Recombinant Factor IX Concentrates	5
Profilnine® SD (Factor IX complex)	• The prevention and control of bleeding in patients with factor IX deficiency (hemophilia B)	Human Plasma-derived Coagulation Factor IX Concentrates	7

Agent(s)	FDA Indication(s)	Notes	Ref#
Lyophilized concentrate for reconstitution for intravenous use	Profilnine SD contains non-therapeutic levels of factor VII and is not indicated for use in the treatment of VII deficiency		

Rebinyn®
 	
(Coagulation Factor IX [recombinant], GlycoPEGylated)
 	
Powder for solution for intravenous use
	• Adults and children with hemophilia B (congenital Factor IX deficiency) for:
	  ○ On-demand treatment and control of bleeding episodes
	  ○ Perioperative management of bleeding
	  ○ Routine prophylaxis to reduce the frequency of bleeding episodes
	
	Limitations of Use:
	
	Rebinyn is not indicated for immune tolerance induction in patients with hemophilia B
		Recombinant Factor IX Concentrates	8

Rixubis®
 	
(Coagulation Factor IX [recombinant])
 	
Lyophilized powder for solution for intravenous use
	• Adults and children with hemophilia B for:
	  ○ On-demand treatment and control of bleeding episodes
	  ○ Perioperative management of bleeding
	  ○ Routine prophylaxis to reduce the frequency of bleeding episodes
	
	Rixubis is not indicated for induction of immune tolerance in patients with Hemophilia B
		Recombinant Factor IX Concentrates	9

CLINICAL RATIONALE

Hemophilia B	Hemophilia B, also called Factor IX (FIX) deficiency or Christmas disease, is a genetic disorder caused by missing or defective Factor IX, a clotting protein. Although it is passed down from parents to children, about 1/3 of cases are caused by a spontaneous mutation.(10) The main goal of any therapy is to completely prevent bleeding. The current World Hemophilia Federation Guidelines for the Management of Hemophilia state:(14)

	• Both virus-inactivated plasma-derived and recombinant clotting factor concentrates (CFCs), as well as other hemostasis products when appropriate can be used for treatment of bleeding and prophylaxis in people with hemophilia • Prophylaxis is the standard of care for people with severe hemophilia, and for some people with moderate hemophilia or for those with a severe bleeding phenotype and/or a high risk of spontaneous life-threatening bleeding • Episodic CFC replacement should not be considered a long-term option for the management of hemophilia as it does not alter its natural history of spontaneous bleeding and related complications • Emerging therapies in development with alternative modes of delivery (e.g., subcutaneous injection) and novel targets may overcome the limitations of standard CFC replacement therapy (i.e., need for intravenous administration, short half-life, risk of inhibitor formation) • The development of gene therapies for hemophilia has advanced significantly, with product registration likely in the near future • Gene therapy should make it possible or some people with hemophilia to aspire to and attain much better health outcomes and quality of life than that attainable with currently available hemophilia therapies • Given the ongoing advances transforming the hemophilia treatment landscape, it is important to establish systems to constantly monitor developments in emerging and gene therapies for hemophilia and make them available as soon as possible following approval by regulatory authorities The MASAC suggests the number of doses required for provision of home therapy varies greatly and is dependent upon the type of hemophilia (FVIII, FIX), the level of severity (severe, moderate, mild), the presence of an inhibitor, the prescribed regimen (on-demand, prophylaxis, immune tolerance), the number of bleeding episodes experienced regardless of the prescribed regimen, individual pharmacokinetics, the products utilized, and the level of physical activity. For patients on prophylaxis, a minimum of one major dose and two minor doses should be available in addition to the prophylactic doses utilized monthly. For patients with severe or moderate hemophilia treated on-demand, the number of doses required to be available at home may be based upon historical bleeding patterns, with at least one major and two minor doses added to assure a level of safety.(11) A major dose is defined as a correction of clotting factor that achieves a level of 60-100+% clotting factor activity that is utilized to treat a bleeding episode that is expected to require a higher hemostatic level such as when bleeds occur in a

	target joint, or joint/area with a risk of significant sequelae (e.g., hip, head, GI bleed, etc.). A minor dose is defined as a correction of clotting factor that achieves a level of 30-60% clotting factor activity that is utilized to treat a bleeding episode that is treated early, in a non-critical area and treatable with a lower hemostatic level (e.g., early non-major joints, small muscle bleeds, and skin/soft tissue, etc.).(11) The Medical and Scientific Advisory Council (MASAC) and National Hemophilia Foundation (NHF) guidelines on treatment of hemophilia B recommend Recombinant FIX (rFIX) products over plasma-derived products as the treatment of choice.(13) In view of the demonstrated benefits of prophylaxis (regular/scheduled administration of clotting factor concentrate to prevent bleeding) begun at a young age in persons with hemophilia A or B, MASAC recommends that prophylaxis be considered standard of care therapy for individuals with severe hemophilia B (factor IX less than 1%) including those with inhibitors. Prophylactic therapy may also be considered for persons with moderate and mild hemophilia with a severe phenotype. Prophylactic therapy should be instituted early (prior to the onset of frequent bleeding).(12)

Safety	• **AlphaNine SD** has no known FDA labeled contraindications(1)
	• **Alprolix** is contraindicated in:(2)
	  ○ Individuals who have a known history of hypersensitivity reactions, including anaphylaxis, to the product or its excipients
	• **BeneFIX** is contraindicated in:(3)
	  ○ Patients who have manifested life-threatening, immediate hypersensitivity reactions, including anaphylaxis, to the product or its components, including hamster protein
	• **Idelvion** is contraindicated in:(4)
	  ○ Patients who have had life-threatening hypersensitivity reactions to Idelvion or its components, including hamster proteins
	• **Ixinity** is contraindicated in:(5)
	  ○ Patients with known hypersensitivity to Ixinity or its excipients, including hamster protein
	• **Profilnine** has no known FDA labeled contraindications(7)
	• **Rebinyn** is contraindicated in:(8)
	  ○ Patients who have known hypersensitivity to Rebinyn or its components, including hamster proteins
	• **Rixubis** is contraindicated in:(9)
	  ○ Known hypersensitivity to Rixubis or its excipients including hamster protein

	○ Disseminated intravascular coagulation (DIC) ○ Signs of fibrinolysis

REFERENCES

Number	Reference
1	AlphaNine SD prescribing information. Grifols USA, LLC. November 2022.
2	Alprolix prescribing information. Bioverativ Therapeutics Inc. May 2023.
3	BeneFIX prescribing information. Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC. November 2022.
4	Idelvion prescribing information. CSL Behring Lengnau AG. June 2023.
5	Ixinity prescribing information. Medexus Pharma, Inc. November 2022.
6	Reference no longer used
7	Profilnine prescribing information. Grifols USA, LLC. November 2022.
8	Rebinyn prescribing information. Novo Nordisk. August 2022.
9	Rixubis prescribing information. Takeda Pharmaceuticals America, Inc. March 2023.
10	National Hemophilia Foundation. Bleeding Disorders A-Z/Types/Hemophilia B. Accessed at: https://www.hemophilia.org/bleeding-disorders-a-z/types/hemophilia-b.
11	Medical and Scientific Advisory Committee. MASAC recommendation regarding doses of clotting factor concentrate in the home. MASAC Document #242. June 2016.
12	Medical and Scientific Advisory Committee. MASAC Recommendation Concerning Prophylaxis for Hemophilia A and B with and without Inhibitors. MASAC Document #267. April 2022.
13	Medical and Scientific Advisory Council (MASAC) MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders. Document #280. August 2023.

Number	Reference
14	Srivastave A, Santagostino E, Dougall A, et al. World Federation of Hemophilia Guidelines for the Management of Hemophilia. 3rd edition. August 2020.
15	Reference no longer used

ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
85100028002 1	Alphanine sd	coagulation factor ix for inj	1000 UNIT ; 1500 UNIT ; 500 UNIT	Dependent on patient weight and number of doses			
85100028402 1	Alprolix	coagulation factor ix (recomb) (rfixfc) for inj	1000 UNIT ; 2000 UNIT ; 250 UNIT ; 3000 UNIT ; 4000 UNIT ; 500 UNIT	Dependent on patient weight and number of doses			
85100028206 4	Benefix	coagulation factor ix (recombinant) for inj kit	1000 UNIT ; 2000 UNIT ; 250 UNIT ; 3000 UNIT ; 500 UNIT	Dependent on patient weight and number of doses			
85100028352 1	Idelvion	coagulation factor ix (recomb) (rix-fp) for inj	1000 UNIT ; 2000 UNIT ; 250 UNIT ; 3500 UNIT ; 500 UNIT	Dependent on patient weight and number of doses			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
85100028202 1	Ixinity ; Rixubis	coagulation factor ix (recombinant) for inj	1000 UNIT ; 1500 UNIT ; 2000 UNIT ; 250 UNIT ; 3000 UNIT ; 500 UNIT	Dependent on patient weight and number of doses			
85100030021	Profilnine	factor ix complex for inj	1000 UNIT ; 1500 UNIT ; 500 UNIT	Dependent on patient weight and number of doses			
85100028452145	Rebinyn	coagulation factor ix recomb glycopegylated for inj	3000 UNIT	Dependent on patient weight and number of doses			
85100028452 1	Rebinyn	coagulation factor ix recomb glycopegylated for inj	1000 UNIT ; 2000 UNIT ; 3000 UNIT ; 500 UNIT	Dependent on patient weight and number of doses			

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Preferred and Non-Preferred Agents to be determined by client**

Preferred Agents	Non-Preferred Agents
AlphaNine SD Alprolix BeneFIX	

Module	Clinical Criteria for Approval

Idelvion Ixinity Profilnine Rebinyn Rixubis	

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Agents Eligible for Continuation of Therapy
All target agents are eligible for continuation of therapy

      1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR**
      2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR**

   B. BOTH of the following:
      1. The patient has a diagnosis of hemophilia B (also known as Factor IX deficiency, Christmas disease) AND ONE of the following:
         A. The patient is currently experiencing a bleed AND BOTH of the following:
            1. The patient is out of medication **AND**
            2. The patient needs to receive a ONE TIME emergency supply of medication **OR**
         B. BOTH of the following:
            1. The requested agent is being used for ONE of the following:
               A. Prophylaxis **OR**
               B. On-demand use for bleeds **OR**
               C. Peri-operative management of bleeding **AND**
            2. If the client has preferred agent(s) then ONE of the following:
               A. The requested agent is a preferred agent **OR**

Module	Clinical Criteria for Approval
	B. The patient has tried and had an inadequate response to ALL preferred agent(s) **OR** C. The patient has an intolerance, or hypersensitivity to ALL of the preferred agent(s) **OR** D. The patient has an FDA labeled contraindication to ALL of the preferred agent(s) **AND** 2. If the patient has an FDA labeled indication, ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., prescriber working in a hemophilia treatment center [HTC], hematologist with hemophilia experience) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 4. The prescriber must provide the actual prescribed dose with ALL of the following: A. Patient's weight **AND** B. Severity of the factor deficiency (i.e., severe is less than 1% factor activity, moderate is greater than or equal to 1 to less than or equal to 5% factor activity, mild is greater than5 to 40% factor activity) **AND** C. Inhibitor status **AND** D. Intended use/regimen: prophylaxis, on-demand, peri-operative **AND** 5. ONE of the following: A. The patient will NOT be using the requested agent in combination with another Factor IX agent included in this program **OR** B. There is support for the use of more than one unique Factor IX agent (medical records required) **Length of Approval:** One time emergency use: up to 2 weeks, Peri-operative dosing: 1 time per request, On-demand: up to 3 months, Prophylaxis: up to 12 months Note: If Quantity Limit applies, please see Quantity Limit criteria **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process (if current request is for a ONE TIME emergency use or the patient

Module	Clinical Criteria for Approval
	ONLY has previous approvals for emergency use, must use Initial Evaluation) (Note: patients not previously approved for the requested agent will require initial evaluation review) **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., prescriber working in a hemophilia treatment center [HTC], hematologist with hemophilia experience) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 4. The prescriber must provide the actual prescribed dose with ALL of the following: A. Patient's weight **AND** B. Severity of the factor deficiency (i.e., severe is less than 1% factor activity, moderate is greater than or equal to 1 to less than or equal to 5% factor activity, mild is greater than 5 to 40% factor activity) **AND** C. Inhibitor status **AND** D. Intended use/regimen: (e.g., prophylaxis, on-demand, peri-operative) **AND** 5. ONE of the following: A. The prescriber communicated with the patient (via any means) regarding the frequency and severity of the patient's bleeds and has verified that the patient does not have greater than 5 on-demand doses on hand **OR** B. There is support for the patient having more than 5 on-demand doses on hand **AND** 6. ONE of the following: A. The patient will NOT be using the requested agent in combination with another Factor IX agent included in this program **OR** B. There is support for the use of more than one unique Factor IX agent (medical records required) **Length of Approval:** On-demand: up to 3 months, Peri-operative dosing: 1 time per request, Prophylaxis: up to 12 months NOTE: If Quantity Limit applies, please see Quantity Limit criteria

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the requested agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit defined by BOTH of the following: A. The requested quantity (dose) is within the FDA labeled dosing **AND**

Module	Clinical Criteria for Approval
	B. The requested quantity (number of doses) is appropriate based on intended use (e.g., prophylaxis, on-demand, peri-operative) **OR** 2. There is support for exceeding the defined program quantity limit (dose and number of doses) (medical records required) **Length of Approval:** For initial one-time emergency use: up to 2 weeks Prophylaxis: up to 12 months Both initial and renewal Peri-operative dosing: 1 time per request Both initial and renewal On-demand: up to 3 months

Hepatitis C Direct Acting Antivirals

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Epclusa®, Sofosbuvir/Velpatasvir (sofosbuvir/velpatasvir) Oral tablet	• Treatment of adult and pediatric patients 3 years of age and older with chronic hepatitis C genotype 1, 2, 3, 4, 5, or 6 infection: ○ Without cirrhosis or with compensated cirrhosis ○ With decompensated cirrhosis in combination with ribavirin		1
Harvoni®, Ledipasvir/Sofosbuvir (ledipasvir/sofosbuvir) Oral tablet/Oral pellets	• Treatment of chronic hepatitis C in adults and pediatric patients 3 years of age and older: ○ For patients with genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis ○ For patients with genotype 1 infection with decompensated cirrhosis in combination with ribavirin ○ For patients with genotype 1 or 4 infection who are liver transplant recipients without cirrhosis or with compensated cirrhosis in combination with ribavirin		2
Mavyret®	• Treatment of adult and pediatric patients 3 years and older with chronic hepatitis C who have:		3

Agent(s)	FDA Indication(s)	Notes	Ref#
(glecaprevir/pibrentasvir) Oral tablet	○ Genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A) ○ Genotype 1 infection who previously have been treated with a regimen containing an HCV NS5A inhibitor or an NS3/4A protease inhibitor, but not both		
Sovaldi® (sofosbuvir) Oral tablet/Oral pellets	• Treatment of adult patients with chronic HCV genotype 1, 2, 3, or 4 infection without cirrhosis or with compensated cirrhosis as a component of a combination antiviral treatment regimen • Treatment of pediatric patients 3 years of age and older with genotype 2 or 3 chronic HCV infection without cirrhosis or in combination with ribavirin for patients with compensated cirrhosis		4
Viekira Pak® (ombitasvir/paritaprevir/ritonavir co-packaged with dasavuvir) Oral tablet	• Treatment of adult patients with chronic hepatitis C virus who have: ○ Genotype 1b without cirrhosis or with compensated cirrhosis ○ Genotype 1a without cirrhosis or with compensated cirrhosis used in combination with ribavirin		5

Agent(s)	FDA Indication(s)	Notes	Ref#
Vosevi® (sofosbuvir/velpatasvir/voxilaprevir) Oral tablet	• Treatment of adult patients with HCV infection without cirrhosis or compensated cirrhosis (Child-Turcotte-Pugh A) who have: ○ Genotype 1, 2, 3, 4, 5, or 6 infection and have previously been treated with an HCV regimen containing an NS5A inhibitor ○ Genotype 1a or 3 infection and have previously been treated with an HCV regimen containing sofosbuvir without an NS5A inhibitor		6
Zepatier® (elbasvir/grazoprevir) Oral tablet	• Treatment of chronic hepatitis C genotype 1 or 4 infection in adult and pediatric patients 12 years of age and older or weighing at least 30 kg. Zepatier is indicated for use with ribavirin in certain patient populations		7

CLINICAL RATIONALE

Hepatitis C	Hepatitis C is an infection of the liver caused by the Hepatitis C virus (HCV), a blood-borne virus. Today, most people become infected with HCV by sharing needles or other equipment to inject drugs. Hepatitis C infection can either be acute or chronic. Acute HCV infection is defined as presenting within 6 months following exposure to the virus. In 2018, the reported acute hepatitis C case count in the United States corresponded to a rate of 1.2 cases per 100,000 population, an over 71% increase from the reported incidence rate in 2014. The infection is defined as chronic if the virus is present beyond 6 months following exposure. More than 50% of people who become infected with HCV develop

	chronic infection. Chronic hepatitis C is a serious disease that can result in cirrhosis, liver cancer, and death.(9) The American Association for the Study of Liver diseases (AASLD) along with the Infectious Diseases society of America (IDSA) recommend the following:(8) • One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years and older • One-time HCV testing should be performed for all persons less than 18 years old with activities, exposures, or conditions or circumstances associated with an increased risk of HCV infection • Prenatal HCV testing as part of routine prenatal care is recommended with each pregnancy • Periodic repeat HCV testing should be offered to all persons with activities, exposures, or conditions or circumstances associated with an increased risk of HCV exposure • Annual HCV testing is recommended for all persons who inject drugs, for HIV-infected men who have unprotected sex with men, and men who have sex with men taking pre-exposure prophylaxis (PrEP) Risk activities: • Injection drug use (current or ever, including those who injected only once) • Intranasal illicit drug use • Use of glass crack pipes • Male engagement in sex with men • Engagement in chem sex (defined as the intentional combining of sex with the use of particular nonprescription [illicit] drugs in order to facilitate or enhance the sexual encounter) Risk exposures: • Persons on long-term hemodialysis (ever) • Persons with percutaneous/parenteral exposures in an unregulated setting • Healthcare, emergency medical, and public safety workers after needlestick, sharps, or mucosal exposure to HCV-infected blood • Children born to HCV-infected women • Recipients of a prior transfusion or organ transplant, including persons who:

	○ Were notified that they received blood from a donor who later tested positive for HCV ○ Received a transfusion of blood or blood components, or underwent an organ transplant before July 1992 ○ Received clotting factor concentrates produced before 1987 • Persons who were ever incarcerated Other conditions and circumstances: • HIV infection or HBV infection • Sexually active persons about to start pre-exposure prophylaxis (PrEP) for HIV • Chronic liver disease and/or chronic hepatitis, including unexplained elevated alanine aminotransferase (ALT) levels • Solid organ donors (living and deceased) and solid organ transplant recipients
AASLD/IDSA guidelines on when and in whom to initiate HCV therapy	The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response (SVR) (defined as the continued absence of detectable HCV RNA for at least 12 weeks after completion of therapy). According to the AASLD/IDSA guidelines, treatment is recommended for all patients with acute or chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Treatment should be initiated early because delaying therapy may decrease the benefits of SVR and increase the rates of liver-related mortality.(8) Although the prevalence of chronic HCV is lower in children than adults, an estimated 3.5-5 million children worldwide have chronic HCV infection. Data from the National Health and Nutrition Examination Survey (NHANES) collected between 2003 and 2010 indicates that 0.2% of 6 to 11 year olds (31,000 children) and 0.4% of 12 to 19 year olds (101,000 adolescents) in the US are HCV antibody positive.(11) Birth to an HCV-infected mother is a known risk for infection and these children should be evaluated and tested for HCV. The rate of mother-to-child transmission (MTCT) of HCV infection is approximately 5%, although rates are higher among women with inadequately controlled HIV co-infection, and women with higher HCV-RNA levels, or viral loads (greater than 6 log IU/mL). Identifying, following, and treating exposed children is recommended. The basis for

	evaluation early in life is HCV-RNA testing, as maternal antibodies and consequently anti-HCV assay positivity may persist for 18 months. About 25% to 50% of infected infants spontaneously resolve HCV infection (loss of previously detectable HCV RNA) by 3 years of age. HCV RNA is more expensive than an antibody-based test; and there is no intervention or treatment that will occur prior to age 3 because of lack of approved drugs for this age group and to allow for possible spontaneous clearance.(11)

Simplified Treatment	Direct-acting antiviral agents (DAAs) offer the potential for highly effective, interferon-free (and in many cases, ribavirin-free) regimens for the majority of hepatitis C virus infected patients. Regimen selection varies by genotype and other patient factors, such as the presence of cirrhosis and treatment history. Patients who are co-infected with HCV and either hepatitis B or HIV should be treated as those mono-infected with HCV.(12)
	
	The National Academies of Science, Engineering, and Medicine have proposed a strategy to reduce cases of chronic HCV infection by 90% by 2030. Data shows that HCV treatment can be effectively provided by a broad range of health care professionals with differing expertise – including specialists, primary care physicians, nurse practitioners, clinical pharmacy specialists, physician assistants, and registered nurses- without compromising treatment efficacy or safety. AASLD/IDSA has created simplified regimens to treat HCV in adults without cirrhosis or compensated cirrhosis who have not been previously treated for their infection to allow for the expansion of healthcare professionals who prescribe antiviral therapy and increase the number of persons treated. These simplified treatment algorithms are designed to be used by any health care provider knowledgeable about HCV disease and treatment, including those without extensive experience, who have timely access to a specialist. Any patients not included in the simplified treatment regimens should be seen by a specialist.(12)
	
	For patients without cirrhosis, the pretreatment evaluation should include:(12)
	
	• Calculate FIB-4 score
	• Cirrhosis assessment (liver biopsy is not required – a patient is presumed to have cirrhosis if they have a FIB-4 score greater than 3.25 or any of the following findings from a previously performed test
	  ○ Transient elastography indicating cirrhosis (e.g., FibroScan stiffness greater than 12.5 kPa)
	  ○ Noninvasive serologic tests above proprietary cutoffs indicating cirrhosis (e.g., FibroSure, Enhanced Liver Fibrosis Test)

	○ Clinical evidence of cirrhosis (e.g., liver nodularity and/or splenomegaly on imaging, platelet count less than 150,000/mm3) ○ Prior liver biopsy showing cirrhosis • Medication reconciliation • Potential drug-drug interactions assessment • Patient education about proper administration of medications, adherence, and prevention of reinfection Patients without cirrhosis who have any of the following are NOT eligible for simplified treatment:(12) • Prior hepatitis C treatment • Cirrhosis (see simplified treatment for treatment-naive adults with compensated cirrhosis) • Hepatitis B surface antigen (HBsAg) positive • Current pregnancy • Known or suspected hepatocellular carcinoma • Prior liver transplantation The recommended treatment regimens are glecaprevir (300 mg)/pibrentasvir (120 mg) taken with food for 8 weeks or sofosbuvir (400 mg)/velpatasvir (100 mg) for a duration of 12 weeks. For patients with compensated cirrhosis (Child-Turcotte-Pugh class A), the pretreatment evaluation should include:(12) • Calculate FIB-4 score (liver biopsy not required) • Calculate Child-Turcotte-Pugh (CTP) score • Ultra-sound imaging of the liver within the prior 6 months to evaluate for hepatocellular carcinoma (HCC) and sub clinical ascites • Medication reconciliation • Potential drug-drug interaction assessment • Patient education about proper administration of medications, adherence, and prevention of reinfection • Pretreatment laboratory testing: ○ Within 3 months of initiating treatment: ▪ Complete blood count (CBC) ▪ International normalized ratio (INR) ▪ Hepatic function panel (i.e., albumin, total and direct bilirubin, ALT, AST) ▪ Calculated glomerular filtration rate (eGFR) ○ Any time prior to starting antiviral therapy:

	• Quantitative HCV RNA (HCV viral load)
	  ○ HIV antigen/antibody test
	  ○ Hepatitis B surface antigen
	  ○ HCV genotype (if treating with sofosbuvir/velpatasvir)
	• Before initiating antiviral therapy
	  ○ Serum pregnancy testing and counseling about pregnancy risks of HCV medication should be offered to women of childbearing age
	
	Patients with compensated cirrhosis who have any of the following are NOT eligible for simplified treatment:(12)
	
	• Current or prior episode of decompensated cirrhosis, defined as Child-Turcotte-Pugh (CTP) score greater than or equal to 7 (ascites, hepatic encephalopathy, total bilirubin greater than 2.0 mg/dL, albumin less than or equal to 3.5 g/dL, or INR greater than or equal to 7)
	• Prior hepatitis C treatment
	• End-stage renal disease (i.e., eGFR less than 30 mL/min/m^2)
	• HBsAg positive
	• Current pregnancy
	• Known or suspected hepatocellular carcinoma
	• Prior liver transplantation
	
	The recommended regimens for genotype 1-6 are glecaprevir (300 mg)/pibrentasvir (120 mg) taken with food for 8 weeks or for genotypes 1, 2, 4, 5, or 6, sofosbuvir (400 mg)/velpatasvir (100 mg) for a duration of 12 weeks (note for sofosbuvir/velpatasvir: patients with genotype 3 require baseline NS5A resistance-associated substitution (RAS) testing. Those without Y93H can be treated with sofosbuvir/velpatasvir for a duration of 12 weeks).(12)

Efficacy	**Epclusa(1)** Epclusa (sofosbuvir/velpatasvir) contains a hepatitis C nucleotide analog NS5B polymerase inhibitor (sofosbuvir) and a hepatitis C virus NS5A inhibitor (velpatasvir). Efficacy of this combination agent was evaluated in five phase 3 trials (ASTRAL-1, ASTRAL-2, ASTRAL-3, ASTRAL-4, and ASTRAL-5). All these trials included patients who were either treatment naïve or had previously been treated with an interferon based regimen (peginterferon plus ribavirin with or without a protease inhibitor). The primary endpoint for these trials was sustained virologic response at 12 weeks (SVR12) following completion of therapy. ASTRAL-1 was a placebo controlled trial that enrolled patients with HCV infection genotype 1, 2, 4, 5, or 6. Overall, the SVR 12 rate was 99% in patients who

	received Epclusa and 0% in those receiving placebo (95% confidence interval, p less than 0.001). ASTRAL-2 and ASRTAL-3 were randomized, open label trials evaluating efficacy in patients with HCV genotype 2 or 3 respectively. Those with HCV genotype 2 received either Epclusa for 12 weeks or sofosbuvir plus ribavirin for 12 weeks. The SVR12 rates for the two treatment arms were 99% and 94% respectively. Subjects with HCV genotype 3 were randomized to receive either Epclusa for 12 weeks or sofosbuvir plus ribavirin for 24 weeks. The SVR12 rates were 95% and 80% respectively. ASTRAL-4 was an open label trial that evaluated efficacy of Epclusa in patients with decompensated cirrhosis. Patients were randomized to receive one of three treatment regimens: Epclusa for 12 weeks, Epclusa for 24 weeks, or Epclusa plus ribavirin for 12 weeks. SVR12 rates were 83%, 86%, and 94% respectively. ASTRAL-5 was an open-label trial that evaluated 12 weeks of Epclusa in patients with genotype 1, 2, 3, 4, 5, or 6 hepatitis C infection who were coinfected with HIV-1. The patients were all on antiretroviral therapy of various regimens. The primary endpoint was SVR12. The SVR12 ranged from 92-100% depending on genotype and in genotype 1 the subtype. No patient had HIV-1 rebound during treatment and CD4+ counts were stable during treatment. Trial 4062 was on open-label clinical trial that evaluated 12 weeks of treatment with Epclusa in 59 HCV-infected adults with end stage renal disease (ESRD) requiring dialysis. The overall SVR rate was 95%. Of the subjects completing 12 weeks of Epclusa, 1 subject experienced virologic relapse. The efficacy of Epclusa once daily for 12 weeks was evaluated in an open-label trial (Study 1143) in 173 genotype 1, 2, 3, 4, or 6 HCV treatment-naïve or treatment-experienced pediatric subjects 3 years of age and older without cirrhosis or with compensated cirrhosis. In patients 12 years to less than 18 years of age (genotypes 1, 2, 3, 4 and 6), the SVR rates were: • 93% for genotype 1 • 100% for genotypes 2, 3, 4, and 6 In patients 6 years to less than 12 years of age (genotypes 1, 2, 3, and 4) the SVR rates were:

	• 93% for genotype 1 • 91% for genotype 3 • 100% for genotypes 2 and 4 In patients 3 years to less than 6 years of age the SVR rates were: • 83% among all subjects • 88% for genotype 1 • 50% for genotype 2 • 100% for genotype 3 and 4 Trial 2104 was an open-label clinical trial that evaluated 12 weeks of treatment with Epclusa in 79 HCV-infected treatment-naïve and previously treated adult subjects who had undergone liver transplantation. The overall SVR12 rate was 96%. Trial 4062 was an open-label clinical trial that evaluated 12 weeks of treatment with Epclusa in 59 HCV-infected adults with end stage renal disease (ESRD) requiring dialysis. The overall SVR rate was 95%. **Harvoni(2)** Harvoni (ledipasvir/sofosbuvir) is a combination of an NS5A inhibitor (ledipasvir) and nucleotide analog NS5B polymerase inhibitor (sofosbuvir). Its efficacy was evaluated in several phase 2 and 3 clinical trials. These trials enrolled a broad range of patient populations including treatment naïve and treatment experienced patients, those without cirrhosis and with cirrhosis (compensated and decompensated), post-liver transplant patients, pediatric patients who were at least 3 years old or weighed more than 35 kg, as well as those with HIV/HCV co-infection. All the trials had a primary end point of sustained virologic response at 12 weeks (SVR12) following completion of treatment. Overall SVR12 was greater than 90% for the various patient populations. The treatment duration of this agent varies from 8 weeks to 24 weeks. Per the FDA labeling, treatment naïve patients with HCV genotype 1 with RNA of less than 6 million can be successfully treated with 8 weeks of Harvoni. This duration of treatment is not recommended in patients with cirrhosis, HIV, are post-liver transplantation, and/or black or African-American. Treatment experienced patients with cirrhosis may be treated with Harvoni alone for 24 weeks or in combination with ribavirin for 12 weeks. These two regimens are equally efficacious with SVR12 of 96% and 97% respectively.

	Mavyret(3) Mavyret (glecaprevir/pibrentasvir) is a combination of an NS3/4A protease inhibitor (glecaprevir) and an NS5A inhibitor (pibrentasvir). Its safety and efficacy have been demonstrated in treatment naïve patients or patients previously treated with regimens containing peginterferon, ribavirin, and/or sofosbuvir (PRS) with HCV genotype 1, 2, 3, 4, 5 or 6 without cirrhosis or with compensated cirrhosis. Its safety and efficacy has also been demonstrated in patients who have previously been treated with a regimen containing an NS5A inhibitor or an NS3/4A protease inhibitor but not both. Patients with prior treatment with both an NS5A inhibitor and NS3/4A inhibitor were at an increased risk of virologic failure when retreated with Mavyret. The efficacy of Mavyret in treatment naïve or PRS treatment experienced adults with HCV genotype 1, 2, 4, 5, or 6 infection without cirrhosis was evaluated in the ENDURANCE-1, ENDURANCE-4, SURVEYOR-1 (part 2), and SURVEYOR-2 (part 2 and part 4) trials. The SVR12 ranged from 93% to 100% depending on genotype. The EDURANCE-1 trial demonstrated numerically similar efficacy in genotype 1 treatment naïve patients without cirrhosis treated for 8 weeks vs 12 weeks. The SURVEYOR-2 trial also demonstrated very high SVR12 for genotypes 2, 4, 5, or 6 after 8 weeks of treatment. Therefore, the recommended length of therapy for treatment naïve patients without cirrhosis is 8 weeks. The efficacy of Mavyret in treatment naïve or PRS treatment experienced adults with HCV genotypes 1, 2, 4, 5, or 6 infection with compensated cirrhosis was evaluated in the EXPEDITION-1 trial. Patients received Mavyret for 12 weeks. The SVR12 was 99-100% depending on genotype. The efficacy of Mavyret in treatment naïve or PRS treatment experienced adults with HCV genotype 3 infection without cirrhosis or with compensated cirrhosis was evaluated in the ENDURANCE-3 and SURVEYOR-2 (part 3) trial. For patients without cirrhosis the SVR12 was numerically similar for patients without cirrhosis and the recommendation for these patients is to treat for 8 weeks. The overall SVR12 for all patients in these trials ranged from 94.9-98% depending on cirrhosis status and previous treatment. The efficacy of Mavyret in treatment naïve and PRS treatment experienced adults with genotype 2, 4, 5, or 6 without cirrhosis was evaluated in the SURVEYOR-2 (part 2 and part 4), ENDURANCE-4, and SURVEYOR-1 (part 2) trials. SVR12 ranged from 93-100% depending on genotype.

	The efficacy of Mavyret in treatment naïve or PRS treatment experienced adults with HCV genotype 1, 2, 4, 5, or 6 infection with compensated cirrhosis was evaluated in the EXPEDITION-1 trial. The SVR12 ranged from 99-100% depending on genotype. The EXPEDITION-4 trial evaluated treatment naïve and PRS treatment experienced adults with chronic kidney disease stage 4 and 5 and chronic HCV infection without cirrhosis or with compensated cirrhosis. The overall SVR12 was 98%. The MAGELLAN-1 trial evaluated adults who were NS5A inhibitor or NS3/4A protease inhibitor experienced patients without cirrhosis or with compensated cirrhosis. The SVR12 ranged from 92-94% depending on previous treatment. The MAGELLAN-2 trial evaluated patients who were treatment-naïve or PRS treatment-experienced who have had a liver or kidney transplant. The overall SVR12 rate was 98%. The efficacy of Mavyret was evaluated in an open-label study (DORA Part 1) that evaluated adolescent subjects 12 years to less than 18 years without cirrhosis who received Mavyret for 8 or 16 weeks. Treatment duration was chosen to match approved adult durations based on HCV genotype and prior treatment experience. The overall SVR12 rate was 100%. DORA part 2 enrolled patients aged 3 years to less than 12 years and used weight-based dosing of Mavyret. The overall SVR12 rate for the subjects who received the recommended dosage was 98.4%. **Sovaldi (sofosbuvir)(4)** Sovaldi is a nucleotide analog NS5B polymerase inhibitor. It is indicated for use in combination with other DAAs including daclatasvir and simeprevir. It may also be used in combination with peg-interferon and ribavirin. To date, sofosbuvir is the only oral DAA indicated for treatment of patients with hepatocellular carcinoma secondary to chronic HCV infection. The safety and efficacy of Sovaldi was evaluated in five Phase 3 trials in a total of 1724 HCV mono-infected subjects with genotypes 1 to 6 chronic hepatitis C virus, one Phase 3 trial in 223 HSC/HIV-1 coinfected subjects with genotype 1, 2, or 3 HCV, and one trial in 106 pediatric subjects 3 years of age and older with genotype 2 or 3 HCV. The efficacy of Sovaldi (SVR12) is dependent on the

	combination regimen in which it is used, the patient's genotype, and patient's treatment history (range 82% - 100%). The most common adverse events of sofosbuvir when used with ribavirin include fatigue headache and insomnia. Nausea, insomnia, and anemia were the most common adverse events when sofosbuvir was used in combination with ribavirin and peg-interferon. **Viekira Pak(5)** Viekira Pak (ombitasvir/paritaprevir/ritonavir co-packaged with dasabuvir) is a combination therapy containing a hepatitis C virus NS3/4A protease inhibitor (paritaprevir), a CYP3A inhibitor (ritonavir), a hepatitis C virus NS5A inhibitor (ombitasvir), and a hepatitis C NS5B palm polymerase inhibitor (dasabuvir). Safety and efficacy of this combination was evaluated in trials including treatment naïve, previous failures, cirrhotic and non-cirrhotic genotype 1 patients. The studies (SAPPHIRE-1, SAPPHIRE-II, PEARL-II, PEARL-III, PEARL-IV, TURQUOISE-II, AND TURQUIOISE-III) all had a primary efficacy endpoint of SVR12. Patients with genotype 1a infection without cirrhosis were evaluated in the SAPPHIRE-I, SAPPHIRE-II, and PEARL-IV trials. The SVR12 ranged from 95-97% depending on previous treatment. Patients with genotype 1b infection without cirrhosis were evaluated in the PEARL-II and PEARL-III trials. SVR12 for both of these studies was 100%. Patients with genotype 1a and genotype 1b infection with compensated cirrhosis were evaluated in the TURQUOISE-II and TURQUOISE-IV trials. The SVR12 ranged from 89-100% depending on genotype subtype and length of treatment. Treatment guidelines recommend that patients that have failed a previous protease inhibitor containing regimen receive ledipasvir/sofosbuvir. Ombitasvir/paritaprevir/ritonavir + dasabuvir is not a recommended regimen in previous protease inhibitor failures due to risk of resistance. **Vosevi(6)** Vosevi (sofosbuvir/velpatasvir/voxilaprevir) is a fixed-dose combination of a hepatitis C virus nucleotide analog NS5B polymerase inhibitor (sofosbuvir), an HCV NS5A inhibitor (velpatasvir), and an HCV NS3/4A protease inhibitor

	(voxilaprevir). Efficacy of this combination agent was evaluated in two phase 3 trials. The primary endpoint in both trials was SVR12. The efficacy of Vosevi in patients with hepatitis C genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis who were treatment experienced with a NS5A inhibitor (POLARIS-1 trial). The SVR12 ranged from 91-100% depending on genotype. The efficacy of Vosevi in patients with hepatitis C genotype 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis who previously failed a hepatitis C direct acting antiviral (POLARIS-4 trial). The SVR12 ranged from 94-100% depending on genotype and in genotype 1, the subtype. Additional benefit of this combination agent over sofosbuvir/velpatasvir has not been shown in patients with genotype 1b, 2, 4, 5, or 6 infection who were previously treated with sofosbuvir without an NS5A inhibitor. **Zepatier(7)** Zepatier (elbasvir/grazoprevir) is a combination regimen of an NS5A replication inhibitor (elbasvir) and an NS3/4A protease inhibitor (grazoprevir). Its efficacy was evaluated in several phase 2 and 3 clinical trials. All the trials had a primary end point of sustained virologic response at 12 weeks (SVR12) following completion of treatment. Efficacy of Zepatier in treatment naïve patients with HCV genotype 1 with or without cirrhosis was evaluated in the C-EDGE TN and C-EDGE COINFECTION trials. Subjects in both trials received Zepatier for 12 weeks. SVR12 was 95% in both trials. There were no significant differences in SVR12 between cirrhotic and non-cirrhotic patients. The C-EDGE TE trial evaluated efficacy of this combination in treatment experienced HCV genotype 1 patients with or without cirrhosis who had previously failed peginterferon plus ribavirin. Subjects received Zepatier monotherapy for 12 weeks or Zepatier with ribavirin for 16 weeks. SVR12 rates in the two treatment groups were 94% and 97% respectively. Efficacy in HCV genotype 1 patients with or without cirrhosis who had previously failed peginterferon, ribavirin, plus a protease inhibitor was evaluated in the C-SALVAGE trial. This was an open label, single arm trial. All subjects received Zepatier plus ribavirin for 12 weeks. Overall SVR12 was 96%. Efficacy of Zepatier in patients with HCV genotype 1 with or without cirrhosis and who had Chronic Kidney Disease (CKD) stage 4 (eGFR 15-29 mL/min/1.73 m^2) or CKD Stage 5 (eGFR less than 15 mL/min/1.73 m^2), including patients on

	hemodialysis was evaluated in the C-SURFER trial. Patients were randomized to receive either Zepatier for 12 weeks or placebo for 12 weeks followed by 12 weeks of Zepatier (deferred treatment group). Overall SVR12 was 99%. There were no significant differences with regard to safety in the Zepatier group versus placebo group. These trials found that presence of NS5A amino acid polymorphisms in patients with HCV genotype 1a was associated with reduced efficacy of Zepatier regardless of treatment history or cirrhosis status. It is recommended to test for NS5A polymorphisms in HCV genotype 1a patients prior to starting treatment with this combination. If the polymorphism is present, addition of ribavirin to the treatment regimen and extension of the duration of treatment to 16 weeks is recommended. Efficacy of Zepatier in HCV genotype 4 patients was evaluated in the C-SCAPE, C-EDGE TE, C-EDGE TN, and C-EDGE COINFECTION trials. Treatment naïve patients in these trials received Zepatier for 12 weeks while those who were treatment experienced received Zepatier plus ribavirin for 12 to 16 weeks. SVR12 in the treatment naïve and treatment experienced patients was 97% and 100% respectively.

Safety	• Epclusa (sofosbuvir/velpatasvir) has the following contraindication(s):(1)
	  ○ Epclusa and ribavirin combination regimen is contraindicated in patients for whom ribavirin is contraindicated
	• Harvoni (ledipasvir/sofosbuvir) has the following contraindication(s):(2)
	  ○ If used in combination with ribavirin, all contraindications to ribavirin also apply to Harvoni combination therapy
	• Mavyret (glecaprevir/pibrentasvir) has the following contraindication(s):(3)
	  ○ Patients with severe hepatic impairment (Child-Turcotte-Pugh B or C) or those with any history of prior hepatic decompensation
	  ○ Coadministration with atazanavir or rifampin
	• Sovaldi (sofosbuvir) has the following contraindication(s):(4)
	  ○ When used in combination with peginterferon alfa/ribavirin or ribavirin alone, all contraindications to peginterferon alfa and/or ribavirin also apply to Sovaldi combination therapy
	  ○ Because ribavirin may cause birth defects and fetal death, Sovaldi in combination with peginterferon alfa and/or ribavirin is contraindicated in pregnant women and men whose female partners are pregnant
	• Viekira PAK (paritaprevir/ritonavir/ombitasvir + dasabuvir) has the following contraindication(s):(5)

	○ Patients with moderate to severe hepatic impairment [decompensated cirrhosis (Child-Turcotte-Pugh B or C)] ○ Known hypersensitivity to ritonavir (e.g., toxic epidermal necrolysis, Steven-Johnson syndrome) ○ Co-administration with drugs that are: highly dependent on CYP3A for clearance; moderate or strong inducers of CYP3A and strong inducers of CYP2C8; and strong inhibitors of CYP2C8 ○ If Viekira is administered with ribavirin, the contraindications to ribavirin also apply to this combination regimen • Vosevi (sofosbuvir, velpatasvir, and voxilaprevir) has the following contraindications(s):(6) ○ Co-administration with rifampin. • Zepatier (elbasvir/grazoprevir) has the following contraindication(s):(7) ○ Patients with moderate or severe hepatic impairment [decompensated cirrhosis (Child-Turcotte-Pugh B or C)] ○ Organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors, strong CYP3A inducers, and efavirenz ○ If Zepatier is administered with ribavirin, the contraindications to ribavirin also apply
Risk of Hepatitis B infection reactivation with HCV Direct Acting Antivirals	In October of 2016, the FDA issued a safety alert concerning risk of reactivation of hepatitis B viral (HBV) infection in patients treated with HCV direct acting antivirals (DAA). At the time of the alert, the FDA had identified 24 cases of HBV infection reactivation in patients who had been treated with an HCV DAA. In a few of these cases, the HBV reactivation resulted in serious liver problems or death. As a result, the FDA has required labeling for all HCV DAAs to include a boxed warning for HBV infection reactivation. In addition, the FDA has recommended that all patients be screened for evidence of current or prior HBV infection before starting treatment with HCV DAAs and be monitored for HBV reactivation during and after treatment with an HCV DAA.(10)

REFERENCES

Number	Reference
1	Epclusa prescribing information. Gilead. April 2022.
2	Harvoni prescribing information. Gilead. March 2020.
3	Mavyret prescribing information. AbbVie. October 2023.

Number	Reference
4	Sovaldi prescribing information. Gilead. March 2020.
5	Viekira Pak prescribing information. Abbvie Inc. December 2019.
6	Vosevi prescribing information. Gilead. November 2019.
7	Zepatier prescribing information. Merck. May 2022.
8	AASLD/IDSA HCV Guidance: Recommendations for Testing, Managing, and Testing Hepatitis C. Available at www.hcvguidelines.org.
9	The Center for Disease Control and Prevention. Viral Hepatitis Statistics and Surveillance. Available at http://www.cdc.gov/hepatitis/statistics.
10	Direct-Acting Antivirals for Hepatitis C: FDA Drug Safety Communication-Risk of Hepatitis B Reactivation. Available at: http://www.fda.gov.
11	AASLD/IDSA HCV Guidance: Unique and Key populations - HCV in children. https://www.hcvguidelines.org/unique-populations/children.
12	Bhattacharya D, Aronsohn A, Price J, Lo Re V; AASLD-IDSA HCV Guidance Panel . Hepatitis C Guidance 2023 Update: AASLD-IDSA Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Clin Infect Dis*. Published online May 25, 2023. doi:10.1093/cid/ciad319

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

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<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
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Module	Clinical Criteria for Approval		
	Epclusa (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Sovaldi** (sofosbuvir) **Viekira PAK** (ombitasvir/paritaprevir/ritonavir + dasabuvir) **Zepatier** (elbasvir/grazoprevir)	
	Genotype 2 **Epclusa** (sofosbuvir/velpatasvir) **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 2** **Sovaldi** (sofosbuvir)	
	Genotype 3 **Epclusa** (sofosbuvir/velpatasvir) **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 3** **Sovaldi** (sofosbuvir)	
	Genotype 4 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 4** **Sovaldi** (sofosbuvir) **Zepatier** (elbasvir/grazoprevir)	
	Genotype 5 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 5**	

Module	Clinical Criteria for Approval
	Genotype 6 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 6**	

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has a diagnosis of hepatitis C genotype 1, 2, 3, 4, 5, or 6 **AND**
2. ONE of the following:
   A. The patient is treatment naive **OR**
   B. The patient was previously treated (i.e., treatment experienced) with ONLY peg-interferon and ribavirin with or without an HCV protease inhibitor **OR**
   C. The patient has decompensated cirrhosis **AND**
3. If the patient has an FDA labeled indication, then ONE of the following:
   A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**
   B. There is support for the use of the requested agent for the patient's age for the requested indication **AND**
4. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection **AND**
5. If the screening for HBV was positive for current or prior HBV infection, the prescriber will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent **AND**
6. If the client has preferred agent(s) for the patient's specific factors (e.g., age, genotype, cirrhosis status, treatment naive vs treatment experienced, previous treatment), then ONE of the following:
   A. The requested agent is a preferred agent for the patient's specific factors (e.g., age, genotype, cirrhosis status, treatment naive vs treatment experienced, previous treatment) **OR**
   B. The patient has been treated with the requested non-preferred agent in the past 30 days **OR**
   C. The patient has an intolerance or hypersensitivity to ALL of the preferred agent(s) for the patient's specific factors (e.g., age, genotype,

Module	Clinical Criteria for Approval
	cirrhosis status, treatment naive vs treatment experienced, previous treatment) **OR** D. The patient has an FDA labeled contraindication to ALL of the preferred agent(s) for the patient's specific factors (e.g., age, genotype, cirrhosis status, treatment naive vs treatment experienced, previous treatment) **OR** E. There is support for the use of the requested non-preferred agent over the preferred agent(s) **AND** 7. ONE of the following: A. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, hepatologist, or infectious disease) or has consulted with a specialist in the area of the patient's diagnosis **OR** B. ALL of the following: 1. The patient is treatment naive **AND** 2. The patient does NOT have cirrhosis or has compensated cirrhosis **AND** 3. The requested agent is supported in AASLD guidelines for simplified treatment **AND** 4. The patient meets all of the qualifications for AASLD guidelines simplified treatment (please see Patients Who Qualify for Simplified Treatment tables below) **AND** **Patients Eligible for Simplified HCV Treatment** Adults with chronic HCV infection, including persons living with HIV: • Infected with any genotype • Have NOT previously received HCV treatment • Without cirrhosis OR with compensated cirrhosis (Child-Pugh A) as determined by: ○ Liver stiffness > 12.5 kPa by FibroScan ○ FIB-4 > 3.25 ○ Noninvasive serologic test ○ Live biopsy

Module	Clinical Criteria for Approval
	○ Live nodularity or splenomegaly on imaging ○ Platelet count < 150,000/mm^3
	Patients Excluded from Simplified HCV Treatment
	Adults with chronic HCV infection: • Previously received HCV treatment • Hepatitis B surface antigen-positive • Compensated cirrhosis (Child-Pugh A) with end-stage renal disease (i.e., eGFR less than 30 mL/min/m^2) • Current or prior decompensated cirrhosis, defined by Child-Pugh score greater than or equal to 7 • Current pregnancy • Known or suspected hepatocellular carcinoma • Prior liver transplantation
	8. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 9. The patient meets all requirements and will use the requested agent in a treatment regimen noted in Table 1 (FDA labeling) or 2 (AASLD/IDSA guidelines for decompensated cirrhosis) **AND** 10. The requested length of therapy does NOT exceed the length of therapy noted in Table 1 (FDA labeling) or 2 (AASLD/IDSA guidelines for decompensated cirrhosis) for the patient's treatment regimen **Length of Approval:** Up to the duration of treatment as determined in Tables 1 or 2. NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Table 1: Epclusa or Sofosbuvir/Velpatasvir Treatment Recommendations based on FDA labeling**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
<table>
<tr><th>Genotype</th><th>Patients 3 years of age and older*</th><th>Treatment</th><th>Duration</th></tr>
<tr><td>1, 2, 3, 4, 5, or 6</td><td>Patients without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)</td><td>Epclusa, Sofosbuvir/Velpatasvir</td><td>12 weeks</td></tr>
<tr><td>1, 2, 3, 4, 5, or 6</td><td>Patients with decompensated cirrhosis (Child-Turcotte-Pugh B and C)</td><td>Epclusa + ribavirin, Sofosbuvir/Velpatasvir + ribavirin</td><td>12 weeks</td></tr>
</table>
*HCV/HIV-1 co-infection, follow recommendation in table above
Table 2: Epclusa or Sofosbuvir/Velpatasvir Decompensated Cirrhosis Treatment Recommendations based on AASLD/IDSA Guidelines for unique populations
<table>
<tr><th>Genotype</th><th>Patient Population*</th><th>Treatment</th><th>Duration</th></tr>
<tr><td>1, 2, 3, 4, 5, or 6</td><td>Patients with decompensated cirrhosis (Child-Turcotte-Pugh B and C) who are ribavirin ineligible (i.e., patients with history of intolerance, contraindication, or</td><td>Epclusa, Sofosbuvir/Velpatasvir</td><td>24 weeks</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>hypersensitivity to ribavirin)</td><td></td><td></td></tr>
<tr><td>1, 2, 3, 4, 5, or 6</td><td>Patients with decompensated cirrhosis (Child-Turcotte-Pugh B and C) in whom prior sofosbuvir- or NS5A inhibitor (e.g., daclatasvir, elbasvir, ledipasvir, ombitasvir, velpatasvir) - based treatment failed</td><td>Epclusa with weight-based ribavirin (low initial dose of ribavirin [600 mg] is recommended for patients with Child-Turcotte-Pugh class C cirrhosis), Sofosbuvir/Velpatasvir with weight-based ribavirin (low initial dose of ribavirin [600 mg] is recommended for patients with Child-Turcotte-Pugh class C cirrhosis)</td><td>24 weeks</td></tr>
</table>
*HCV/HIV-1 co-infection, follow recommendation in table above</td></tr>
<tr><td>Harvoni and Ledipasvir/Sofosbuvir</td><td>
<table>
<tr><th>Preferred Agents</th><th>Non-Preferred Agents</th><th>Applicable Formulary</th></tr>
<tr><td>Genotype 1

Epclusa (sofosbuvir/velpatasvir
Harvoni (ledipasvir/sofosbuvir)
Ledipasvir/Sofosbuvir
Sofosbuvir/Velpatasvir
Mavyret (glecaprevir/pibrentasvir)
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)</td><td>Genotype 1

Sovaldi (sofosbuvir)
Viekira PAK (ombitasvir/paritaprevir/ritonavir + dasabuvir)
Zepatier (elbasvir/grazoprevir)</td><td></td></tr>
<tr><td>Genotype 2

Epclusa (sofosbuvir/velpatasvir)
Sofosbuvir/Velpatasvir</td><td>Genotype 2

Sovaldi (sofosbuvir)</td><td></td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval		
	Mavyret (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)		
	Genotype 3 **Epclusa** (sofosbuvir/velpatasvir) **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 3** **Sovaldi** (sofosbuvir)	
	Genotype 4 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 4** **Sovaldi** (sofosbuvir) **Zepatier** (elbasvir/grazoprevir)	
	Genotype 5 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 5**	
	Genotype 6 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 6**	

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The patient has a diagnosis of hepatitis C genotype 1, 4, 5, or 6 **AND** 2. The prescriber has provided the patient's baseline HCV RNA level if the patient has genotype 1 **AND** 3. ONE of the following: A. The patient is treatment naive **OR** B. The patient was previously treated (i.e., treatment experienced) with peg-interferon and ribavirin with or without an HCV protease inhibitor **OR** C. The patient has decompensated cirrhosis **AND** 4. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection **AND** 5. If the screening for HBV was positive for current or prior HBV infection, the prescriber will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent **AND** 6. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 7. If the client has preferred agent(s) for the patient's specific factors (e.g., age, genotype, cirrhosis status, treatment naive vs treatment experienced, previous treatment), then ONE of the following: A. The requested agent is a preferred agent for the patient's specific factors **OR** B. The patient has been treated with the requested non-preferred agent in the past 30 days **OR** C. The patient has an intolerance or hypersensitivity to ALL of the preferred agent(s) for the patient's specific factors **OR** D. The patient has an FDA labeled contraindication to ALL of the preferred agent(s) for the patient's specific factors **OR** E. There is support for the use of the requested non-preferred agent over the preferred agent(s) **AND** 8. ONE of the following: A. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, hepatologist, or infectious disease) or has consulted with a specialist in the area of the patient's diagnosis **OR** B. ALL of the following:

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
1. The patient is treatment naive AND
2. The patient does NOT have cirrhosis or has compensated cirrhosis AND
3. The requested agent is supported in AASLD guidelines for simplified treatment AND
4. The patient meets all of the qualifications for AASLD guidelines simplified treatment (please see Patients Who Qualify for Simplified Treatment tables below) AND

Patients Eligible for Simplified HCV Treatment

Adults with chronic HCV infection, including persons living with HIV:
• Infected with any genotype
• Have NOT previously received HCV treatment
• Without cirrhosis OR with compensated cirrhosis (Child-Pugh A) as determined by:
  ○ Liver stiffness > 12.5 kPa by FibroScan
  ○ FIB-4 > 3.25
  ○ Noninvasive serologic test
  ○ Live biopsy
  ○ Live nodularity or splenomegaly on imaging
  ○ Platelet count < 150,000/mm^3

Patients Excluded from Simplified HCV Treatment

Adults with chronic HCV infection:
• Previously received HCV treatment
• Hepatitis B surface antigen-positive
• Compensated cirrhosis (Child-Pugh A) with end-stage renal disease (i.e., eGFR less than 30 mL/min/m^2)
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</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>

Current or prior decompensated cirrhosis, defined by Child-Pugh score greater than or equal to 7
Current pregnancy
Known or suspected hepatocellular carcinoma
Prior liver transplantation

<ol start="9">
The patient does NOT have any FDA labeled contraindications to the requested agent AND
The patient meets all requirements and will use the requested agent in a treatment regimen noted in Table 3 (FDA labeling) or 4 (AASLD/IDSA guidelines for decompensated cirrhosis) AND
The requested length of therapy does NOT exceed the length of therapy noted in Table 3 (FDA labeling) or 4 (AASLD/IDSA guidelines for decompensated cirrhosis) for the patient’s treatment regimen

Length of Approval: Up to the duration of treatment as determined in Table 3 or 4.

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Table 3: Harvoni or Ledipasvir/Sofosbuvir Treatment Recommendations based on FDA labeling
<table>
<tr><th>Genotype</th><th>Patients 3 years of age and older*</th><th>Treatment</th><th>Duration</th></tr>
<tr><td>1</td><td>Treatment-naive with initial viral load of less than 6 M IU/mL and without cirrhosis, HIV infection, history of liver transplantation</td><td>Harvoni, Ledipasvir/Sofosbuvir</td><td>8 weeks NOTE approve 8 weeks length of therapy ONLY if prescriber is</td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval			
		and/or are not black or African-American		**requesting 8 weeks of therapy**
	1	Treatment-naive without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)	Harvoni, Ledipasvir/Sofosbuvir	12 weeks
	1	Treatment-experienced (i.e., patients who have failed therapy with either peg-interferon + ribavirin +/- an HCV protease inhibitor [e.g., boceprevir, paritaprevir, simeprevir, telaprevir]) without cirrhosis	Harvoni, Ledipasvir/Sofosbuvir	12 weeks
	1	Treatment-experienced (i.e., patients who have failed therapy with either peg-interferon + ribavirin +/- an HCV protease inhibitor [e.g., boceprevir,	Harvoni + ribavirin, Ledipasvir/Sofosbuvir + ribavirin	12 weeks

Module	Clinical Criteria for Approval			
		paritaprevir, simeprevir, telaprevir]) with compensated cirrhosis (Child-Turcotte-Pugh A) and eligible for ribavirin		
	1	Treatment-experienced (i.e., patients who have failed therapy with either peg-interferon + ribavirin +/- an HCV protease inhibitor [e.g., boceprevir, paritaprevir, simeprevir, telaprevir]) with compensated cirrhosis (Child-Turcotte-Pugh A) and ineligible for ribavirin (i.e., patients with a history of intolerance, contraindication, or hypersensitivity to ribavirin)	Harvoni, Ledipasvir/Sofosbuvir	24 weeks

Module	Clinical Criteria for Approval			
	1	Treatment-naive and treatment-experienced (i.e., patients who have failed therapy with either peg-interferon + ribavirin +/- an HCV protease inhibitor [e.g., boceprevir, paritaprevir, simeprevir, telaprevir]) with decompensated cirrhosis (Child-Turcotte-Pugh B or C)	Harvoni + ribavirin, Ledipasvir/Sofosbuvir + ribavirin	12 weeks
	1 or 4	Treatment-naive and treatment-experienced (i.e., patients who have failed therapy with either peg-interferon + ribavirin +/- an HCV protease inhibitor [e.g., boceprevir, paritaprevir, simeprevir, telaprevir]) liver transplant recipients without cirrhosis, or with	Harvoni + ribavirin, Ledipasvir/Sofosbuvir + ribavirin	12 weeks

Module	Clinical Criteria for Approval

	compensated cirrhosis (Child-Turcotte-Pugh A)		
4, 5, or 6	Treatment-naive and treatment-experienced (i.e., patients who have failed therapy with either peg-interferon + ribavirin +/- an HCV protease inhibitor [e.g., boceprevir, paritaprevir, simeprevir, telaprevir]) without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)	Harvoni, Ledipasvir/Sofosbuvir	12 weeks

*HCV/HIV-1 co-infection, follow recommendation in table above

Table 4: Harvoni or Ledipasvir/Sofosbuvir Decompensated Cirrhosis Treatment Recommendations based on AASLD Guidelines for unique populations

Genotype	Patients 3 years of age and older*	Treatment	Duration

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
<table>
<tr><td>1, 4, 5, or 6</td><td>Patients with decompensated cirrhosis (Child-Turcotte-Pugh B or C) AND are ribavirin ineligible (i.e., patients with history of intolerance, contraindication, or hypersensitivity to ribavirin)</td><td>Harvoni, Ledipasvir/Sofosbuvir</td><td>24 weeks</td></tr>
<tr><td>1, 4, 5, or 6</td><td>Patients with decompensated cirrhosis (Child-Turcotte-Pugh B or C) previously treated with sofosbuvir-based treatment failure</td><td>Harvoni + low initial dose of ribavirin (600 mg); increase as tolerated, Ledipasvir/Sofosbuvir + low initial dose of ribavirin (600 mg); increase as tolerated</td><td>24 weeks</td></tr>
</table>
*HCV/HIV-1 co-infection, follow recommendations in table above
</td></tr>
<tr><td>Mavyret</td><td>
<table>
<tr><th>Preferred Agents</th><th>Non-Preferred Agents</th><th>Applicable Formulary</th></tr>
<tr><td>Genotype 1

Epclusa (sofosbuvir/velpatasvir)
Harvoni (ledipasvir/sofosbuvir)
Ledipasvir/Sofosbuvir
Sofosbuvir/Velpatasvir
Mavyret (glecaprevir/pibrentasvir)</td><td>Genotype 1

Sovaldi (sofosbuvir)
Viekira PAK (ombitasvir/paritaprevir/ritonavir + dasabuvir)
Zepatier (elbasvir/grazoprevir)</td><td></td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval		
	Vosevi (sofosbuvir/velpatasvir/voxilaprevir)		
	Genotype 2 **Epclusa** (sofosbuvir/velpatasvir) **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 2** **Sovaldi** (sofosbuvir)	
	Genotype 3 **Epclusa** (sofosbuvir/velpatasvir) **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 3** **Sovaldi** (sofosbuvir)	
	Genotype 4 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 4** **Sovaldi** (sofosbuvir) **Zepatier** (elbasvir/grazoprevir)	
	Genotype 5 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 5**	
	Genotype 6 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir)	**Genotype 6**	

Module	Clinical Criteria for Approval
	Ledipasvir/Sofosbuvir **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has a diagnosis of hepatitis C genotype 1, 2, 3, 4, 5, or 6 **AND**
2. If the patient has an FDA labeled indication, then ONE of the following:
    A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**
    B. There is support for the use of the requested agent for the patient's age for the requested indication **AND**
3. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection **AND**
4. If the screening for HBV was positive for current or prior HBV infection, the prescriber will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent **AND**
5. If the client has preferred agent(s) for the patient's specific factors (e.g., age, genotype, cirrhosis status, treatment naive vs treatment experienced, previous treatment), then ONE of the following:
    A. The requested agent is a preferred agent for the patient's specific factors **OR**
    B. The patient has been treated with the requested non-preferred agent in the past 30 days **OR**
    C. The patient has an intolerance or hypersensitivity to ALL of the preferred agent(s) for the patient's specific factors **OR**
    D. The patient has an FDA labeled contraindication to ALL of the preferred agent(s) for the patient's specific factors **OR**
    E. There is support for the use of the requested non-preferred agent over the preferred agent(s) **AND**
6. ONE of the following:
    A. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, hepatologist, or infectious disease) or has consulted with a specialist in the area of the patient's diagnosis **OR**
    B. ALL of the following:
        1. The patient is treatment naive **AND**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
2. The patient does NOT have cirrhosis or has compensated cirrhosis AND
3. The requested agent is supported in AASLD guidelines for simplified treatment AND
4. The patient meets all of the qualifications for AASLD guidelines simplified treatment (please see Patients Who Qualify for Simplified Treatment tables below) AND

Patients Eligible for Simplified HCV Treatment Algorithm

Adults with chronic HCV infection, including persons living with HIV:
• Infected with any genotype
• Have NOT previously received HCV treatment
• Without cirrhosis OR with compensated cirrhosis (Child-Pugh A) as determined by:
  ○ Liver stiffness > 12.5 kPa by FibroScan
  ○ FIB-4 > 3.25
  ○ Noninvasive serologic test
  ○ Live biopsy
  ○ Live nodularity or splenomegaly on imaging
  ○ Platelet count < 150,000/mm^3

Patients Excluded from Simplified HCV Treatment Algorithm

Adults with chronic HCV infection:
• Previously received HCV treatment
• Hepatitis B surface antigen-positive Compensated cirrhosis (Child-Pugh A) with end-stage renal disease (i.e., eGFR less than 30 mL/min/m^2)
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</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>

Current or prior decompensated cirrhosis, defined by Child-Pugh score greater than or equal to 7
Current pregnancy
Known or suspected hepatocellular carcinoma
Prior liver transplantation

<ol start="7">
The patient has not been previously treated with the requested agent AND
The patient does NOT have any FDA labeled contraindications to the requested agent AND
The patient meets all requirements and will use the requested agent will in a treatment regimen noted in Table 5 (FDA labeling) AND
The requested length of therapy does NOT exceed the length of therapy noted in Table 5 (FDA labeling) for the patient’s treatment regimen

Length of Approval: Up to the duration of treatment as determined in Table 5.

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Table 5: Mavyret Treatment Recommendations based on FDA labeling
<table>
<tr><th>Genotype</th><th>Patient Population - adults and pediatric patients 3 years of age and older*+</th><th>Treatment</th><th>Duration - No Cirrhosis</th><th>Duration - Compensated Cirrhosis (Child-Turcotte-Pugh A)</th></tr>
<tr><td>1, 2, 3, 4, 5, or 6</td><td>Liver or kidney transplant recipients</td><td>Mavyret</td><td>12 weeks</td><td>12 weeks</td></tr>
<tr><td>1</td><td>Liver or kidney transplant recipients who are treatment</td><td>Mavyret</td><td>16 weeks</td><td>16 weeks</td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval				
		experienced with an NS5A inhibitor (e.g., daclatasvir, elbasvir, ledipasvir, ombitasvir, velpatasvir) but without prior treatment with an NS3/4A protease inhibitor (PI)			
	3	Liver or kidney transplant recipients who are treatment experienced with PRS (i.e., Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor)	Mavyret	16 weeks	16 weeks
	1, 2, 3, 4, 5, or 6	Treatment naive	Mavyret	8 weeks	8 weeks
	1	Treatment experienced with	Mavyret	16 weeks	16 weeks

Module	Clinical Criteria for Approval				
		an NS5A inhibitor (e.g., daclatasvir, elbasvir, ledipasvir, ombitasvir, velpatasvir) but without prior treatment with an NS3/4A protease inhibitor (PI)			
	1	Treatment experienced with an NS3/4A protease inhibitor (e.g., simeprevir, boceprevir, telaprevir) but without prior treatment with an NS5A inhibitor	Mavyret	12 weeks	12 weeks
	1, 2, 4, 5, or 6	Treatment experienced with PRS (i.e., Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A	Mavyret	8 weeks	12 weeks

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>PI or NS5A inhibitor)</td><td></td><td></td><td></td></tr>
<tr><td>3</td><td>Treatment experienced with PRS (i.e., Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor)</td><td>Mavyret</td><td>16 weeks</td><td>16 weeks</td></tr>
</table>
*HCV/HIV-1 co-infection, follow recommendations in the table above

+ Patients with any degree of kidney impairment (including those on hemodialysis), follow recommendations in the table above</td></tr>
<tr><td>Sovaldi</td><td>
<table>
<tr><th>Preferred Agents</th><th>Non-Preferred Agents</th><th>Applicable Formulary</th></tr>
<tr><td>Genotype 1

Epclusa (sofosbuvir/velpatasvir)
Harvoni (ledipasvir/sofosbuvir)
Ledipasvir/Sofosbuvir
Sofosbuvir/Velpatasvir
Mavyret (glecaprevir/pibrentasvir)</td><td>Genotype 1

Sovaldi (sofosbuvir)
Viekira PAK (ombitasvir/paritaprevir/ritonavir + dasabuvir)
Zepatier (elbasvir/grazoprevir)</td><td></td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval		
	Vosevi (sofosbuvir/velpatasvir/voxilaprevir)		
	Genotype 2 **Epclusa** (sofosbuvir/velpatasvir) **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 2** **Sovaldi** (sofosbuvir)	
	Genotype 3 **Epclusa** (sofosbuvir/velpatasvir) **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 3** **Sovaldi** (sofosbuvir)	
	Genotype 4 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 4** **Sovaldi** (sofosbuvir) **Zepatier** (elbasvir/grazoprevir)	
	Genotype 5 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 5**	
	Genotype 6 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir)	**Genotype 6**	

Module	Clinical Criteria for Approval
	Ledipasvir/Sofosbuvir **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   - A. The patient is a pediatric patient with a diagnosis of hepatocellular carcinoma secondary to chronic hepatitis C genotype 2 or 3 AND if the patient has an FDA labeled indication, ONE of the following:
     1. The patient's age is within FDA labeling for the requested agent for the requested indication **OR**
     2. There is support for using the requested agent for the patient's age for the requested indication **OR**
   - B. The patient is a pediatric patient with a diagnosis of hepatitis C genotype 2 or 3 AND ALL of the following:
     1. If the patient has an FDA labeled indication, then ONE of the following:
        - A. The patient's age is within FDA labeling for the requested agent for the requested indication **OR**
        - B. There is support for using the requested agent for the patient's age for the requested indication **AND**
     2. ONE of the following:
        - A. The patient has an intolerance or hypersensitivity to BOTH Epclusa and Mavyret **OR**
        - B. The patient has an FDA labeled contraindication to BOTH Epclusa and Mavyret **OR**
        - C. There is support for the use of the requested agent over BOTH Epclusa and Mavyret (e.g., the patient is currently taking the requested agent) **AND**
     3. ONE of the following:
        - A. The patient is treatment naïve **OR**
        - B. The patient was previously treated (i.e., treatment experienced) with ONLY peg-interferon and ribavirin **OR**
   - C. The patient is an adult and has a diagnosis of hepatocellular carcinoma secondary to chronic hepatitis C genotype 1, 2, 3, or 4 **OR**

Module	Clinical Criteria for Approval
	D. The patient is an adult with a diagnosis of hepatitis C genotype 1, 2, 3, or 4 AND BOTH of the following: 1. ONE of the following: A. The patient is treatment naïve **OR** B. The patient was previously treated (i.e., treatment experienced) with ONLY peg-interferon and ribavirin **AND** 2. If the client has preferred agent(s) for the patient's specific factors (e.g., age, genotype, cirrhosis status, treatment naïve vs treatment experienced, previous treatment), then ONE of the following: A. The patient has been treated with the requested non-preferred agent in the past 30 days **OR** B. The patient has an intolerance or hypersensitivity to ALL of the preferred agent(s) for the patient's specific factors **OR** C. The patient has an FDA labeled contraindication to ALL of the preferred agent(s) for the patient's specific factors **OR** D. There is support for the use of the requested non-preferred agent over the preferred agent(s) **AND** 2. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection **AND** 3. If the HBV screening was positive for current or prior HBV infection, the prescriber will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent **AND** 4. ONE of the following: A. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, hepatologist, infectious disease) or has consulted with a specialist in the area of the patient's diagnosis **OR** B. ALL of the following: 1. The patient is treatment naive **AND** 2. The patient does NOT have cirrhosis or has compensated cirrhosis **AND** 3. The requested agent is supported in AASLD guidelines for simplified treatment **AND** 4. The patient meets all the qualifications for AASLD guidelines simplified treatment (please see Patients Who Qualify for Simplified Treatment tables below) **AND**

Module	Clinical Criteria for Approval

	Patients Eligible for Simplified HCV Treatment
	
	Adults with chronic HCV infection, including persons living with HIV:
	
	• Infected with any genotype
	• Have NOT previously recieved HCV treatment
	• Without cirrhosis OR with compensated cirrhosis (Child-Pugh A) as deteremined by:
	  ○ Liver stiffness > 12.5 kPa by FibroScan
	  ○ FIB-4 > 3.25
	  ○ Noninvasive serologic test
	  ○ Live biopsy
	  ○ Live nodularity or splenomeglaly on imaging
	  ○ Platelet count < 150,000/mm^3
	
	Patients Excluded from Simplified HCV Treatment
	
	Adults with chronic HCV infection:
	
	• Previoulsy received HCV treatment
	• Hepatitis B surface antigen-positive
	• Compensated crirhosis (Child-Pugh A) with end-stage renal disease (i.e., eGFR less than 30 mL/min/m^2)
	• Current or prior decompensated cirrhosis, defined by Child-Pugh score greater than or equal to 7
	• Current pregnancy
	• Known or suspected hepatocellular carcinoma
	• Prior liver transplantation

Module	Clinical Criteria for Approval

5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND**
6. The patient meets all requirements and will use the requested agent will in a treatment regimen noted in Table 6 or 7 (FDA labeling) **AND**
7. The requested length of therapy does NOT exceed the length of therapy noted in Table 6 or 7 (FDA labeling) for the patient's treatment regimen

Length of Approval: Up to the duration of treatment as determined in Table 6 or 7.

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Table 6: Sovaldi Treatment Recommendations in Adult Patients with Genotype 1, 2, 3, or 4 Based on FDA Labeling

Genotype	Patient population*	Treatment	Duration
1 or 4	Treatment naïve without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)	Sovaldi + Peg-interferon alfa + ribavirin	12 weeks
1	Treatment naïve without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A) and are interferon ineligible defined as one or more of the following: • Intolerance to interferon • Autoimmune hepatitis and other autoimmune disorders	Sovaldi + ribavirin	24 weeks

Module	Clinical Criteria for Approval			
		• Hypersensitivity to PEG interferon or any of its components • Decompensated hepatic disease • Major uncontrolled depressive illness • A baseline neutrophil count below 1500/µL • A baseline platelet count below 90,000/µL • A baseline hemoglobin below 10 g/dL • A history of preexisting cardiac disease)		
	2	Treatment naïve or treatment experienced (i.e., patients who have failed an interferon based regimen with or without ribavirin) without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)	Sovaldi + ribavirin	12 weeks
	3	Treatment naïve or treatment experienced (i.e., patients who have	Sovaldi + ribavirin	24 weeks

Module	Clinical Criteria for Approval

	failed an interferon based regimen with or without ribavirin) without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)		
1-4	With hepatocellular carcinoma awaiting liver transplantation	Sovaldi + ribavirin	Up to 48 weeks

*HCV/HIV-1 co-infection, follow recommendations in table above

Table 7: Sovaldi and Ribavirin with or without Peg-interferon Treatment Recommendations for Pediatric Patients 3 Years of Age and Older Based on FDA Labeling

Genotype	Patient population*	Treatment	Duration
2	Treatment naïve and treatment experienced (i.e., patients who have failed an interferon-based regimen with or without ribavirin) without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)	Sovaldi + ribavirin	12 weeks
3	Treatment naïve and treatment experienced (i.e., patients who have failed an	Sovaldi + ribavirin	24 weeks

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>interferon-based regimen with or without ribavirin) without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)</td><td></td><td></td></tr>
<tr><td>2 or 3</td><td>Pediatric patients with hepatocellular carcinoma awaiting liver transplantation</td><td>Sovaldi + ribavirin</td><td>48 weeks</td></tr>
</table>
*HCV/HIV-1 co-infection, follow recommendations in table above
</td></tr>
<tr><td>Viekira Pak</td><td>
<table>
<tr><th>Preferred Agents</th><th>Non-Preferred Agents</th><th>Applicable Formulary</th></tr>
<tr><td>Genotype 1

Epclusa (sofosbuvir/velpatasvir
Harvoni (ledipasvir/sofosbuvir)
Ledipasvir/Sofosbuvir
Sofosbuvir/Velpatasvir
Mavyret (glecaprevir/pibrentasvir)
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)</td><td>Genotype 1

Sovaldi (sofosbuvir)
Viekira PAK (ombitasvir/paritaprevir/ritonavir + dasabuvir)
Zepatier (elbasvir/grazoprevir)</td><td></td></tr>
<tr><td>Genotype 2

Epclusa (sofosbuvir/velpatasvir)
Sofosbuvir/Velpatasvir
Mavyret (glecaprevir/pibrentasvir)
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)</td><td>Genotype 2

Sovaldi (sofosbuvir)</td><td></td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval

Genotype 3 **Epclusa** (sofosbuvir/velpatasvir) **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 3** **Sovaldi** (sofosbuvir)	
Genotype 4 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 4** **Sovaldi** (sofosbuvir) **Zepatier** (elbasvir/grazoprevir)	
Genotype 5 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 5**	
Genotype 6 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 6**	

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has a diagnosis of hepatitis C genotype 1 **AND**
2. The prescriber has provided the patient's subtype **AND**

Module	Clinical Criteria for Approval
	3. ONE of the following: A. The patient is treatment naive **OR** B. The patient was previously treated (i.e., treatment experienced) with ONLY peg-interferon and ribavirin **AND** 4. If the patient has an FDA labeled indication, ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for the use of the requested agent for the patient's age for the requested indication **AND** 5. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection **AND** 6. If the screening for HBV was positive for current or prior HBV infection, the prescriber will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent **AND** 7. If the client has preferred agent(s) for the patient's specific factors (e.g., age, genotype, cirrhosis status, treatment naive vs treatment experienced, previous treatment), then ONE of the following: A. The patient has been treated with the requested non-preferred agent in the past 30 days **OR** B. The patient has an intolerance or hypersensitivity to ALL of the preferred agent(s) for the patient's specific factors **OR** C. The patient has an FDA labeled contraindication to ALL of the preferred agent(s) for the patient's specific factors **OR** D. There is support for the use of the requested non-preferred agent over the preferred agent(s) **AND** 8. ONE of the following: A. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, hepatologist, or infectious disease) or has consulted with a specialist in the area of the patient's diagnosis **OR** B. ALL of the following: 1. The patient is treatment naive **AND** 2. The patient does NOT have cirrhosis or has compensated cirrhosis **AND** 3. The requested agent is supported in AASLD guidelines for simplified treatment **AND** 4. The patient meets all the qualifications for AASLD guidelines simplified treatment (please see Patients Who Qualify for Simplified Treatment tables below) **AND**

Module	Clinical Criteria for Approval

	Patients Eligible for Simplified HCV Treatment
	
	Adults with chronic HCV infection, including persons living with HIV:
	
	• Infected with any genotype
	• Have NOT previously received HCV treatment
	• Without cirrhosis OR with compensated cirrhosis (Child-Pugh A) as determined by:
	  ○ Liver stiffness > 12.5 kPa by FibroScan
	  ○ FIB-4 > 3.25
	  ○ Noninvasive serologic test
	  ○ Live biopsy
	  ○ Live nodularity or splenomegaly on imaging
	  ○ Platelet count < 150,000/mm^3
	
	Patients Excluded from Simplified HCV Treatment
	
	Adults with chronic HCV infection:
	
	• Previously received HCV treatment
	• Hepatitis B surface antigen-positive
	• Compensated cirrhosis (Child-Pugh A) with end-stage renal disease (i.e., eGFR less than 30 mL/min/m^2)
	• Current or prior decompensated cirrhosis, defined by Child-Pugh score greater than or equal to 7
	• Current pregnancy
	• Known or suspected hepatocellular carcinoma
	• Prior liver transplantation

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
9. The patient does NOT have any FDA labeled contraindications to the requested agent AND
10. The patient meets all requirements and will use the requested agent in a treatment regimen noted in Table 8 (FDA labeling) AND
11. The requested length of therapy does NOT exceed the length of therapy noted in Table 8 (FDA labeling) for the patient's treatment regimen

Length of Approval: Up to the duration as determined in Table 8.

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Table 8: Viekira PAK Treatment Recommendations based on FDA labeling:
<table>
<tr><th>Genotype</th><th>Patient Population*</th><th>Treatment</th><th>Duration</th></tr>
<tr><td>1a</td><td>Without cirrhosis</td><td>Viekira PAK + ribavirin</td><td>12 weeks</td></tr>
<tr><td>1a</td><td>With compensated cirrhosis</td><td>Viekira PAK + ribavirin</td><td>24 weeks</td></tr>
<tr><td>1b</td><td>With or without compensated cirrhosis</td><td>Viekira PAK</td><td>12 weeks</td></tr>
<tr><td>1a or 1b</td><td>Post liver transplant with normal hepatic function (i.e., Metavir less than or equal to 2)</td><td>Viekira PAK + ribavirin</td><td>24 weeks</td></tr>
</table>
*HCV/HIV-1 co-infection, follow recommendations in table above
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td>Vosevi</td><td>
<table>
<tr><th>Preferred Agents</th><th>Non-Preferred Agents</th><th>Applicable Formulary</th></tr>
<tr><td>Genotype 1

Epclusa (sofosbuvir/velpatasvir
Harvoni (ledipasvir/sofosbuvir)
Ledipasvir/Sofosbuvir
Sofosbuvir/Velpatasvir
Mavyret (glecaprevir/pibrentasvir)
Vosevi
(sofosbuvir/velpatasvir/voxilaprevir)</td><td>Genotype 1

Sovaldi (sofosbuvir)
Viekira PAK
(ombitasvir/paritaprevir/ritonavir + dasabuvir)
Zepatier (elbasvir/grazoprevir)</td><td></td></tr>
<tr><td>Genotype 2

Epclusa (sofosbuvir/velpatasvir)
Sofosbuvir/Velpatasvir
Mavyret (glecaprevir/pibrentasvir)
Vosevi
(sofosbuvir/velpatasvir/voxilaprevir)</td><td>Genotype 2

Sovaldi (sofosbuvir)</td><td></td></tr>
<tr><td>Genotype 3

Epclusa (sofosbuvir/velpatasvir)
Sofosbuvir/Velpatasvir
Mavyret (glecaprevir/pibrentasvir)
Vosevi
(sofosbuvir/velpatasvir/voxilaprevir)</td><td>Genotype 3

Sovaldi (sofosbuvir)</td><td></td></tr>
<tr><td>Genotype 4

Epclusa (sofosbuvir/velpatasvir)
Harvoni (ledipasvir/sofosbuvir)
Ledipasvir/Sofosbuvir
Sofosbuvir/Velpatasvir
Mavyret (glecaprevir/pibrentasvir)
Vosevi
(sofosbuvir/velpatasvir/voxilaprevir)</td><td>Genotype 4

Sovaldi (sofosbuvir)
Zepatier (elbasvir/grazoprevir)</td><td></td></tr>
<tr><td>Genotype 5</td><td>Genotype 5</td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
<table>
<tr><td>Epclusa (sofosbuvir/velpatasvir)
Harvoni (ledipasvir/sofosbuvir)
Ledipasvir/Sofosbuvir
Sofosbuvir/Velpatasvir
Mavyret (glecaprevir/pibrentasvir)
Vosevi
(sofosbuvir/velpatasvir/voxilaprevir)</td><td></td><td></td></tr>
<tr><td>Genotype 6

Epclusa (sofosbuvir/velpatasvir)
Harvoni (ledipasvir/sofosbuvir)
Ledipasvir/Sofosbuvir
Sofosbuvir/Velpatasvir
Mavyret (glecaprevir/pibrentasvir)
Vosevi
(sofosbuvir/velpatasvir/voxilaprevir)</td><td>Genotype 6</td><td></td></tr>
</table>
Target Agent(s) will be approved when ALL of the following are met:

1. The patient has a diagnosis of hepatitis C genotype 1, 2, 3, 4, 5, or 6 AND
2. If genotype 1, the prescriber has provided the patient’s subtype AND
3. The patient is NOT treatment naive AND
4. The patient has NOT been previously treated with the requested agent AND
5. If the patient has an FDA labeled indication, then ONE of the following:
A. The patient’s age is within FDA labeling for the requested indication for the requested agent OR
B. There is support for the use of the requested agent for the patient’s age for the requested indication AND
6. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection AND
7. If the screening for HBV was positive for current or prior HBV infection, the prescriber will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent AND
8. If the client has preferred agent(s) for the patient’s specific factors (e.g., age, genotype, cirrhosis status, treatment naive vs treatment experienced, previous treatment), then ONE of the following:
A. The patient has been treated with the requested non-preferred agent in the past 30 days OR
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</table>

Module	Clinical Criteria for Approval
	B. The patient has an intolerance or hypersensitivity to ALL of the preferred agent(s) for the patient's specific factors **OR** C. The patient has an FDA labeled contraindication to ALL of the preferred agent(s) for the patient's specific factors **OR** D. There is support for the use of the requested non-preferred agent over the preferred agent(s) **AND** 9. ONE of the following: A. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, hepatologist, or infectious disease) or has consulted with a specialist in the area of the patient's diagnosis **OR** B. ALL of the following: 1. The patient is treatment naive **AND** 2. The patient does NOT have cirrhosis or has compensated cirrhosis **AND** 3. The requested agent is supported in AASLD guidelines for simplified treatment **AND** 4. The patient meets all the qualifications for AASLD guidelines simplified treatment (please see Patients Who Qualify for Simplified Treatment tables below) **AND** **Patients Eligible for Simplified HCV Treatment** Adults with chronic HCV infection, including persons living with HIV: • Infected with any genotype • Have NOT previously received HCV treatment • Without cirrhosis OR with compensated cirrhosis (Child-Pugh A) as deteremined by: ○ Liver stiffness > 12.5 kPa by FibroScan ○ FIB-4 > 3.25 ○ Noninvasive serologic test ○ Live biopsy ○ Live nodularity or splenomegaly on imaging

Module	Clinical Criteria for Approval
	○ Platelet count < 150,000/mm^3
	Patients Excluded from Simplified HCV Treatment
	Adults with chronic HCV infection: • Previously received HCV treatment • Hepatitis B surface antigen-positive • Compensated crirhosis (Child-Pugh A) with end-stage renal disease (i.e., eGFR less than 30 mL/min/m^2) • Current or prior decompensated cirrhosis, defined by Child-Pugh score greater than or equal to 7 • Current pregnancy • Known or suspected hepatocellular carcinoma • Prior liver transplantation
	10. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 11. The patient meets all requirements and will use the requested agent in a treatment regimen noted in Table 9 **AND** 12. The requested length of therapy does NOT exceed the length of therapy noted in Table 9 (FDA labeling) for the patient's regimen **Length of Approval**: Up to the duration of treatment as determined in Table 9. NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Table 9: Vosevi Treatment Recommendations based on FDA labeling**

Genotype	Patient Population*	Patients Previously Treated with an	Duration

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td></td><td>HCV Regimen containing:</td><td></td></tr>
<tr><td>1, 2, 3, 4, 5, or 6</td><td>Without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)</td><td>An NS5A inhibitor (e.g., daclatasvir, elbasvir, ledipasvir, ombitasvir, velpatasvir)</td><td>12 weeks</td></tr>
<tr><td>1a or 3</td><td>Without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)</td><td>Sofosbuvir without an NS5A inhibitor+</td><td>12 weeks</td></tr>
</table>
*HCV/HIV-1 co-infection, follow recommendations in table above
+ - Sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (simeprevir)
</td></tr>
<tr><td>Zepatier</td><td>
<table>
<tr><th>Preferred Agents</th><th>Non-Preferred Agents</th><th>Applicable Formulary</th></tr>
<tr><td>Genotype 1

Epclusa (sofosbuvir/velpatasvir
Harvoni (ledipasvir/sofosbuvir)
Ledipasvir/Sofosbuvir
Sofosbuvir/Velpatasvir
Mavyret (glecaprevir/pibrentasvir)
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)</td><td>Genotype 1

Sovaldi (sofosbuvir)
Viekira PAK (ombitasvir/paritaprevir/ritonavir + dasabuvir)
Zepatier (elbasvir/grazoprevir)</td><td></td></tr>
<tr><td>Genotype 2</td><td>Genotype 2

Sovaldi (sofosbuvir)</td><td></td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval		
	Epclusa (sofosbuvir/velpatasvir) **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)		
	Genotype 3 **Epclusa** (sofosbuvir/velpatasvir) **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 3** **Sovaldi** (sofosbuvir)	
	Genotype 4 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 4** **Sovaldi** (sofosbuvir) **Zepatier** (elbasvir/grazoprevir)	
	Genotype 5 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 5**	
	Genotype 6 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 6**	

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The patient has a diagnosis of hepatitis C genotype 1 or 4 **AND** 2. BOTH of the following: A. If genotype 1, the prescriber has provided the patient's subtype **AND** B. If the subtype 1a, the prescriber has tested the patient for NS5A polymorphisms **AND** 3. ONE of the following: A. The patient is treatment naïve **OR** B. The patient was previously treated (i.e., treatment experienced) with ONLY peg-interferon and ribavirin with or without an HCV protease inhibitor **AND** 4. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for the use of the requested agent for the patient's age for the requested indication **AND** 5. The prescriber has screened the patient for current or prior hepatitis B viral (HBV) infection **AND** 6. If the screening for HBV was positive for current or prior HBV infection, the prescriber will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent **AND** 7. If the client has preferred agent(s) for the patient's specific factors (e.g., age, genotype, cirrhosis status, treatment naïve vs treatment experienced, previous treatment), then ONE of the following: A. The patient has been treated with the requested non-preferred agent in the past 30 days **OR** B. The patient has an intolerance or hypersensitivity to ALL of the preferred agent(s) for the patient's specific factors **OR** C. The patient has FDA labeled contraindication to ALL of the preferred agent(s) for the patient's specific factors **OR** D. There is support for the use of the requested non-preferred agent over the preferred agent(s) **AND** 8. ONE of the following: A. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, hepatologist, or infectious disease) or has consulted with a specialist in the area of the patient's diagnosis **OR** B. ALL of the following: 1. The patient is treatment naive **AND**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>2. The patient does NOT have cirrhosis or has compensated cirrhosis AND
3. The requested agent is supported in AASLD guidelines for simplified treatment AND
4. The patient meets all the qualifications for AASLD guidelines simplified treatment (please see Patients Who Qualify for Simplified Treatment tables below) AND

Patients Eligible for Simplified Treatment

Adults with chronic HCV infection, including persons living with HIV:

• Infected with any genotype
• Have NOT previously received HCV treatment
• Without cirrhosis OR with compensated cirrhosis (Child-Pugh A) as determined by:
○ Liver stiffness > 12.5 kPa by FibroScan
○ FIB-4 > 3.25
○ Noninvasive serologic test
○ Live biopsy
○ Live nodularity or splenomegaly on imaging
○ Platelet count < 150,000/mm^3

Patients Excluded from Simplified HCV Treatment

Adults with chronic HCV infection:

• Previously received HCV treatment
• Hepatitis B surface antigen-positive
• Compensated cirrhosis (Child-Pugh A) with end-stage renal disease (i.e., eGFR less than 30 mL/min/m^2)</td></tr>
</table>

Module	Clinical Criteria for Approval

- Current or prior decompensated cirrhosis, defined by Child-Pugh score greater than or equal to 7
- Current pregnancy
- Known or suspected hepatocellular carcinoma
- Prior liver transplantation

9. The patient does NOT have any FDA labeled contraindications to the requested agent **AND**
10. The patient meets all requirements and will use the requested agent in a treatment regimen noted in Table 10 (FDA labeling) **AND**
11. The requested length of therapy does NOT exceed the length of therapy noted in Table 10 (FDA labeling) for the patient's treatment regimen

Length of Approval: Up to the duration of treatment as determined in Table 10

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Table 10: Zepatier Treatment Recommendations based on FDA labeling

Genotype	Patient Population*	Treatment	Duration
1a	Treatment-naïve or PegIFN/RBV-experienced without baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93	Zepatier	12 weeks
1a	Treatment-naïve or PegIFN/RBV-experienced with baseline NS5A polymorphisms at	Zepatier + ribavirin	16 weeks

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>amino acid positions 28, 30, 31, or 93</td><td></td><td></td></tr>
<tr><td>1b</td><td>Treatment-naïve or PegIFN/RBV-experienced</td><td>Zepatier</td><td>12 weeks</td></tr>
<tr><td>1a or 1b</td><td>PegIFN/RBV/protease inhibitor-experienced</td><td>Zepatier + ribavirin</td><td>12 weeks</td></tr>
<tr><td>4</td><td>Treatment-naive</td><td>Zepatier</td><td>12 weeks</td></tr>
<tr><td>4</td><td>PegIFN/RBV-experienced</td><td>Zepatier + ribavirin</td><td>16 weeks</td></tr>
</table>
*HCV/HIV-1 co-infection, follow dosage recommendations in the table above
</td></tr>
<tr><td>New to Market Hepatitis C Agents</td><td>
<table>
<tr><th>Preferred Agents</th><th>Non-Preferred Agents</th><th>Applicable Formulary</th></tr>
<tr><td>Genotype 1

Epclusa (sofosbuvir/velpatasvir
Harvoni (ledipasvir/sofosbuvir)
Ledipasvir/Sofosbuvir
Sofosbuvir/Velpatasvir
Mavyret (glecaprevir/pibrentasvir)
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)</td><td>Genotype 1

Sovaldi (sofosbuvir)
Viekira PAK (ombitasvir/paritaprevir/ritonavir + dasabuvir)
Zepatier (elbasvir/grazoprevir)</td><td></td></tr>
<tr><td>Genotype 2

Epclusa (sofosbuvir/velpatasvir)
Sofosbuvir/Velpatasvir
Mavyret (glecaprevir/pibrentasvir)
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)</td><td>Genotype 2

Sovaldi (sofosbuvir)</td><td></td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval

Genotype 3 **Epclusa** (sofosbuvir/velpatasvir) **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 3** **Sovaldi** (sofosbuvir)	
Genotype 4 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 4** **Sovaldi** (sofosbuvir) **Zepatier** (elbasvir/grazoprevir)	
Genotype 5 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 5**	
Genotype 6 **Epclusa** (sofosbuvir/velpatasvir) **Harvoni** (ledipasvir/sofosbuvir) **Ledipasvir/Sofosbuvir** **Sofosbuvir/Velpatasvir** **Mavyret** (glecaprevir/pibrentasvir) **Vosevi** (sofosbuvir/velpatasvir/voxilaprevir)	**Genotype 6**	

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has an FDA labeled diagnosis for the requested agent **AND**
2. The requested agent is FDA labeled for treatment of the patient's genotype **AND**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
3. If the patient has an FDA labeled indication, then ONE of the following:
A. The patient's age is within FDA labeling for the requested indication for the requested agent OR
B. There is support for the use of the requested agent for the patient's age for the requested indication AND
4. If FDA labeling for the requested agent requires patients are tested for hepatitis B viral (HBV) infection prior to starting treatment with the requested agent BOTH of the following
A. The prescriber has screened the patient for current or prior HBV AND
B. If the HBV screening was positive for current or prior HBV infection, the prescriber will monitor the patient for HBV flare-up or reactivation during and after treatment with the requested agent AND
5. The patient does NOT have any FDA labeled contraindications to the requested agent AND
6. ONE of the following:
A. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, hepatologist, or infectious disease) or has consulted with a specialist in the area of the patient's diagnosis OR
B. ALL of the following:
1. The patient is treatment naive AND
2. The patient does NOT have cirrhosis or has compensated cirrhosis AND
3. The requested agent is supported in AASLD guidelines for simplified treatment AND
4. The patient meets all the qualifications for AASLD guidelines simplified treatment (please see Patients Who Qualify for Simplified Treatment tables below) AND
<table>
<tr><th>Patients Eligible for Simplified HCV Treatment</th></tr>
<tr><td>Adults with chronic HCV infection, including persons living with HIV:
• Infected with any genotype
• Have NOT previously received HCV treatment
• Without cirrhosis OR with compensated cirrhosis (Child-Pugh A) as determined by:</td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval
	○ Liver stiffness > 12.5 kPa by FibroScan ○ FIB-4 > 3.25 ○ Noninvasive serologic test ○ Live biopsy ○ Live nodularity or splenomegaly on imaging ○ Platelet count < 150,000/mm^3
	Patients Excluded from Simplified HCV Treatment
	Adults with chronic HCV infection: • Previously received HCV treatment • Hepatitis B surface antigen-positive • Compensated cirrhosis (Child-Pugh A) with end-stage renal disease (i.e., eGFR less than 30 mL/min/m^2) • Current or prior decompensated cirrhosis, defined by Child-Pugh score greater than or equal to 7 • Current pregnancy • Known or suspected hepatocellular carcinoma • Prior liver transplantation
	7. If the client has preferred agent(s) for the patient's specific factors (e.g., age, genotype, cirrhosis status, treatment naive vs treatment experienced, previous treatment), then ONE of the following: A. The requested agent is a preferred agent for the patient's specific factors (e.g., age, genotype, cirrhosis status, treatment naive vs treatment experienced, previous treatment) **OR** B. The patient has been treated with the requested non-preferred agent in the past 30 days **OR** C. The patient has an intolerance or hypersensitivity to ALL of the preferred agent(s) for the patient's specific factors (e.g., age, genotype, cirrhosis status, treatment naive vs treatment experienced, previous treatment) **OR**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
D. The patient has an FDA labeled contraindication to ALL of the preferred agent(s) for the patient's specific factors (e.g., age, genotype, cirrhosis status, treatment naive vs treatment experienced, previous treatment) OR
E. There is support for the use of the requested non-preferred agent over the preferred agent(s) AND
8. The patient meets all requirements and will use the requested agent in a treatment regimen noted in Table 11 (FDA labeling) AND
9. The requested length of therapy does NOT exceed the length of therapy noted in Table 11 (FDA labeling) for the patient's treatment regimen

Length of Approval: Up to the duration of treatment as determined in Table 11.

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Table 11: Treatment Recommendations based on FDA labeling
<table>
<tr><th>Agent(s)</th><th>FDA labeled indication(s)</th><th>Genotype</th><th>Treatment Regimen</th><th>FDA labeled dose</th><th>Duration</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
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</table>
</td></tr>
</table>

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td>Epclusa and Sofosbuvir/ Velpatasvir</td><td>
Quantity Limit for the Target Agent(s) will be approved when BOTH of the following are met:

1. The requested length of therapy does NOT exceed the length of therapy noted in Table 1 (FDA labeling) or 2 (AASLD/IDSA guidelines for decompensated cirrhosis) for the patient's treatment regimen AND
2. ONE of the following:
A. The requested quantity (dose) does NOT exceed the program quantity limit OR
B. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following:
1. The requested agent is Epclusa 200 mg/50 mg packets AND BOTH of the following:
A. The requested quantity (dose) does NOT exceed 2 packets per day AND
B. There is support for why the patient cannot take 1 tablet of the 400 mg/100 mg tablet OR
2. The requested agent is Epclusa 200 mg/50 mg tablet AND BOTH of the following:
1. The requested quantity (dose) does NOT exceed 2 tablets per day AND
2. There is support for why the patient cannot take 1 tablet of the 400 mg/100mg tablet

Length of Approval: Up to the duration of treatment as determined in Tables 1 or 2.

Table 1: Epclusa or Sofosbuvir/Velpatasvir Treatment Recommendations based on FDA labeling
<table>
<tr><th>Genotype</th><th>Patients 3 yearrs of age and older*</th><th>Treatment</th><th>Duration</th></tr>
<tr><td>1,2, 3, 4, 5, or 6</td><td>Patients without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)</td><td>Epclusa, Sofosbuvir/Velpatasvir</td><td>12 weeks</td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval

1, 2, 3, 4, 5, or 6	Patients with decompensated cirrhosis (Child-Turcotte-Pugh B and C)	Epclusa + ribavirin, Sofosbuvir/Velpatasvir + ribavirin	12 weeks

*HCV/HIV-1 co-infection, follow recommendations in table above

Table 2: Epclusa or Sofosbuvir/Velpatasvir Decompensated Cirrhosis Treatment Recommendations based on AASLD/IDSA Guidelines for Unique populations

Genotype	Patient population*	Treatment	Duration
1, 2, 3, 4, 5, or 6	Patients with decompensated cirrhosis (Child-Turcotte-Pugh B and C) who are ribavirin ineligible (i.e., patients with history of intolerance, contraindication, or hypersensitivity to ribavirin)	Epclusa, Sofosbuvir/Velpatasvir	24 weeks
1, 2, 3, 4, 5, or 6	Patients with decompensated cirrhosis (Child-Turcotte-Pugh B and C) in whom prior sofosbuvir- or NS5A inhibitor (e.g., daclatasvir, elbasvir, ledipasvir,	Epclusa with weight-based ribavirin (low initial dose of ribavirin [600 mg] is recommended for patients with Child-Turcotte-Pugh class C cirrhosis), Sofsobuvir/Velpatasvir with weight-based ribavirin (low initial dose of ribavirin [600 mg] is recommended for patients	24 weeks

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>ombitasvir, velpatasvir) - based treatment failed</td><td>with Child-Turcotte-Pugh class C cirrhosis)</td><td></td></tr>
</table>
*HCV/HIV-1 co-infection, follow recommendations in table above
</td></tr>
<tr><td>Harvoni and Ledipasvir/ Sofosbuvir</td><td>
Quantity Limit for the Target Agent(s) will be approved when BOTH of the following are met:

1. The requested length of therapy does NOT exceed the length of therapy noted in Table 3 (FDA labeling) or 4 (AASLD/IDSA guidelines for decompensated cirrhosis) for the patient’s treatment regimen AND
2. ONE of the following:
A. The requested quantity (dose) does NOT exceed the program quantity limit OR
B. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following:
1. The requested agent is Harvoni 45 mg/200 mg oral pellets AND BOTH of the following:
A. The requested quantity (dose) does NOT exceed 2 packets daily AND
B. There is support for why the patient cannot take 1 tablet of Harvoni 90 mg/400 mg strength OR
2. The requested agent is Harvoni 45 mg/200 mg tablet AND BOTH of the following:
A. The requested quantity (dose) does NOT exceed 2 tablets daily AND
B. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit

Length of Approval: Up to the duration of treatment as determined in Table 3 or 4.

Table 3: Harvoni or Ledipasvir/Sofosbuvir Treatment Recommendations based on FDA labeling
<table>
<tr><th>Genotype</th><th>Patients 3 years of age and older*</th><th>Treatment</th><th>Treatment Duration</th></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval			
	1	Treatment-naïve with initial viral load of less than 6 M IU/mL and without cirrhosis, HIV infection, history of liver transplantation and/or are not black or African-American	Harvoni, Ledipasvir/Sofosbuvir	8 weeks NOTE approve 8 weeks length of therapy only if prescriber is requesting 8 weeks of therapy
	1	Treatment-naïve without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)	Harvoni, Ledipasvir/Sofosbuvir	12 weeks
	1	Treatment-experienced (i.e., patients who have failed therapy with either peg-interferon + ribavirin +/- an HCV protease inhibitor [e.g., boceprevir, paritaprevir, simeprevir, telaprevir]) without cirrhosis	Harvoni, Ledipasvir/Sofosbuvir	12 weeks
	1	Treatment-experienced (i.e., patients who have failed	Harvoni + ribavirin, Ledipasvir/Sofosbuvir + ribavirin	12 weeks

Module	Clinical Criteria for Approval			
		therapy with either peg-interferon + ribavirin +/- an HCV protease inhibitor [e.g., boceprevir, paritaprevir, simeprevir, telaprevir]) with compensated cirrhosis (Child-Turcotte-Pugh A) and eligible for ribavirin		
	1	Treatment-experienced (i.e., patients who have failed therapy with either peg-interferon + ribavirin +/- an HCV protease inhibitor [e.g., boceprevir, paritaprevir, simeprevir, telaprevir]) with compensated cirrhosis (Child-Turcotte-Pugh A) and ineligible for ribavirin (i.e., patients with a history of intolerance, contraindication,	Harvoni, Ledipasvir/Sofosbuvir	24 weeks

Module	Clinical Criteria for Approval			
		or hypersensitivity to ribavirin)		
	1	Treatment-naïve and treatment-experienced (i.e., patients who have failed therapy with either peg-interferon + ribavirin +/- an HCV protease inhibitor [e.g., boceprevir, paritaprevir, simeprevir, telaprevir]) with decompensated cirrhosis (Child-Turcotte-Pugh B or C)	Harvoni + ribavirin, Ledipasvir/Sofosbuvir + ribavirin	12 weeks
	1 or 4	Treatment-naïve and treatment-experienced (i.e., patients who have failed therapy with either peg-interferon + ribavirin +/- an HCV protease inhibitor [e.g., boceprevir, paritaprevir, simeprevir, telaprevir]) liver	Harvoni + ribavirin, Ledipasvir/Sofosbuvir + ribavirin	12 weeks

Module	Clinical Criteria for Approval			
		transplant recipients without cirrhosis, or with compensated cirrhosis (Child-Turcotte-Pugh A)		
	4, 5, or 6	Treatment-naïve and treatment-experienced (i.e., patients who have failed therapy with either peg-interferon + ribavirin +/- an HCV protease inhibitor [e.g., boceprevir, paritaprevir, simeprevir, telaprevir]) without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)	Harvoni, Ledipasvir/Sofosbuvir	12 weeks

*HCV/HIV-1 co-infection, follow recommendation in table above

Table 4: Harvoni or Ledipasvir/Sofosbuvir Decompensated Cirrhosis Treatment Recommendations based on AASLD Guidelines for unique populations

Genotype	Patients 3 years of age and older*	Treatment	Treatment Duration

<table>
<tr><th>Module</th><th colspan="4">Clinical Criteria for Approval</th></tr>
<tr><td></td><td colspan="4"><table>
<tr><td>1, 4, 5, or 6</td><td>Patients with decompensated cirrhosis (Child-Turcotte-Pugh B or C) AND are ribavirin ineligible (i.e., patients with history of intolerance, contraindication, or hypersensitivity to ribavirin)</td><td>Harvoni, Ledipasvir/Sofosbuvir</td><td>24 weeks</td></tr>
<tr><td>1, 4, 5, or 6</td><td>Patients with decompensated cirrhosis (Child-Turcotte-Pugh B or C) previously treated with sofosbuvir-based treatment failure</td><td>Harvoni + low initial dose of ribavirin (600 mg); increase as tolerated, Ledipasvir/Sofosbuvir + low initial dose of ribavirin (600 mg); increase as tolerated</td><td>24 weeks</td></tr>
<tr><td colspan="4"></td></tr>
</table></td></tr>
<tr><td>Mavyret</td><td colspan="4">Quantity Limit for the Target Agent(s) will be approved when BOTH of the following are met:

1. The requested length of therapy does NOT exceed the length of therapy noted in Table 5 (FDA labeling) for the patient’s treatment regimen AND
2. ONE of the following:
A. The requested quantity (dose) does NOT exceed the program quantity limit OR
B. The requested quantity (dose) exceeds the program quantity limit AND ALL of the following:
1. The requested agent is Mavyret 50 mg/20 mg packets AND
2. The requested quantity (dose) does NOT exceed 6 packets per day AND</td></tr>
</table>

Module	Clinical Criteria for Approval

3. There is support for why the patient cannot take 3 tablets of the 100 mg/40 mg tablet

Length of Approval: Up to the duration of treatment as determined in Table 5.

Table 5: Mavyret Treatment Recommendations based on FDA labeling

Genotype	Patient Population - adults and pediatric patients 3 years of age and older*+	Treatment	Duration - No Cirrhosis	Duration - Compensated Cirrhosis (Child-Turcotte-Pugh A)
1, 2, 3, 4, 5, or 6	Liver or kidney transplant recipients	Mavyret	12 weeks	12 weeks
1	Liver or kidney transplant recipients who are treatment experienced with an NS5A inhibitor (e.g., daclatasvir, elbasvir, ledipasvir, ombitasvir, velpatasvir) but without prior treatment with an NS3/4A protease inhibitor (PI)	Mavyret	16 weeks	16 weeks

Module	Clinical Criteria for Approval				
	3	Liver or kidney transplant recipients who are treatment experienced with PRS (i.e., Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor)	Mavyret	16 weeks	16 weeks
	1, 2, 3, 4, 5, or 6	Treatment naïve	Mavyret	8 weeks	8 weeks
	1	Treatment experienced with an NS5A inhibitor (e.g., daclatasvir, elbasvir, ledipasvir, ombitasvir, velpatasvir) but without prior	Mavyret	16 weeks	16 weeks

Module	Clinical Criteria for Approval				
		treatment with an NS3/4A protease inhibitor (PI)			
	1	Treatment experienced with an NS3/4A protease inhibitor (e.g., simeprevir, boceprevir, telaprevir) but without prior treatment with an NS5A inhibitor	Mavyret	12 weeks	12 weeks
	1, 2, 4, 5, or 6	Treatment experienced with PRS (i.e., Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or	Mavyret	8 weeks	12 weeks

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>NS5A inhibitor)</td><td></td><td></td><td></td></tr>
<tr><td>3</td><td>Treatment experienced with PRS (i.e., Prior treatment experience with regimens containing interferon, pegylated interferon, ribavirin, and/or sofosbuvir, but no prior treatment experience with an HCV NS3/4A PI or NS5A inhibitor)</td><td>Mavyret</td><td>16 weeks</td><td>16 weeks</td></tr>
</table>
*HCV/HIV-1 co-infection, follow recommendations in the table above
+Patients with any degree of kidney impairment (including those on hemodialysis), follow recommendations in the table above</td></tr>
<tr><td>Sovaldi</td><td>Quantity Limit for the Target Agent(s) will be approved when BOTH of the following are met:

1. The requested length of therapy does NOT exceed the length of therapy noted in Table 6 or 7 (FDA labeling) for the patient’s treatment regimen AND
2. ONE of the following:
A. The requested quantity (dose) does NOT exceed the program quantity limit OR
B. The requested agent is Sovaldi 200 mg oral pellets AND BOTH of the following:
1. The requested quantity (dose) does NOT exceed 2 packets daily AND
2. There is support for why the patient cannot take 1 tablet of Sovaldi 400 mg strength OR</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
C. The requested agent is Sovaldi 200 mg tablets AND BOTH of the following:
1. The requested quantity (dose) does NOT exceed 2 tablets daily AND
2. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit

Length of Approval: Up to the duration of treatment as determined in Table 6 or 7.

Table 6: Sovaldi Treatment Recommendations in Adult Patients with Genotype 1, 2, 3, or 4 Based on FDA Labeling
<table>
<tr><th>Genotype</th><th>Patient population*</th><th>Treatment</th><th>Duration</th></tr>
<tr><td>1 or 4</td><td>Treatment naïve without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)</td><td>Sovaldi + Peg-interferon alfa + ribavirin</td><td>12 weeks</td></tr>
<tr><td>1</td><td>Treatment naïve without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A) and are interferon ineligible defined as one or more of the following:
• Intolerance to interferon
• Autoimmune hepatitis and other autoimmune disorders
• Hypersensitivity to PEG interferon or any of its components</td><td>Sovaldi + ribavirin</td><td>24 weeks</td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval			
		• Decompensated hepatic disease • Major uncontrolled depressive illness • A baseline neutrophil count below 1500/µL • A baseline platelet count below 90,000/µL • A baseline hemoglobin below 10 g/dL • A history of preexisting cardiac disease)		
	2	Treatment naïve or treatment experienced (i.e., patients who have failed an interferon based regimen with or without ribavirin) without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)	Sovaldi + ribavirin	12 weeks
	3	Treatment naïve or treatment experienced (i.e., patients who have failed an interferon based regimen with or without ribavirin) without cirrhosis or	Sovaldi + ribavirin	24 weeks

Module	Clinical Criteria for Approval

	with compensated cirrhosis (Child-Turcotte-Pugh A)		
1-4	With hepatocellular carcinoma awaiting liver transplantation	Sovaldi + ribavirin	Up to 48 weeks

*HCV/HIV-1 co-infection, follow recommendations in table above

Table 7: Sovaldi and Ribavirin with or without Peg-interferon Treatment Recommendations for Pediatric Patients 3 years of Age and Older Based on FDA labeling

Genotype	Patient population*	Treatment	Duration
2	Treatment naïve and treatment experienced (i.e., patients who have failed an interferon based regimen with or without ribavirin) without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)	Sovaldi + ribavirin	12 weeks
3	Treatment naïve and treatment experienced (i.e., patients who have failed an interferon based regimen with or	Sovaldi + ribavirin	24 weeks

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>without ribavirin) without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)</td><td></td><td></td></tr>
<tr><td>2 or 3</td><td>Pediatric patients with hepatocellular carcinoma awaiting liver transplantation</td><td>Sovaldi + ribavirin</td><td>48 weeks</td></tr>
</table>
*HCV/HIV-1 co-infection, follow recommendations in table above
</td></tr>
<tr><td>Viekira Pak</td><td>
Quantity Limit for the Target Agent(s) will be approved when BOTH of the following are met:

1. The requested length of therapy does NOT exceed the length of therapy noted in Table 8 (FDA labeling) for the patient's treatment regimen AND
2. The requested quantity (dose) does NOT exceed the program quantity limit

Length of Approval: Up to the duration as determined in Table 8.

Table 8: Viekira PAK Treatment Recommendations based on FDA labeling
<table>
<tr><th>Genotype</th><th>Patient Population*</th><th>Treatment</th><th>Duration</th></tr>
<tr><td>1a</td><td>Without cirrhosis</td><td>Viekira PAK + ribavirin</td><td>12 weeks</td></tr>
<tr><td>1a</td><td>With compensated cirrhosis</td><td>Viekira PAK + ribavirin</td><td>24 weeks</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
<table>
<tr><td>1b</td><td>With or without compensated cirrhosis</td><td>Viekira PAK</td><td>12 weeks</td></tr>
<tr><td>1a or 1b</td><td>Post liver transplant with normal hepatic function (i.e., Metavir less than or equal to 2)</td><td>Viekira PAK + ribavirin</td><td>24 weeks</td></tr>
</table>
*HCV/HIV-1 co-infection, follow recommendations in table above
</td></tr>
<tr><td>Vosevi</td><td>
Quantity Limit for the Target Agent(s) will be approved when BOTH of the following are met:

1. The requested length of therapy does NOT exceed the length of therapy noted in Table 9 (FDA labeling) for the patient’s regimen AND
2. The requested quantity (dose) does NOT exceed the program quantity limit

Length of Approval: Up to the duration of treatment as determined in Table 9.

Table 9: Vosevi Treatment Recommendations based on FDA labeling
<table>
<tr><th>Genotype</th><th>Patient Population*</th><th>Patients Previously Treated with an HCV Regimen Containing:</th><th>Duration</th></tr>
<tr><td>1, 2, 3, 4, 5, or 6</td><td>Without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)</td><td>An NS5A inhibitor (e.g., daclatasvir, elbasvir, ledipasvir, ombitasvir, velpatasvir)</td><td>12 weeks</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
<table>
<tr><td>1a or 3</td><td>Without cirrhosis or with compensated cirrhosis (Child-Turcotte-Pugh A)</td><td>Sofosbuvir without an NS5A inhibitor+</td><td>12 weeks</td></tr>
</table>
*HCV/HIV-1 co-infection, follow recommendations in table above
+ - Sofosbuvir with or without any of the following: peginterferon alfa/ribavirin, ribavirin, HCV NS3/4A protease inhibitor (simeprevir)
</td></tr>
<tr><td>Zepatier</td><td>
Quantity Limit for the Target Agent(s) will be approved when BOTH of the following are met:

1. The requested length of therapy does NOT exceed the length of therapy noted in Table 10 (FDA labeling) for the patient’s treatment regimen AND
2. The requested quantity (dose) does NOT exceed the program quantity limit

Length of Approval: Up to the duration of treatment as determined in Table 10.

Table 10: Zepatier Treatment Recommendations based on FDA labeling
<table>
<tr><th>Genotype</th><th>Patient Population*</th><th>Treatment</th><th>Duration</th></tr>
<tr><td>1a</td><td>Treatment-naïve or PegIFN/RBV-experienced without baseline NS5A polymorphisms at amino acid positions 28, 30, 31, or 93</td><td>Zepatier</td><td>12 weeks</td></tr>
<tr><td>1a</td><td>Treatment-naïve or PegIFN/RBV-experienced with baseline NS5A polymorphisms at</td><td>Zepatier + ribavirin</td><td>16 weeks</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
<table>
<tr><td></td><td>amino acid positions 28, 30, 31, or 93</td><td></td><td></td></tr>
<tr><td>1b</td><td>Treatment-naïve or PegIFN/RBV-experienced</td><td>Zepatier</td><td>12 weeks</td></tr>
<tr><td>1a or 1b</td><td>PegIFN/RBV/protease inhibitor-experienced</td><td>Zepatier + ribavirin</td><td>12 weeks</td></tr>
<tr><td>4</td><td>Treatment-naive</td><td>Zepatier</td><td>12 weeks</td></tr>
<tr><td>4</td><td>PegIFN/RBV-experienced</td><td>Zepatier + ribavirin</td><td>16 weeks</td></tr>
</table>
*HCV/HIV-1 co-infection, follow dosage recommendations in the table above
</td></tr>
<tr><td>New to Market Hepatitis C Agents</td><td>
Quantity Limit for the Target Agent(s) will be approved when BOTH of the following are met:

1. The requested length of therapy does NOT exceed the length of therapy noted in Table 11 (FDA labeling) for the patient’s treatment regimen AND
2. ONE of the following:
A. The requested quantity (dose) does NOT exceed the program quantity limit OR
B. BOTH of the following:
1. The requested quantity (dose) is greater than the program quantity limit AND
2. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit

Length of approval: Up to the duration of treatment as determined in Table 11.

Table 11: Treatment Recommendations based on FDA labeling

<table>
<tr><th>Agent(s)</th><th>FDA labeled indication(s)</th><th>Genotype</th><th>Treatment Regimen</th><th>FDA labeled dose</th><th>Treatment Duration</th></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval

Hereditary Angioedema

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Berinert® (C1 esterase inhibitor, [human]) Freeze-dried powder for reconstitution for intravenous use	Treatment of acute abdominal, facial, or laryngeal hereditary angioedema (HAE) attacks in adult and pediatric patients The safety and efficacy of Berinert for prophylactic therapy have not been established		1
CINRYZE® (C1 esterase inhibitor, [human]) Lyophilized powder for reconstitution for intravenous use	Routine prophylaxis against angioedema attacks in adults, adolescents, and pediatric patients (6 years of age and older) with Hereditary Angioedema (HAE)		2
Firazyr® (icatibant)* Injection for subcutaneous use	Treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years of age and older	*generic available	3
HAEGARDA® (C1 esterase inhibitor [human]) Freeze-dried powder for reconstitution for subcutaneous injection	Routine prophylaxis to prevent Hereditary Angioedema (HAE) attacks in patients 6 years of age and older		4
Orladeyo® (berotralstat) Capsule	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years and older Limitations of Use: The safety and effectiveness of Orladeyo for the treatment of acute HAE attacks have not		5

Agent(s)	FDA Indication(s)	Notes	Ref#
	been established. Orladeyo should not be used for treatment of acute HAE attacks. Additional doses or doses of Orladeyo higher than 150 mg once daily are not recommended due to the potential for QT prolongation		
RUCONEST® (C1 esterase inhibitor, [recombinant]) Lyophilized powder for reconstitution for intravenous use	Treatment of acute attacks in adult and adolescent patients with hereditary angioedema (HAE) Limitations of Use: Effectiveness was not established in HAE patients with laryngeal attacks		6
TAKHZYRO® (lanadelumab-flyo) Injection solution for subcutaneous use	Prophylaxis to prevent attacks of hereditary angioedema (HAE) in adult and pediatric patients 2 years and older		7

CLINICAL RATIONALE

Hereditary Angioedema	Hereditary Angioedema (HAE) is an autosomal dominant disease. HAE is characterized by recurrent episodes/attacks of nonpruritic, nonpitting, subcutaneous or submucosal edema that may involve the extremities, bowels, genitalia, trunk, face, tongue, or larynx. Angioedema attacks typically last 3 to 5 days from start to resolution, with increased morbidity and mortality if not treated with effective medication. Lack of clinical efficacy in treating HAE symptoms with antihistamines, corticosteroids, or epinephrine, is an important indicator for diagnosis.(8,9) HAE can be divided into two types, HAE due to C1INH deficiency (HAE-C1INH) and HAE with normal C1INH (HAE-nl-C1INH). HAE-C1INH can be subdivided into Type 1, characterized by deficient levels of C1 esterase inhibitor (C1-INH) protein and function, and Type 2, characterized by normal levels of C1-INH protein with diminished C1-INH activity (i.e., dysfunctional C1-INH protein). The prevalence of HAE-C1INH Type 1 and 2 is approximately 1 in 50,000 persons worldwide, and approximately 6,000 affected individuals in the United States.(8) HAE-C1INH Types 1 and 2 occur as a result of a mutation in the SERPING1 gene, which

	codes for C1-INH, and ultimately leads to the increased accumulation of bradykinin. Bradykinin has been credited in all HAE types for involvement in attacks through increasing vascular permeability via the B2 receptor.(8,9) HAE-nl-C1INH, previously referred to as Type 3 HAE, is characterized by both normal C1-INH protein and functional levels. It may also be bradykinin mediated based on the lack of response to antihistamines, corticosteroids, epinephrine, and the favorable response to bradykinin pathway-targeted medications.(8,9) HAE-nl-C1INH can be further subdivided into 5 subtypes:(8) • HAE FXII: due to mutation in F12, the gene encoding coagulation FXII • HAE-PLG: due to mutations in PLG, the gene encoding plasminogen • HAE-ANGPT1: due to mutations in ANGPT1, the gene encoding angiopoietin-1 • HAE-KNG1: due to a mutation in kininogen-1 gene • HAE-unknown: patients for whom the responsible mutation has not yet been defined The World Allergy Organization and European Academy of Allergy and Clinical Immunology (WAO/EAACI) recognize two additional subtypes of HAE-nl-C1INH. HAE-HS3ST6, which results from a mutation in the heparan sulfate 3-O-sulfotransferase 6 gene, and HAE-MYOF, which results from a mutation in the myoferlin gene.(9) Symptoms of HAE-C1INH typically begin in the first or second decade of life (sometimes as young as 2 years of age) and persist throughout the patient's lifetime. Almost all patients with HAE-C1INH will manifest symptoms by the age of 20.(8,9) An acute attack that causes death is most often a result of abdominal or laryngeal involvement. Triggers for attacks vary and may be traceable to a source (e.g., minor trauma or stress); however, episodes often occur without a defined precipitating factor.(9) HAE-nl-C1INH has a similar clinical presentation to HAE-C1INH with some differences. The face and tongue are more frequently affected, with fewer abdominal symptoms. While HAE-nl-C1INH is also an autosomal dominant disorder, penetrance is variable and often lower than patients with HAE-C1INH.(8,9) In addition to clinical presentation and an assessment of family history, HAE diagnosis typically includes a laboratory workup of C4, C1-INH antigenic level, and C1-INH function. C4, the natural substrate for C1 esterase, is considered the single best screening test for C1-INH deficiency.(8,9) In order to further distinguish between Type 1 and Type 2 HAE, the C1-INH antigenic level and/or functional activity is measured. The 2017 update to the international consensus from WAO/EAACI recommend patients with suspected HAE should have blood

	levels of C1-INH function, C1-INH protein, and C4 assessed, and the tests should be repeated to confirm diagnosis of HAE Type 1 or 2. A diagnosis of Type 1 can be confirmed with a decrease in C1-INH function, C1-INH protein level, and C4 levels. A diagnosis of Type 2 can be confirmed with a decrease in C1-INH function and C4 level with an increase or normal level of C1-INH protein level.(9) The US HAE Association Medical Advisory Board (2020) indicates further repeated testing is neither necessary nor useful once C1INH deficiency has been established by laboratory testing. The guidelines also recommend evaluating current medications that affect bradykinin and that can cause angioedema (e.g., angiotensin converting-enzyme inhibitors and estrogen replacement) and stopping these when appropriate. Genetic sequencing is not usually necessary to establish the diagnosis due to the high sensitivity and specificity of biochemical tests currently available. Genetic screening may be beneficial in prenatal testing, when biochemical testing is repeatedly equivocal, or to differentiate between HAE-C1INH and acquired C1INH. The board also recommends that patients see prescribers that are HAE experts to optimize individual treatment plans, assist with coordinating care, and provide important patient and family education.(8) HAE-nl-C1INH does not have validated biochemical testing to confirm the diagnosis. Genetic testing may be more helpful in confirming HAE-nl-C1INH for the subtypes with common mutations. The diagnosis of HAE-nl-C1INH can be suspected in patients with normal C1INH levels and the presence of angioedema. Genetic tests for factor XII, plasminogen, angiopoetin-1, and kininogen-1 should be performed when available. A diagnosis of HAE-U should involve input from an HAE specialist.(8) ***On-Demand Treatment Recommendations*** The 2021 update to the international consensus from WAO/EAACI and the US HAE Association Medical Advisory Board 2020 indicate that all patients with laboratory confirmed HAE-C1INH should have at least two standard doses of an FDA labeled on-demand treatment for acute attacks.(8,9) Currently, clinical evidence supporting the use of more than one agent used to treat acute attacks at the same time is lacking. The 2021 update to the international consensus from WAO/EAACI recommend all HAE-C1INH attacks considered for on-demand therapy be treated with either C1-INH, ecallantide, or icatibant.(9) US HAE Association Medical Advisory Board 2020 recommends early treatment options of acute attacks for HAE-C1INH and HAE-nl-C1INH consist of plasma derived nanofiltered C1-INH (Berinert), recombinant human C1-INH (RUCONEST), ecallantide (KALBITOR), or icatibant (Firazyr). The medication selection should

	be individualized based on patient response and all attacks should be considered for treatment irrespective of anatomical location. Patients that self-administer treatment should seek medical care if the features of their attack are unusual, response to treatment is inadequate, or they experience an airway attack. Fresh frozen plasma can be used if none of the FDA labeled on-demand treatments are available. The board notes that numerous open-labeled reports have revealed successful responses for each of the on-demand treatments for HAE-n1-C1INH attacks.(8)
	
	Short-Term Prophylaxis Recommendations
	
	Patients may need prophylactic treatment prior to planned surgeries or procedures, particularly dental surgeries. Trauma and/or stress are well-known provocateurs of acute attacks.(8) The 2021 update to the international consensus from WAO/EAACI recommends that short-term prophylaxis should be used prior to procedures that can induce an attack. C1-INH should be used as close as possible to the start of the procedure. Second-line options for short-term prophylaxis include fresh frozen plasma and androgens, but neither have the safety or efficacy of intravenous C1-INH.(9)
	
	US HAE Association Medical Advisory Board 2020 recommends the following:(8)
	
	• HAE-C1INH:
	  ○ Short-term prophylaxis can be either a single dose of plasma derived C1INH (pdC1INH [CINRYZE, HAEGARDA]) or a course of anabolic androgen
	  ○ A single dose of 20 IU/kg pdC1INH can be given 1 to 12 hours before the stressor
	  ○ Anabolic androgens (i.e., danazol at 400 to 600 mg/day) can be administered 5-7 days before procedure or stressor and continued for 2-5 days after
	  ○ Recombinant human C1INH (rhC1INH [RUCONEST]) at 50 IU/kg has also been successfully used for short-term prophylaxis
	  ○ On-demand treatment needs to be available regardless of the use of short-term prophylaxis
	• HAE-nl-C1INH:
	  ○ There is no data on short-term prophylaxis
	  ○ For patients with a confirmed diagnosis, the same approach as HAE-C1INH may be used with the important caveat that on-demand therapy be available if needed

	Long-Term Prophylaxis Recommendations
	
	The 2021 update to the international consensus from WAO/EAACI recommends the following:(9)
	
	• Long-term prophylaxis should be considered for all severely symptomatic patients, taking into account the disease activity, frequency of attacks, quality of life, availability of health care resources, and failure to achieve adequate control with appropriate on-demand therapy
	• All patients should be evaluated for prophylaxis at least once a year or during every office visit, and once started, efficacy and safety of long-term prophylaxis should be assessed regularly
	• Plasma-derived C1-INH, lanadelumab, and berotralstat are recommended as first-line therapy and androgens are second-line therapy
	• Antifibrinolytics are not recommended for long-term prophylaxis
	
	US HAE Association Medical Advisory Board 2020 recommends the following:(8)
	
	• HAE-C1INH
	  ○ Long-term prophylaxis should be individualized and consider attack severity, frequency, comorbid conditions, and patient experience/preference
	  ○ Medication options can be divided into two broad categories: first-line and second-line
	  ○ First-line options include C1-INH (IV CINRYZE and SC HAEGARDA), and a monoclonal inhibitor of plasma kallikrein (TAKHZYRO)
	  ○ Second-line options include anabolic androgens (i.e., danazol) and antifibrinolytics (epsilon aminocaproic acid or tranexamic acid)
	  ○ Second-line options should be reserved for when first-line agents are not available or when the patient will only accept oral therapy
	• HAE-nI-C1INH:
	  ○ Long-term prophylaxis has not been studied in patients with HAE-nI-C1INH
	  ○ There are 2 strategies frequently used for prophylaxis in patients with HAE-nI-C1INH: hormonal therapy and antifibrinolytics
	• Monitoring:
	  ○ Attack frequency and severity should be evaluated by the physician on an ongoing basis
	  ○ Patients keep a record of all of their attacks, regardless of severity (mild, moderate, or severe). These records should include

	description of attack, treatment of attack, response to treatment, and any adverse effects of treatment ○ The attack log should be provided to the treating physicians and reviewed on a regular basis by a means (i.e., in person or electronically) predetermined between the patient and the physician ○ When patients self-administer or receive on-demand medications, there must be a plan to have the patient report this use in a timely manner ○ Review potential triggers, updated list of current medications, and immunizations at each office visit There are currently two plasma-derived C1-INHs that are FDA labeled for prophylaxis, HAEGARDA and CINRYZE, and one kallikrein inhibitor that is FDA labeled for prophylaxis, TAKHZYRO. Additionally, Orladeyo offers a preventative therapy to HAE patients that need an oral route of administration. The clinical trials for HAEGARDA and TAKHZYRO included patients with a pretreatment attack rate of 3.3 and 3.5 attacks per month. The clinical trials for CINRYZE required patients to have at least 2 attacks per month. The Institute for Clinical and Economic Review (ICER) completed a cost-comparison review of the three prophylaxis agents against on-demand therapy. It was found that the prophylaxis would be more cost effective for patients experiencing 3.3 attacks or more per month, while the on-demand treatment(s) would be more cost effective for patients experiencing fewer than 3.3 attacks per month.(11) ICER completed a Real-World Evaluation of the prophylactic agents, noting a decrease in severe attack rates for CINRYZE, HAEGARDA, and TAKHZYRO with rates similar to those noted in clinical trials. A separate analysis of TAKHZYRO showed 64% of patients that initiated therapy with TAKHZYRO achieved an attack free status during the first 6 months of therapy. Of those that were attack free, 74% had a dose reduction to every 4 weeks.(12) ***Special Population Recommendations:*** The 2021 update to the international consensus from WAO/EAACI recommends the following for children and pregnant women with HAE:(9) • C1-INH is recommended as first-line therapy for acute attacks, short-term and long-term prophylaxis in children, pregnancy, and lactation. C1-INH is considered safe and effective during pregnancy and lactation • Attenuated androgens can be used second-line for short-term prophylaxis in children when C1-INH is unavailable. Although, US HAE Association

<table>
<tr><td></td><td>Medical Advisory Board 2020 does NOT recommend the use of androgens for use in children.(8)
• Antifibrinolytics are preferred to androgens as second-line therapy for long-term prophylaxis in children
• Androgens and antifibrinolytics are secreted in breast milk and in contrast to androgens, tranexamic acid was found to be safe during breastfeeding</td></tr>
<tr><td>Efficacy</td><td>TAKHZYRO:(7)

The efficacy of TAKHZYRO for the prevention of angioedema attacks in patients 12 years of age and older with Type I or II HAE was demonstrated in a multicenter, randomized, double-blind, placebo-controlled parallel-group study (Trial 1, NCT02586805).(7)

The study included 125 adult and pediatric patients (12 years of age and older) with Type I or II HAE who experienced at least one investigator-confirmed attack per 4 weeks during the run-in period. Patients were randomized into 1 of 4 parallel treatment arms, stratified by baseline attack rate, in a 3:2:2:2 ratio (placebo, lanadelumab-flyo 150 mg every 4 weeks, lanadelumab-flyo 300 mg every 4 weeks, or lanadelumab-flyo 300 mg every 2 weeks by subcutaneous injection) for the 26-week treatment period. Patients 18 years of age and older were required to discontinue other prophylactic HAE medications prior to entering the study; however, all patients were allowed to use rescue medications for treatment of breakthrough HAE attacks.(7)

All TAKHZYRO treatment arms produced clinically meaningful and statistically significant reductions in the mean HAE attack rate compared to placebo across all primary and secondary endpoints in the Intent-to-Treat population (ITT).(7)

<table>
<tr><th>Endpoint statistics</th><th>Placebo (N=41)</th><th>TAKHZYRO 150 mg every 4 weeks</th><th>TAKHZYRO 300 mg every 4 weeks</th><th>TAKHZYRO 300 mg every 2 weeks</th></tr>
<tr><td colspan="5">Number of HAE attacks from day 0 to day 182</td></tr>
<tr><td>Least squares mean (95% CI) monthly attack rate</td><td>1.97

(1.64, 2.36)</td><td>0.48

(0.31, 0.73)</td><td>0.53

(0.36, 0.77)</td><td>0.26

(0.14, 0.46)</td></tr>
</table>
</td></tr>
</table>

(attacks/4 weeks)				
% reduction relative to placebo (95% CI)		76 (61, 85)	73 (59, 82)	87 (76, 93)
Adjusted p-values		<0.001	<0.001	<0.001
Number of HAE attacks requiring acute treatment from day 0 to day 182				
Least squares mean (95% CI) monthly attack rate (attacks/4 weeks)	1.64 (1.34, 2.00)	0.31 (0.18, 0.53)	0.42 (0.28, 0.65)	0.21 (0.11, 0.40)
% reduction relative to placebo (95% CI)		81 (66, 89)	74 (59, 84)	87 (75, 93)
Adjusted p-values		<0.001	<0.001	<0.001
Number of moderate or severe HAE attacks from day 0 to day 182				
Least squares mean (95% CI) monthly attack rate (attacks/4 weeks)	1.22 (0.97, 1.52)	0.36 (0.22, 0.58)	0.32 (0.20, 0.53)	0.20 (0.11, 0.39)
% reduction relative to placebo (95% CI)		70 (50, 83)	73 (54, 84)	83 (67, 92)
Adjusted p-values		<0.001	<0.001	<0.001

	The mean reduction in HAE attack rate was consistently higher across the TAKHZYRO treatment arms compared to placebo regardless of the baseline history of prior long-term prophylaxis, laryngeal attacks, or attack rate during the run-in period.(7) Additional pre-defined exploratory endpoints included the percentage of patients who were attack free for the entire 26-week treatment period and the percentage of patients achieving threshold (greater than or equal to 50%, greater than or equal to 70%, greater than or equal to 90%) reductions in HAE attack rates compared to run-in during the 26-week treatment period. A 50% or greater reduction in HAE attack rates was observed in 100% of patients on 300 mg every 2 weeks or every 4 weeks and 89% on 150 mg every 4 weeks compared to 32% of placebo patients. A 70% or greater reduction in HAE attack rates was observed in 89%, 76%, and 79% of patients on 300 mg every 2 weeks, 300 mg every 4 weeks, and 150 mg every 4 weeks, respectively, compared to 10% of placebo patients. A 90% or greater reduction in HAE attack rates was observed 67%, 55%, and 64% of patients on 300 mg every 2 weeks, 300 mg every 4 weeks, and 150 mg every 4 weeks, respectively, compared to 5% of placebo patients.(7) The percentage of attack-free patients for the entire 26-week treatment period was 44%, 31%, and 39% in the TAKHZYRO 300 mg every 2 weeks, 300 mg every 4 weeks, and 150 mg every 4 weeks groups respectively, compared to 2% of placebo patients.(7) Trial 2 (NCT02741596) is a rollover into an open-label extension study. Patients that completed Trial 1 were eligible to be rolled over regardless of randomization in Trial 1. Patients received a single dose of TAKHZYRO 300 mg at study entry and were followed until the first HAE attack occurred. All efficacy endpoints were exploratory in this uncontrolled, unblinded study. At week 4 post-dose, approximately 80% of patients who had been in the 300 mg every 2 weeks treatment group (N=25) in Trial 1 remained attack-free. After the first HAE attack, all patients received open-label treatment with TAKHZYRO 300 mg every 2 weeks.(7)
Safety	Berinert, CINRYZE, and HAEGARDA are contraindicated in patients with a history life-threatening hypersensitivity reactions, including anaphylaxis, to C1-INH preparations or its excipients.(1,2,4) RUCONEST is contraindicated in patients with the following:(6) • History of allergy to rabbits or rabbit-derived products

	• History of immediate hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations Firazyr, Orladeyo, and TAKHZYRO have no FDA labeled contraindications for use.(3,5,7)

REFERENCES

Number	Reference
1	Berinert prescribing information. CSL Behring GmbH. September 2021.
2	CINRYZE prescribing information. Takeda Pharmaceuticals America, Inc. February 2023.
3	Firazyr prescribing information. Takeda Pharmaceuticals America, Inc. January 2024.
4	HAEGARDA prescribing information. CSL Behring GmbH. January 2022.
5	Orladeyo prescribing information. BioCryst Pharmaceuticals, Inc. November 2023.
6	RUCONEST prescribing information. Bioconnection B.V. April 2020.
7	TAKHZYRO prescribing information. Takeda Pharmaceuticals America, Inc. February 2023.
8	Busse PJ, Christiansen SC, Riedl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *The Journal of Allergy and Clinical Immunology in Practice*. 2021;9(1):132-150.e3. doi:10.1016/j.jaip.2020.08.046
9	Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema—The 2021 revision and update. *Allergy*. 2022;77(7):1961-1990. doi:10.1111/all.15214
10	Reference no longer used.
11	Lin GA, Agboola F, University of Washington School of Pharmacy Modeling Group, et al. *Prophylaxis for Hereditary Angioedema With Lanadelumab and C1 Inhibitors: Effectiveness and Value*.; 2018. https://icer.org/wp-content/uploads/2020/10/ICER_HAE_Final_Evidence_Report_111518-1.pdf

Number	Reference
12	Bloudek L, Jaksa A, McKenna A, et al. *Observational Real-World Evidence Update; Prophylaxis of Hereditary Angioedema With Takhzyro and C1 Inhibitors: Effectiveness and Value.*; 2021. https://digirepo.nlm.nih.gov/master/borndig/9918401082906676/9918401082906676.pdf

ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
85802022064	Berinert	c1 esterase inh	500 UNIT	based on CDC 90th percentile for men and women averaged to 247.5 lbs or 112.5 kg (112.5 kg * 20 IU/kg=2,250 IU/500 IU/bottle=4.5 or 5 bottles or 2500 units/attack x 2 attacks/month = 10 vials/28 days			
85802022002120	Cinryze	C1 Esterase Inhibitor (Human) For IV Inj 500 Unit	500 UNIT	1,000 IU every 3 days = 10,000 IU/30 days/500 u/vial = 20 vials			
85802022002130	Haegarda	C1 Esterase Inhibitor (Human) For Subcutane	2000 UNIT	*QL calculation based on CDC 90 percentile for weight in adults, averaged for men and women, and rounded to the nearest even dose to reduce waste (112.5 kg individual). See Special Clinical Criteria Table ** Do not wildcard PA- detail to GPI 14			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
		ous Inj 2000 Unit					
85802022002140	Haegarda	C1 Esterase Inhibitor (Human) For Subcutaneous Inj 3000 Unit	3000 UNIT	*QL calculation based on CDC 90 percentile for weight in adults, averaged for men and women, and rounded to the nearest even dose to reduce waste (112.5 kg individual). See Special Clinical Criteria Table ** Do not wildcard PA- detail to GPI 14			

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Berinert, Firazyr, icatibant, or Ruconest	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** All target agents are eligible for continuation of therapy

Module	Clinical Criteria for Approval
	1. The patient has been treated with the requested agent (starting on samples is not approvable) **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. ONE of the following: A. The patient has a diagnosis of hereditary angioedema (HAE) due to C1INH deficiency (HAE-C1INH [Type 1 or Type 2]) confirmed by ONE of the following: 1. The patient's diagnosis has been confirmed with measurements of C1-INH protein level, C1-INH function level, and C4 level as follows: A. Type 1 HAE: Decreased quantities of C4 level, C1-INH protein level, and C1-INH function level **OR** B. Type 2 HAE: Decreased quantities of C4 level and C1-INH function level (C1-INH protein level may be normal or elevated) **OR** 2. The patient's diagnosis has been confirmed by mutation in the C1-INH gene altering protein synthesis and/or function **OR** B. The patient has a diagnosis of hereditary angioedema (HAE) with normal C1INH (HAE-nl-C1INH) evidenced by BOTH of the following: 1. The patient has levels within the normal range for C1-INH protein level, C1-INH function level, and C4 level **AND** 2. ONE of the following: A. The patient's diagnosis is associated with a mutation in ONE of the following genes: 1. Coagulation factor FXII (mutation in F12) 2. Plasminogen 3. Angiopoietin-1 4. Kininogen-1 5. Heparan sulfate 3-O-sulfotransferase 6 gene 6. Myoferlin gene **OR** B. The patient has a diagnosis of HAE-U that has been confirmed by an HAE specialist (medical records required) AND 2. If the client has preferred agent(s), then ONE of the following: A. The requested agent is a preferred agent **OR**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
B. The patient has tried and had an inadequate response to the preferred agent(s) for on-demand use OR
C. The patient has an intolerance or hypersensitivity to the preferred agent(s) for on-demand use OR
D. The patient has an FDA labeled contraindication to ALL the preferred agent(s) for on-demand use AND
2. If the patient has an FDA labeled indication, then ONE of the following:
A. The patient’s age is within FDA labeling for the requested indication for the requested agent OR
B. There is support for using the requested agent for the patient’s age for the requested indication AND
3. Medications known to cause angioedema (i.e., ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate AND
4. The requested agent will be used to treat acute HAE attacks AND
5. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:
<table>
<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Firazyr</td><td>icatibant</td></tr>
</table>
A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
C. There is support for the use of the requested brand agent over the generic equivalent AND
6. The prescriber is a specialist in the area of the patient’s diagnosis (e.g., allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis AND
7. The patient will NOT be using the requested agent in combination with another agent indicated for the treatment of acute HAE attacks (i.e., Berinert, Firazyr, icatibant, KALBITOR, RUCONEST) AND
8. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 6 months
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] AND
2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND
3. The patient has had clinical benefit with the requested agent AND
4. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:

<table>
<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Firazyr</td><td>icatibant</td></tr>
</table>

A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
C. There is support for the use of the requested brand agent over the generic equivalent AND
5. The prescriber has communicated (via any means) with the patient regarding the frequency and severity of attacks and has verified that the patient does not have greater than 1-month supply (sufficient for 2 acute HAE attacks) currently on-hand AND
6. The patient will NOT be using the requested agent in combination with another agent indicated for the treatment of acute HAE attacks (i.e., Berinert, Firazyr, icatibant, KALBITOR, RUCONEST) AND
7. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 12 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td>Cinryze, Haegarda, Orladeyo, or Takhzyro</td><td>

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Agents Eligible for Continuation of Therapy
All target agents are eligible for continuation of therapy

   1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR**
   2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR**

   B. ALL of the following:
   1. The patient has a diagnosis of hereditary angioedema (HAE) due to C1INH deficiency [HAE-C1INH (Type 1 or Type 2)] evidenced by ONE of the following:
      A. The patient's diagnosis has been confirmed with measurements of C1-INH protein level, C1-INH function level, and C4 level as follows:
         1. Type 1 HAE: Decreased quantities of C4 level, C1-INH protein level, and C1-INH function level **OR**
         2. Type 2 HAE: Decreased quantities of C4 level and C1-INH function level (C1-INH protein level may be normal or elevated) **OR**

      B. The patient's diagnosis has been confirmed by mutation in the C1-INH gene altering protein synthesis and/or function **AND**
   2. The requested agent is being prescribed for HAE prophylaxis **AND**
   3. The patient has a history of at least three moderate to severe acute HAE attacks per month (e.g., airway swelling, severe abdominal pain, painful facial swelling) **AND**
   4. If the client has preferred agent(s), then ONE of the following:
      A. The requested agent is a preferred agent **OR**
      B. The patient has tried and had an inadequate response to the preferred agent(s) **OR**

</td></tr>
</table>

Module	Clinical Criteria for Approval
	C. The patient has an intolerance or hypersensitivity to the preferred agent(s) **OR** D. The patient has an FDA labeled contraindication to ALL the preferred agent(s) **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. If TAKHZYRO is requested, ONE of the following: A. The patient is an adult or 12 years of age or older AND ONE of the following: 1. The patient is initiating therapy with the requested agent **OR** 2. The patient has been treated with the requested agent for less than 6 consecutive months **OR** 3. The patient has been treated with the requested agent for at least 6 consecutive months AND ONE of the following: A. The patient has been free of acute HAE attacks for at least 6 consecutive months and ONE of the following: 1. The patient's dose will be reduced to 300 mg every 4 weeks **OR** 2. There is support for therapy using 300 mg every 2 weeks **OR** B. The patient has NOT been free of acute HAE attacks for at least 6 consecutive months **OR** B. The patient is 6 to less than 12 years of age AND ONE of the following: 1. The patient is initiating therapy with the requested agent **OR** 2. The patient has been treated with the requested agent for less than 6 consecutive months **OR** 3. The patient has been treated with the requested agent for at least 6 consecutive months AND ONE of the following: A. The patient has been free of acute HAE attacks for at least 6 consecutive months and ONE of the following: 1. The patient's dose will be reduced to 150 mg every 4 weeks **OR** 2. There is support for therapy using 150 mg every 2 weeks **OR** B. The patient has NOT been free of acute HAE attacks for at least 6 consecutive months **OR** C. The patient is 2 to less than 6 years of age **AND** 4. Medications known to cause angioedema (i.e., ACE-Inhibitors, estrogens, angiotensin receptor blockers) have been evaluated and discontinued when appropriate **AND**

Module	Clinical Criteria for Approval
	5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. The patient will NOT be using the requested agent in combination with another agent indicated for prophylaxis of HAE attacks (i.e., CINRYZE, HAEGARDA, Orladeyo, TAKHZYRO) **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 3 months for CINRYZE, 4 months for HAEGARDA, 6 months for Orladeyo, and 9 months for TAKHZYRO NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient has had clinical benefit with the requested agent as indicated by ONE of the following: A. The patient has had a decrease in the frequency of acute HAE attacks from baseline (prior to therapy with the requested agent) **OR** B. The patient has had a decrease in use of on-demand therapy **AND** 4. The patient will NOT be using the requested agent in combination with another agent indicated for prophylaxis of HAE attacks (i.e., CINRYZE, HAEGARDA, Orladeyo, TAKHZYRO) **AND** 5. If TAKHZYRO is requested, ONE of the following: A. The patient is an adult or 12 years of age or older AND ONE of the following: 1. The patient is initiating therapy with the requested agent **OR** 2. The patient has been treated with the requested agent for less than 6 consecutive months **OR** 3. The patient has been treated with the requested agent for at least 6 consecutive months AND ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient has been free of acute HAE attacks for at least 6 consecutive months and ONE of the following: 1. The patient's dose will be reduced to 300 mg every 4 weeks **OR** 2. There is support for therapy using 300 mg every 2 weeks **OR** B. The patient has NOT been free of acute HAE attacks for at least 6 consecutive months **OR** B. The patient is 6 to less than 12 years of age AND ONE of the following: 1. The patient is initiating therapy with the requested agent **OR** 2. The patient has been treated with the requested agent for less than 6 consecutive months **OR** 3. The patient has been treated with the requested agent for at least 6 consecutive months AND ONE of the following: A. The patient has been free of acute HAE attacks for at least 6 consecutive months and ONE of the following: 1. The patient's dose will be reduced to 150 mg every 4 weeks **OR** 2. There is support for therapy using 150 mg every 2 weeks **OR** B. The patient has NOT been free of acute HAE attacks for at least 6 consecutive months **OR** C. The patient is 2 to less than 6 years of age **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Berinert, Firazyr, icatibant, or Ruconest	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) is within the program quantity limit (allows for 2 acute HAE attacks per month) **OR**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>2. The requested quantity (dose) exceeds the program quantity limit and there is support for therapy with a higher dose or quantity for the requested indication (e.g., frequency of attacks within the past 3 months has been greater than 2 attacks per month)

Length of Approval: Initial - 6 months; Renewal - 12 months</td></tr>
<tr><td>Cinryze, Haegarda, Orladeyo, or Takhzyro</td><td>Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met:

1. The requested quantity (dose) is within the FDA labeled dosing for the requested indication AND within the quantity limit OR
2. The requested quantity (dose) exceeds the program quantity limit AND there is support for therapy with a higher dose or quantity for the requested indication

Length of Approval: Initial: 3 months for CINRYZE, 4 months for HAEGARDA, 6 months for Orladeyo, and 9 months for TAKHZYRO; Renewal: 12 months

HAEGARDA WEIGHT-BASED QUANTITY LIMITS: EXTENDED DOSING TABLE
<table>
<tr><th>Weight

(lb)</th><th>Weight (kg)</th><th>Quantity Limit of 3000 IU vials

per 28 days</th><th>Quantity Limit of 2000 IU vials

per 28 days</th><th>Number of

3000 IU vials used per dose</th><th>Number of

2000 IU vials used per dose</th></tr>
<tr><td>greater than 330-365</td><td>greater than 150-166</td><td>16</td><td>16</td><td>2</td><td>2</td></tr>
<tr><td>greater than 293-330</td><td>greater than 133-150</td><td>24</td><td>0</td><td>3</td><td>0</td></tr>
<tr><td>greater than 255-293</td><td>greater than 116-133</td><td>0</td><td>32</td><td>0</td><td>4</td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval					
	greater than 220-255	greater than 100-116	8	16	1	2
	greater than 182.6-220	greater than 83-100	16	0	2	0
	greater than 145-182.6	greater than 66-83	8	8	1	1
	greater than 110-145	greater than 50-66	0	16	0	2
	greater than or equal to 75-110	greater than or equal to 34-50	8	0	1	0
	less than 75	less than 34	0	8	0	1

Hetlioz (tasimelteon)

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Hetlioz® (tasimelteon*) Capsules*	Treatment of Non-24-Hour Sleep-Wake Disorder (Non-24 SWD) in adults Treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in patients 16 years of age and older	*generic available	1
Hetlioz LQ™ (tasimelteon) Oral suspension	Treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) in pediatric patients 3 to 15 years of age		1

CLINICAL RATIONALE

Non-24 Hour Sleep-Wake Disorder	Non-24 hour sleep-wake disorder (Non-24) is a circadian rhythm sleep disorder that is due to the failure of the biological clock to synchronize to a 24-hour day.(2) Numerous biological processes require an endogenous, entrainable oscillation with a period of about 24 hours, also known as the circadian rhythm. Retinal rods, cones, and ganglion cells that express the photopigment melanopsin play a key role in circadian photoentrainment. Light that reaches the photoreceptors activates the suprachiasmatic nuclei (SCN), which contains the master biological clock, activating a regulatory feedback loop that inhibits melatonin synthesis. In totally blind patients, the circadian process can become desynchronized due to the absence of light input into the master biological clock.(5) Patients with Non-24 typically find their sleep time gradually delaying by minutes to hours every day, rather than sleeping at roughly the same time every day. Cycles of body temperature and hormone rhythms also follow a non-24 hour rhythm. If Non-24 is not detected and addressed, and the person attempts to stay on a 24-hour schedule, the symptoms of chronic sleep deprivation will accumulate, such as excessive daytime sleepiness, fatigue, depression, difficulty

	concentrating, and memory problems. Non-24 hour sleep-wake disorder can be severely disabling as it causes extreme difficulty for the individual attempting to maintain social and career obligations.(2) The condition primarily occurs in blind individuals, and at least 50% of the totally blind (i.e., those with no light perception) are thought to suffer from the disorder.(3) The American Academy of Sleep Medicine (AASM) guidelines on treatment of circadian rhythm disorders recommends clinicians use strategically timed administration of melatonin for treatment of Non-24-Hour Sleep-Wake Disorder in blind adults (vs. no treatment). The suggestion carried a “Weak” recommendation as there were only 3 studies that met the task force’s inclusion criteria for analysis and the level of evidence from these small trials was low. The task force states th no serious adverse reactions to melatonin have been described to date and therefore benefits of use appear to outweigh any potential harm.(3)
Efficacy	The effectiveness of Hetlioz in the treatment of Non-24-Hour Sleep-Wake Disorder(Non-24) was established in two randomized double-masked, placebo-controlled, multicenter, parallel-group studies (Studies 1 and 2) in totally blind patients with Non-24. In study 1, 84 patients with Non-24 (median age 54 years) were randomized to receive Hetlioz 20 mg or placebo, one hour prior to bedtime, at the same time every night for up to 6 months. Study 2 was a randomized withdrawal trial in 20 patients with Non-24 (median age 55 years) that was designed to evaluate the maintenance of efficacy of Hetlioz after 12 weeks. Patients were treated for approximately 12 weeks with Hetlioz 20 mg one hour prior to bedtime, at the same time every night.(1) Efficacy endpoints for nighttime total sleep time and daytime nap duration were based on the 25% of nights with the least nighttime sleep, and the 25% of days with the most daytime nap time. Treatment with Hetlioz resulted in a significant improvement, compared with placebo, for both endpoints in Study 1 and Study 2.(1)
Smith-Magenis Syndrome (SMS)	Smith-Magenis Syndrome (SMS) is genetic condition resulting in developmental delays, cognitive impairment, behavioral abnormalities, sleep disturbances, distinctive physical features, and childhood abdominal obesity. SMS is a result of a deletion of the retinoic acid induced 1 (RAI1) gene in chromosome 17p11.2. Most cases are the result of de novo deletions, but rare occurrences of inherited cases have occurred.(7) The diagnosis of SMS is established via a combination of clinical features and genetic testing. Clinical features suspect of SMS include the following:(6) • Subtly distinctive facial appearance that becomes more evident with age

	• Mild to moderate infantile hypotonia with feeding difficulties and failure to thrive • Some level of developmental delay and/or intellectual disability, including early speech delays with or without associated hearing loss • Distinct neurobehavioral phenotype that includes stereotypic and maladaptive behaviors • Sleep disturbance • Short stature (prepubertal) • Childhood obesity • Minor skeletal anomalies, including brachydactyly • Signs of peripheral neuropathy • Ophthalmologic abnormalities • Otolaryngologic abnormalities The presence of either a heterozygous deletion at chromosome 17p11.2 that includes RAI1 or a heterozygous intragenic RAI1 pathogenic variant are definitive of a SMS diagnosis.(6) Sleep disturbances are a major clinical characteristic of SMS. The sleep disturbances are believed to be attributed to a primary disturbance of the circadian clock, with RAI1 functioning as a positive regulator of the circadian locomotor output cycles kaput (CLOCK) gene transcription. The dysregulation of CLOCK results in dysregulation of other circadian clock components. Patients with SMS also have elevated levels of daytime melatonin resulting in daytime sleepiness. The sleep disturbances manifest as fragmented sleep cycles with a reduction in total sleep time. Patients may complain of frequent nighttime awakenings, parasomnias, and excessive daytime sleepiness.(7) Sleep disturbances contribute to behavioral problems typical to SMS, and normalizing sleep habits, improved both behavior and quality of life for patients and families. There is currently no pharmaceutical standard of care, but melatonin has been used in case reports with some response.(6,7) Hetlioz (tasimelteon) is the first FDA-approved treatment of nighttime sleep disturbance in SMS.(6)
Efficacy	The effectiveness of Hetlioz in the treatment of nighttime sleep disturbances in Smith-Magenis Syndrome (SMS) was established in a 9-week, double-blind, placebo-controlled crossover study in adults and pediatric patients with SMS (Study 3; NCT 02231008). Patients 16 years of age and older received Hetlioz 20 mg capsules, and pediatric patients 3 years to 15 years of age received a weight-based dose of oral suspension. The efficacy comparisons for nighttime sleep quality and total sleep time were based on the 50% of nights with the worst sleep

	quality and the 50% of nights with the least nighttime sleep in each 4-week period. In accordance with the cross-over design, the efficacy comparisons were within patient. Compared to placebo, treatment with Hetlioz resulted in a statistically significant improvement in the 50% worst nights' sleep quality.(1)
Safety	Hetlioz and Hetlioz LQ have no FDA labeled contraindications for use.(1)

REFERENCES

Number	Reference
1	Hetlioz prescribing information. Vanda Pharmaceuticals Inc. January 2023.
2	Non-24-Hour Sleep-Wake Disorder. National Organization for Rare Disorders (NORD). (2023, November 20) https://rarediseases.org/rare-diseases/non-24-hour-sleep-wake-disorder/
3	Auger, R. R., Burgess, H. J., Emens, J. S., Deriy, L. V., Thomas, S. M., & Sharkey, K. M. (2015). Clinical practice guideline for the treatment of intrinsic circadian rhythm sleep-wake disorders: Advanced sleep-wake phase disorder (ASWPD), delayed sleep-wake phase disorder (DSWPD), non-24-hour sleep-wake rhythm disorder (N24SWD), and irregular sleep-wake rhythm disorder (ISWRD). an update for 2015. Journal of Clinical Sleep Medicine, 11(10), 1199–1236. https://doi.org/10.5664/jcsm.5100
4	Reference no longer used.
5	Quera Salva Maria Antonia, Hartley Sarah, Léger Damien, Dauvilliers Yves A. (2017) Non-24-Hour Sleep–Wake Rhythm Disorder in the Totally Blind: Diagnosis and Management. *Frontiers in Neurology*, 8(686), pages 1-7. Doi: 10.3389/fneur.2017.00686.
6	Smith ACM, Boyd KE, Elsea SH, et. al. Smith-Magenis Syndrome. *GeneReviews*. October, 2022; https://www.ncbi.nlm.nih.gov/books/NBK1310/
7	Shayota, B. J., & Elsea, S. H. (2019). Behavior and sleep disturbance in Smith-Magenis syndrome. *Current opinion in psychiatry*, *32*(2), 73–78. https://doi.org/10.1097/YCO.0000000000000474

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. BOTH of the following: 1. The patient has a diagnosis of Non-24-hour sleep-wake disorder **AND** 2. The patient is totally blind (i.e., no light perception) **OR** B. BOTH of the following: 1. The patient has a diagnosis of Smith-Magenis Syndrome (SMS) confirmed by the presence of ONE of the following genetic mutations: A. A heterozygous deletion of 17p11.2 **OR** B. A heterozygous pathogenic variant involving RAI1 **AND** 2. The requested agent is being used to treat nighttime sleep disturbances associated with SMS **OR** C. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., sleep specialist, neurologist, psychiatrist) or has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND**

Module	Clinical Criteria for Approval
	3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., sleep specialist, neurologist, psychiatrist) or has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support of therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

High Dollar Limit

Prior Authorization

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Target Agents(s) will be approved when ALL of the following are met: 1. The patient has an FDA-approved or compendia supported indication for the requested agent **AND** 2. If the request is for a brand agent with an available generic equivalent(s) then ONE of the following: A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent **OR** B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent **OR** C. There is support for the use of the requested brand agent over the generic equivalent **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 4. ONE of the following: A. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support of therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use

High Dollar Compound

Prior Authorization

CLINICAL RATIONALE

	The Compounding Quality Act divides compounding under two laws. Compounding facilities may register under 503B to become a registered outsourcing facility. All other facilities are captured under 503A. A drug compounded under 503A must meet the following requirements:(1)
	
	• The drug product is compounded for an identified individual patient based on the receipt of a valid prescription order, or a notation, approved by the prescribing practitioner, on the prescription order that a compounded product is necessary for the identified patient
	• The compounding of the drug product is performed:
	  ○ By a licensed pharmacist in a state licensed pharmacy or a Federal facility, or by a licensed physician on the prescription order for an individual patient made by a licensed physician or other licensed practitioner authorized by state law to prescribe drugs; or
	  ○ By a licensed pharmacist or licensed physician in limited quantities before the receipt of a valid prescription order for such individual patient and
	  ▪ is based on a history of the licensed pharmacist or licensed physician receiving valid prescription orders for the compounding of the human drug product; and
	  ▪ those orders have been generated solely within an established relationship between the licensed pharmacist or licensed physician and either such patient for whom the prescription order will be provided or the physician or other licensed practitioner who will write such prescription order
	  ○ The drug product is compounded in compliance with the United States Pharmacopoeia (USP) chapters on pharmacy compounding using bulk drug substances, as defined in 21 CFR 207.3(a)(4), that comply with the standards of an applicable USP or National Formulary (NF) monograph, if one exists. If such a monograph does not exist, the drug substance(s) must be a component of an FDA-approved human drug product. If a monograph does not exist and the drug substance is not a component of an FDA-approved human drug product, it must

	appear on a list of bulk drug substances for use in compounding developed by FDA through regulation ○ The drug product is compounded using bulk drug substances that are manufactured by an establishment that is registered under section 510 of the FD&C Act ○ The drug product is compounded using bulk drug substances that are accompanied by valid certificates of analysis for each bulk drug substance ○ The drug product is compounded using ingredients (other than bulk drug substances) that comply with the standards of an applicable USP or NF monograph, if one exists, and the USP chapters on pharmacy compounding ○ The drug product does not appear on the list, published at 21 CFR 216.24, that includes drug products that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective ○ The licensed pharmacist or licensed physician does not compound regularly or in inordinate amounts any drug products that are essentially copies of commercially available drug products ○ The drug product is not a drug product identified by FDA by regulation as a drug product that presents demonstrable difficulties for compounding that reasonably demonstrate an adverse effect on the safety or effectiveness of that drug product ○ The drug product is compounded in a state that has entered into a memorandum of understanding (MOU) with FDA that addresses the distribution of inordinate amounts of compounded drug products interstate and provides for appropriate investigation by a state agency of complaints relating to compounded drug products distributed outside such state; or, in states that have not entered into such an MOU with FDA, the licensed pharmacist, licensed pharmacy, or licensed physician does not distribute, or cause to be distributed, compounded drug products out of the state in which they are compounded, more than 5% of the total prescription orders dispensed or distributed by such pharmacy or physician

REFERENCES

Number	Reference
1	Pharmacy Compounding of Human Drug Products Under Section 503A of the Federal Food, Drug, and Cosmetic Act Guidance. Revision 2. Federal Food and Drug Administration. June 2016. https://www.fda.gov/media/94393/download
2	Section 503A of the Federal Food, Drug, and Cosmetic Act. June 2018. https://www.fda.gov/drugs/human-drug-compounding/section-503a-federal-food-drug-and-cosmetic-act
3	Compounding Quality Act. June 2018. https://www.fda.gov/drugs/human-drug-compounding/text-compounding-quality-act#Section

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	1. The requested compounded agent does NOT have an identical (i.e., same route of administration, dose form, and strength) commercially available FDA labeled agent UNLESS that commercially available agent is the subject of a drug shortage making it unavailable for dispensing **AND** 2. The requested agent does NOT have any modified release compounds **AND** 3. ALL of the prescription ingredients in the requested compounded agent have ONE of the following: A. An FDA labeled indication (including the final route of administration) **OR** B. Documentation of compendia support for all prescription ingredients and routes of administrations **AND** 4. If the requested compounded agent is similar to a commercially available product, but differs in dosage, dosage form, and/or omission of dye, sweetener, flavoring, or preservative, then the requested compounded agent is being compounded to meet a specific patient need for which an FDA labeled product is not available (e.g., compounding of liquid formulations for patients unable to swallow; compounding for patients with sensitivities to dyes, preservatives or fillers; compounding of therapeutic strengths not commercially available when the dose is not above FDA labeled maximum dose) **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 12 months for compounds containing only non-controlled substances; 6 months for compounds containing at least one controlled substance

Homozygous Familial Hypercholesterolemia Agents (HoFH)

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Juxtapid® (lomitapide) Capsule	Adjunct therapy to a low-fat diet and other lipid lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), apolipoprotein B (apo B), and non-high density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH). Limitations of Use: • The safety and effectiveness of Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH, including those with heterozygous familial hypercholesterolemia (HeFH) • The effect of Juxtapid on cardiovascular morbidity and mortality has not been determined		1

CLINICAL RATIONALE

HoFH	Homozygous familial hypercholesterolemia (HoFH) is a rare autosomal semi-dominant disease affecting males and females equally, characterized by markedly elevated levels of low-density lipoprotein cholesterol (LDL-C) from conception and accelerated atherosclerotic cardiovascular disease (ASCVD), often resulting in early death. Estimated global prevalence of HoFH by United Nations world region based on 2020 population data, estimates HoFH prevalence ranging from 1:250,000 to 1:360,000. Inadequate awareness and a disconnect between clinical diagnosis and interpretation of genetic results by health providers and payers contribute to underdiagnosis and undertreatment of HoFH. To address this, the European Atherosclerosis Society (EAS) has recently updated clinical guidance for HoFH care to improve education, early diagnosis,

	and improve cardiovascular health for patients with HoFH worldwide. Recent estimates indicate that about 30,000 people worldwide have HoFH but less than 5% are identified.(2) In 2014, the EAS statement on HoFH focused attention on this rare life-threatening disease which at the time had limited therapeutic options. The last decade has shown great progress in understanding the genetic complexity of HoFH, with new highly efficacious LDL-C-lowering therapies leading to improved survival and quality of life. The 2023 EAS consensus statement includes updated criteria for the clinical diagnosis of HoFH and the recommendation to prioritize phenotypic (clinically suspected in the absence of genetic data) features over genotype.(2) The EAS notes plasma LDL-C is the critical discriminator for clinical diagnosis of HoFH. The updated 2023 clinical criteria recommends an untreated LDL-C of >10 mmol/L (>400 mg/dL) is suggestive of HoFH requiring further investigation to confirm the diagnosis (including a detailed medical and family history and/or genetic testing). Additional criteria includes cutaneous or tendon xanthomas before age of 10 years and/or untreated elevated LDL-C levels consistent with heterozygous FH (HeFH) in both parents (or in digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH). Due to the large variety of lipid-lowering treatments that these patients typically receive, the historic cut-offs for a treated LDL-C are likely now obsolete.(2) However, LDL-C criteria are not the sole guide to diagnosis, given the genetic complexity of HoFH and variability in LDL-C levels and clinical phenotype. The updated 2023 genetic criteria are genetic confirmation of bi-allelic pathogenic/likely pathogenic variants on different chromosomes at the LDLR, ApoB, PCSK9, or LDLRAP1 genes or greater than or equal to 2 such variants at different loci. The benefits outweigh the limitations of genetic testing in HoFH with increased certainty of diagnosis and access to, use of, and compliance with appropriate treatment. A significant limitation of genetic testing has and continues to be accessibility and cost. Additionally predicting individual phenotype and clinical response from genotype is not straightforward, and pathogenicity for many detected DNA variants cannot be definitively established. Some patients with phenotypic HoFH have only one or even no pathogenic variant detected, and some patients with bi-allelic pathogenic variants express HeFH but not HoFH phenotypically.(2) The LDL-C level (i.e., the phenotype) and not the presence of a genetic diagnosis drives therapeutic decisions. Combination lipid-lowering therapy, both

	pharmacologic intervention and lipoprotein apheresis (LA), is foundational, together with lifestyle measures (diet and smoking cessation). Patients should start on a high-intensity statin and ezetimibe rather than statin monotherapy, but most will require additional therapies to attain goal. Within 8 weeks PCSK9-directed therapy should be considered where available. Response to these treatments is dependent on LDL receptor (LDL-R) activity. If patients show >15% additional LDL-C reduction, PCSK9-directed therapy may be continued, but if response is poor, clinicians should consider stopping this therapy. While PCSK9 therapy is likely to reduce the risk of ASCVD events, LDL-C levels will remain substantially above recommended goals for most patients. Other options include LDL receptor–independent therapies (such as evinacumab or lomitapide) and/or LA. Lomitapide is noted to provide better control of LDL-C than LA. Preliminary findings from the Pan-European Project in HoFH including 75 patients with HoFH showed that lomitapide treatment for up to 9 years (median 19 months) resulted in more than half attaining at least 50% reduction from baseline in LDL-C at last visit, with less need for apheresis in a substantial proportion of patients. If LA, evinacumab, or lomitapide are not available, liver transplantation can be considered.(2) The National Organization for Rare Disorders (NORD) states that patients with HoFH should be initially started on statins with preference given to higher potency statins (atorvastatin or rosuvastatin) used at the maximal dose noting that statins can be relatively ineffective in HoFH. This is because the mechanism of action of statins normally “triggers” the liver to express additional LDL receptors (LDL-R). In the most severe cases of HoFH, the LDL-R are completely inactive which makes this response futile. Statins can be effective in individuals with HoFH if there is some residual LDL-R activity, or if they have causal DNA variants in the APOB or PCSK9 genes. Patients with HoFH often require additional treatment strategies including lomitapide and evinacumab-dgnb. Additional treatment options include LA or liver transplantation.(4)
Safety	Juxtapid has a boxed warning for risk of hepatotoxicity.(1) Juxtapid can cause elevations in transaminases and increase hepatic fat, with or without concomitant increases in transaminases. Hepatic steatosis associated with Juxtapid treatment may be a risk factor for progressive liver disease, including steatohepatitis and cirrhosis. Measure ALT, AST, alkaline phosphatase, and total bilirubin before initiating treatment and then ALT and AST regularly as recommended. During treatment, adjust the dose of Juxtapid if the ALT or AST are greater than or equal to three times the upper limit of normal. Discontinue Juxtapid for clinically significant liver toxicity. Because of the risk of hepatotoxicity, Juxtapid is available only through a restricted program under a

	Risk Evaluation and Mitigation Strategy (REMS). Juxtapid should be prescribed only to patients with a clinical or laboratory diagnosis consistent with HoFH. The safety and effectiveness of Juxtapid have not been established in patients with hypercholesterolemia who do not have HoFH. Juxtapid is contraindicated in the following conditions:(1) • Pregnancy • Concomitant use with moderate or strong CYP3A4 inhibitors as this can increase Juxtapid exposure • Patients with moderate or severe hepatic impairment (based on Child-Pugh category B or C) and patients with active liver disease, including unexplained persistent elevations of serum transaminases

REFERENCES

Number	Reference
1	Juxtapid prescribing information. Amryt Pharmaceuticals. September 2020.
2	Cuchel, M., Raal, F. J., Hegele, R. A., Al-Rasadi, K., Arca, M., Averna, M., Bruckert, E., Freiberger, T., Gaudet, D., Harada-Shiba, M., Hudgins, L. C., Kayikcioglu, M., Masana, L., Parhofer, K. G., Roeters van Lennep, J. E., Santos, R. D., Stroes, E. S., Watts, G. F., Wiegman, A., ... Ray, K. K. (2023). 2023 Update on European Atherosclerosis Society Consensus Statement on Homozygous Familial Hypercholesterolaemia: new treatments and clinical guidance. *European Heart Journal*, *44*(25), 2277-2291. https://doi.org/10.1093/eurheartj/ehad197
3	Reference no longer used
4	National Organization for Rare Disorders (NORD). (2023, May 25). Familial Hypercholesterolemia. https://rarediseases.org/rare-diseases/familial-hypercholesterolemia/
5	Gidding, S. S., Champagne, M., de Ferranti, S. D., Defesche, J., Ito, M. K., Knowles, J. W., McCrindle, B., Raal, F., Rader, D., Santos, R. D., Lopes-Virella, M., Watts, G. F., & Wierzbicki, A. S. (2015). The Agenda for Familial Hypercholesterolemia. A Scientific Statement from the American Heart Association. Circulation, 132(22), 2167–2192. https://doi.org/10.1161/cir.0000000000000297
6	Reference no longer used

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when BOTH of the following are met: 1. ONE of the following: A. The patient has the diagnosis of homozygous familial hypercholesterolemia (HoFH) and ALL of the following: 1. ONE of the following: A. Genetic confirmation of bi-allelic pathogenic/likely pathogenic variants on different chromosomes at the *LDLR, Apo-B, PCSK9,* or *LDLRAP1* genes, or greater than or equal to 2 such variants at different loci **OR** B. History of untreated LDL-C greater than 400 mg/dL (greater than 10 mmol/L) AND ONE of the following: 1. The patient had cutaneous or tendon xanthomas before age of 10 years **OR** 2. Untreated elevated LDL-C levels consistent with heterozygous FH in both parents, (or in digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH) **AND** 2. ONE of the following: A. The patient has tried a combination of a high-intensity statin (e.g., atorvastatin 40-80 mg, rosuvastatin 20-40 mg daily) and ezetimibe for 2 months and had an inadequate response **OR** B. The patient has an intolerance or hypersensitivity to ALL combinations of a high-intensity statin and ezetimibe **OR** C. The patient has an FDA labeled contraindication to ALL combinations of a high-intensity statin and ezetimibe **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response to a PCSK9 inhibitor **OR** B. The patient has an intolerance or hypersensitivity to ALL PCSK9 inhibitors **OR** C. The patient has an FDA labeled contraindication to ALL PCSK9 inhibitors **AND** 4. The patient will be using with a low-fat diet and/or other lipid-lowering therapy (e.g., statin, PCSK9 inhibitor, lipoprotein apheresis, evinacumab) **AND**

Module	Clinical Criteria for Approval
	5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, endocrinologist, lipid specialist, geneticist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **OR** B. The patient has another FDA labeled indication for the requested agent and route of administration **OR** C. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved for renewal when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. If the patient has a diagnosis of HoFH, BOTH of the following: A. The patient will continue to use with a low fat diet and/or other lipid-lowering therapy (e.g., statin, PCSK9 inhibitor, lipoprotein apheresis, evinacumab) **AND** B. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, endocrinologist, lipid specialist, geneticist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months

Hypoactive Sexual Desire Disorder (HSDD)

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Addyi® (flibanserin) Tablet	Treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD) as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is NOT due to: • A co-existing medical or psychiatric condition • Problems within the relationship • The effects of a medication or other drug substance. Limitations of Use: • Not indicated for the treatment of HSDD in postmenopausal women or in men. • Not indicated to enhance sexual performance		1
Vyleesi® (bremelanotide) Subcutaneous injection	Treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD), as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is NOT due to: • A co-existing medical or psychiatric condition • Problems within the relationship • The effects of a medication or other drug substance Acquired HSDD refers to HSDD that develops in a patient who previously had no problems with sexual desire. Generalized HSDD refers to HSDD that occurs regardless of the type of stimulation, situation, or partner. Limitations of Use:		2

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Not indicated for the treatment of HSDD in postmenopausal women or in men • Not indicated to enhance sexual performance		

CLINICAL RATIONALE

Hypoactive Sexual Desire Disorder	Hypoactive sexual desire disorder (HSDD) is the most common sexual dysfunction in women. It is associated with medical conditions, including depression, and negative emotional and psychological states. HSDD is defined as persistent and recurrent lack of motivation for sexual activity in women who report a loss of desire to initiate or participate in sexual activity with clinically significant personal distress for a minimum of 6 months. The International Society for the Study of Women's Sexual Health recommends the use of the Decreased Sexual Desire Screener and/or a sexual history to accurately diagnosis and determine type of HSDD. Modifiable contributing factors (e.g., relationship dissatisfaction, stress, fatigue, problems related to arousal, pain, and orgasm) should also be evaluated.(3) Although the underlying biological causes of HSDD remain unknown, generalized HSDD likely involves either a predisposition toward inhibitory processes or neuroadaptations that result in decreased excitation, increased inhibition, or a mixture of the two.(3) Neurotransmitters such a dopamine, estrogen, norepinephrine, progesterone, and testosterone are generally considered to be intrinsic to the excitatory aspects of sexual desire and response. But opioids, prolactin, and serotonin are considered to be inhibitory. Many of the existing pharmacological treatments that are utilized for HSDD target some of the hormones and neurotransmitters involved in these pathways.(4) There are several other variables that contribute to HSDD including psychosocial factors (such as self-image and relationship satisfaction), menopause, medications and substances, and comorbid conditions.(3,4) Treatment for HSDD should be focused on the needs of the patient. First line therapy for HSDD is education (including modification of any potentially contributing factors). This may include cognitive behavior therapy, couples counseling, and office-based counseling. Presently there are two pharmacological options that are specifically indicated for HSDD among premenopausal women, bremelanotide and flibanserin. Flibanserin is considered

	a third line option for premenopausal women, according to the International Society for the Study of Women's Sexual Health treatment algorithm and is taken once daily at bedtime.(3) Bremelanotide is administered via autoinjector and is taken on an as needed basis prior to sexual encounters. Patients should not exceed more than one dose in a 24-hour period or eight doses within a 30-day period.(3,4)

Addyi Efficacy	The efficacy of flibanserin for the treatment of HSDD in premenopausal women was established in three 24-week, randomized, double-blind, placebo-controlled trials (studies 1, 2, and 3). The three trials included premenopausal women with acquired, generalized HSDD of at least 6 months duration. In the clinical trials, acquired HSDD was defined as HSDD that developed in patients who previously had no problems with sexual desire. Generalized HSDD was defined as HSDD that was not limited to certain types of stimulation, situations or partners. The patients were treated with Addyi 100 mg once daily at bedtime (n equal to 1187) or placebo (n equal to 1188). The completion rate across these three trials was 69% and 78% for the Addyi and placebo groups, respectively.(1)
	
	These trials each had two co-primary efficacy endpoints, one for satisfying sexual events (SSEs) and the other for sexual desire:
	
	• The change from baseline to Week 24 in the number of monthly SSEs (i.e., sexual intercourse, oral sex, masturbation, or genital stimulation by the partner). The SSEs were based on patient responses to the following questions: "Did you have a sexual event?" and "Was the sex satisfying for you?"
	• Studies 1 and 2 had a different sexual desire endpoint than study 3:
	  ○ In studies 1 and 2, the sexual desire co-primary endpoint was the change from baseline to Week 24 in the calculated monthly sexual desire score and was based on patient responses to the question: "Indicate your most intense level of sexual desire." Every day, patients rated their sexual desire level from 0 (no desire) to 3 (strong desire) and recorded their response in an electronic Diary (eDiary). These responses were summed over a 28-day period to yield the calculated monthly sexual desire score, which ranged from 0 to 84.
	  ○ In study 3, the desire domain of the Female Sexual Function Index (FSFI Desire) was the sexual desire co-primary endpoint. The desire domain of the FSFI has two questions. The first question asks patients "Over the past 4 weeks, how often did you feel sexual desire or interest?", with responses ranging from 1 (almost never or never) to 5 (almost always or always). The second

	question asks patients “Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?”, with responses ranging from 1 (very low or none at all) to 5 (very high). The FSFI Desire score was calculated by adding the patient’s responses to these two questions then multiplying that sum by 0.6. The FSFI Desire domain score ranged from 1.2 to 6.(1) The three trials had a secondary endpoint that measured bother (a component of distress) related to sexual desire using Question 13 of the Female Sexual Distress Scale-Revised (FSDS-R). This question asks, “How often did you feel: Bothered by low sexual desire?” Patients assessed their sexual distress over a 7-day recall period and responded on a scale of 0 (never) to 4 (always). The desire domain of the Female Sexual Function Index (FSFI Desire) was also used as a secondary endpoint in Studies 1 and 2. (1) In all three trials, Addyi resulted in statistically significant improvement compared to placebo in the change from baseline in monthly SSEs at Week 24. In study 1 and 2, there were no statistically significant differences between Addyi and placebo for the eDiary sexual desire endpoint (change in baseline to Week 24). In contrast, in study 3 there was statistically significant improvement in the change from baseline to Week 24 in sexual desire (using the FSFI Desire Domain) with Addyi compared to placebo. The FSFI Desire Domain findings were consistent across all three trials as were the findings for the secondary endpoint that assessed distress using Question 13 of the FSDS-R.(1) Additional analyses defined responders for each efficacy endpoint by anchoring change from baseline to end of treatment with the Patient's Global Impression of Improvement (PGI-I). The first analysis considered responders to be those who reported being “much improved” or “very much improved.” In this analysis, the absolute difference in the percentage of responders with Addyi and the percentage of responders with placebo across the three trials was 8-9% for SSEs (29-39% for Addyi; 21-31% for placebo), 10-13% for FSFI desire domain (43-48% for Addyi; 31-38% for placebo), and 7-13% for FSDS-R Question 13 (21- 34% for Addyi; 14-25% for placebo). The second analysis considered responders to be those who reported being at least minimally improved. The absolute difference in the percentage of responders with Addyi and the percentage of responders with placebo across the three trials was 10-15% for SSEs (44-48% for Addyi; 33-36% for placebo), 12-13% for FSFI desire domain (43-51% for Addyi; 31-39% for placebo), and 9-12% for FSDS-R Question 13 (50-60% for Addyi; 41-48% for placebo).(1)

Vylessi Efficacy	The efficacy in premenopausal women was evaluated in two identical phase 3, randomized, double-blinded, placebo controlled trials. Both trials included premenopausal women with acquired, generalized HSDD of at least 6 months' duration. A majority of patients (74% in Study 1 and 67% in Study 2) reported HSDD with concomitant decreased arousal. The trials consisted of two phases: a Core Study Phase (24-week placebo-controlled, double-blind treatment period) and an uncontrolled, 52-week Open-label Extension Study Phase. Study participants were randomized to subcutaneous injections of Vyleesi 1.75 mg (n= 635) or placebo (n= 632), self-administered by an autoinjector on an as-needed basis. Patients were instructed to administer the drug approximately 45 minutes prior to anticipated sexual activity. Patients were not to administer more than one dose within a 24-hour period and no more than twelve doses per month. The mean duration of HSDD was approximately 4 years. Across the two trials, the median number of Vyleesi injections was 10 in the 24-week double-blind treatment period and 12 during the uncontrolled open-label extension. Most patients used Vyleesi two to three times per month and no more than once a week.(2) Study 1 and Study 2 had the following co-primary efficacy endpoints: • Change from baseline to end of study (EOS) in the Desire domain from the Female Sexual Function Index (FSFI) (Questions 1 and 2). Question 1 asks patients "Over the past 4 weeks, how often did you feel sexual desire or interest?", with responses ranging from 1 (almost never or never) to 5 (almost always or always). Question 2 asks patients "Over the past 4 weeks, how would you rate your level (degree) of sexual desire or interest?", with responses ranging from 1 (very low or none at all) to 5 (very high). The FSFI Desire domain score was calculated by adding the patient's responses to these two questions then multiplying that sum by 0.6. The FSFI Desire Domain score ranged from 1.2 to 6. An increase in the FSFI Desire domain score over time denotes improvement in sexual desire. • Change from baseline to EOS in the score for feeling bothered by low sexual desire as measured by the Female Sexual Distress Scale – Desire/Arousal/Orgasm Question 13 (FSDS-DAO Q13). This question asks patients, "How often did you feel: Bothered by low sexual desire?" Patients assessed their sexual distress over a 30-day recall period and responded on a scale of 0 (never) to 4 (always). A decrease in the FSDSDAO Q13 score over time denotes improvement in the level of distress associated with low sexual desire. EOS is defined as the patient's last study visit during the double-blind treatment period.(2)

	For patients who completed the double-blind treatment period, the EOS visit occurred at Week 24. In both studies, Vyleesi showed a statistically significant increase in the FSFI Desire Domain score and a statistically significant decrease in the FSDS-DAO Q13 score from baseline to the EOS visit compared to placebo. The magnitude of the treatment differences was similar in both studies. There was no significant difference between treatment groups in the change from baseline to end of study visit in the number of satisfying sexual events (SSEs), a secondary endpoint.(2)
Safety	Addyi carries the following boxed warning: • The use of Addyi and alcohol together close in time increases the risk of severe hypotension and syncope. Counsel patients to wait at least two hours after consuming one or two standard alcoholic drinks before taking Addyi at bedtime or to skip their Addyi dose if they have consumed three or more standard alcoholic drinks that evening.(1) Addyi carries the following contraindications: • Addyi is contraindicated in patients taking a moderate or strong CYP3A4 inhibitor. Concomitant use with moderate or strong CYP3A4 inhibitors increases flibanserin concentrations, which can cause severe hypotension and syncope. • Addyi is contraindicated in patients with hepatic impairment. Use in patients with hepatic impairment increases flibanserin concentrations, which can cause severe hypotension and syncope.(1) Vyleesi is contraindicated in patients who have uncontrolled hypertension or known cardiovascular disease.(2)

REFERENCES

Number	Reference
1	Addyi prescribing information. Sprout Pharmaceuticals Inc. September 2021.
2	Vyleesi prescribing information. AMAG Pharmaceuticals, Inc. October 2020.
3	Clayton, Anita H, et al. “The International Society for the Study of Women’s Sexual Health Process of Care for Management of Hypoactive Sexual Desire Disorder in Women.” Mayo Clinic Proceedings, vol. 93, no. 4, 12 Mar. 2018, pp. 467–487., doi: https://doi.org/10.1016/j.mayocp.2017.11.002.

Number	Reference
4	Pachano Pesantez, G. S., & Clayton, A. H. (2021). Treatment of Hypoactive Sexual Desire Disorder Among Women: General Considerations and Pharmacological Options. *Focus (American Psychiatric Publishing)*, *19*(1), 39–45. https://doi.org/10.1176/appi.focus.20200039

ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
62173515 10	Vyleesi	bremelanotide acet subcutaneous soln auto-inj	1.75 MG/0.3ML	Quantity limit for Vyleesi will allow for 6 doses per 30 days			

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient's benefit plan covers the requested agent **AND** 2. The patient is premenopausal **AND** 3. The patient has had a diagnosis of acquired, generalized hypoactive sexual desire disorder (HSDD) and BOTH of the following: A. The patient's diagnosis is characterized by low sexual desire that causes marked distress or interpersonal difficulty **AND**

Module	Clinical Criteria for Approval
	B. The patient's symptoms of low sexual desire have been present for at least 6 months **AND** 4. The HSDD is NOT due to ANY of the following: A. A co-existing medical or psychiatric condition **OR** B. Problems within the relationship **OR** C. The effects of a medication or other drug substance **AND** 5. The patient has tried and had an inadequate response to other treatment modalities (e.g., education, couples counseling, office-based counseling, cognitive behavioral therapy) **AND** 6. The patient will NOT be using the requested agent in combination with another target agent in this program **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 8 weeks NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's prior authorization process **AND** 2. The patient's benefit plan covers the requested agent **AND** 3. The patient is premenopausal **AND** 4. The patient has had clinical benefit with the requested agent (e.g., HSDD symptoms have improved) **AND** 5. The patient will NOT be using the requested agent in combination with another target agent in this program **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity limit** for the **Target Agent(s)** will be approved when the requested quantity (dose) does NOT exceed the program quantity limit **Length of Approval:** Initial: 8 weeks; Renewal: 12 months

Hyftor (sirolimus)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
HYFTOR® (sirolimus) Topical gel	Treatment of facial angiofibroma associated with tuberous sclerosis in adults and pediatric patients 6 years of age and older		1

CLINICAL RATIONALE

Tuberous Sclerosis Complex	Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder caused by a mutation in either the *TSC1* gene or the *TSC2* gene. TSC is characterized by the development of a variety of benign tumors in multiple organs, including the brain, heart, skin, eyes, kidney, lung, and liver. Seizures are the most frequent presenting neurologic feature of TSC, with more than 80% of patients developing seizures during childhood. Facial angiofibromas, the most obvious cutaneous manifestation of TSC, appear as innumerable pink papules that progressively enlarge and multiply over time. The lesions, which are highly visible markers of disease, may spontaneously bleed, impair vision, and cause emotional distress.(2,6) Diagnosis of TSC is made by clinical diagnostic criteria or genetic analysis.(2,6) Identification of a pathogenic variant in *TSC1* or *TSC2* is sufficient for the diagnosis or prediction of TSC regardless of clinical findings, however 10-15% of patients with TSC meeting clinical diagnostic criteria have no mutation identified by conventional genetic testing. Therefore, failure to identify a pathogenic variant in *TSC1* or *TSC2* does not exclude a diagnosis of TSC. Clinical diagnostic criteria indicate a definitive TSC diagnosis if 2 major features or 1 major feature with 2 minor features are met. Major features are: hypomelanotic macules (greater than or equal to 3, at least 5 mm diameter), angiofibroma (greater than or equal to 3) or fibrous cephalic plaque, ungual fibromas (greater than or equal to 2), shagreen patch, multiple retinal hamartomas, multiple cortical tubers and/or radial migration lines, subependymal nodule (greater than or equal to 2), subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangiomyomatosis,

	angiomyolipomas (greater than or equal to 2); note that a combination of LAM and angiomyolipomas, without other features, does not meet the criteria for a definite diagnosis. Minor features are: "confetti" skin lesions, dental enamel pits (greater than or equal to 3), intraoral fibromas (greater than or equal to 2), retinal achromic patch, multiple renal cysts, nonrenal hamartomas, sclerotic bone lesions.(6) There is no significant risk of malignant transformation of skin lesions associated with TSC. When not prominent, the skin lesions do not require treatment. However, closer surveillance and intervention is recommended for skin lesions that rapidly change in size or number, and for those that cause pain, bleeding, functional impairment, or social problems. Procedures to improve the appearance of skin lesions include dermabrasion, laser therapy, or surgical removal (excision) of a lesion.(2,6) These procedures are not effective, however, in preventing early lesions and therefore have less than satisfactory outcomes. Sirolimus topical gel is FDA approved for the treatment of facial angiofibroma associated with TSC in patients age 6 years and older. Although there is rapid response in practically all patients, the possibility of recurrence is quite high. For severely disfiguring facial angiofibromas, a combination of laser therapy or dermabrasion in conjunction with topical sirolimus can be very useful.(2)
Efficacy	Tuberous sclerosis complex (TSC) is associated with genetic defects in the *TSC1* and *TSC2* genes which results in overactivation of the mTOR pathway and benign tumor formation in multiple organs. Sirolimus inhibits mTOR activation.(1,4,5) A single, randomized, double-blind, vehicle-controlled, multicenter, Phase 3 trial evaluated Hyftor for the treatment of adults and pediatric patients 6 years of age and older with facial angiofibroma associated with definite TSC. The response rates of angiofibromas at weeks 4, 8, and 12 of treatment were 0 each in the placebo group in contrast to 20% (95% CI, 8%-39%; p = .01), 43% (95% CI, 26%-63%; p < .001), and 60% (95% CI, 41%-77%; p < .001), respectively, in the sirolimus group.(1,5) In another evaluation of 33 patients with facial angiofibromas associated with TSC, sirolimus gel treatment improved FA associated with TSC in 23 of the 33 (70%) patients after 3 months of treatment. None of the patients discontinued the treatment due to adverse events.(4)
Safety	HYFTOR is contraindicated in patients with a history of hypersensitivity to sirolimus or any other component of HYFTOR.(1)

REFERENCES

Number	Reference
1	HYFTOR prescribing information. Nobelpharma America, LLC. March 2022.
2	DiMario FJ, et al. Tuberous Sclerosis. National Organization for Rare Disorders (NORD). Last updated May 2023. Available at https://rarediseases.org/rare-diseases/tuberous-sclerosis/.
3	Reference no longer used.
4	Hatano T, Ohno Y, Imai Y, et al. Improved Health-Related Quality of Life in Patients Treated with Topical Sirolimus for Facial Angiofibroma Associated with Tuberous Sclerosis Complex. Orphanet J Rare Dis. 2020 Jun;15:133.
5	Wataya-Kaneda M, Ohno Y, Fujita Y, et al. Sirolimus Gel Treatment vs Placebo for Facial Angiofibromas in Patients with Tuberous Sclerosis Complex. JAMA Dermatology. 2018 Jul;154(7):781-788.
6	Northrup H, Aronow ME, Bebin EM, et al. Updated International Tuberous Sclerosis Complex Diagnostic Criteria and Surveillance and Management Recommendations. Pediatr Neurol. 2021 Oct;123:50-66.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of tuberous sclerosis complex (TSC) confirmed by ONE of the following: A. The patient has two major features OR one major and two minor features of TSC clinical diagnostic criteria (Major features: hypomelanotic macules [greater than or equal to 3, at least 5 mm diameter], angiofibroma [greater than or equal to 3] or fibrous cephalic plaque, ungual fibromas [greater than or equal to 2], shagreen patch, multiple retinal hamartomas, multiple cortical tubers and/or radial migration lines, subependymal nodule [greater than or equal to 2], subependymal giant cell astrocytoma, cardiac rhabdomyoma, lymphangiomyomatosis (LAM)*, angiomyolipomas* [greater than or equal to 2]; *note that a combination of LAM and

Module	Clinical Criteria for Approval
	angiomyolipomas, without other features, does not meet the criteria for a definite diagnosis. Minor features: "confetti" skin lesions, dental enamel pits [greater than or equal to 3], intraoral fibromas [greater than or equal to 2], retinal achromic patch, multiple renal cysts, nonrenal hamartomas, sclerotic bone lesions) **OR** B. The patient has a pathogenic variant in the TSC1 gene or TSC2 gene confirmed by genetic testing **AND** 2. The patient has three or more facial angiofibromas **AND** 3. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., dermatologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 weeks NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., dermatologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Hyperhidrosis

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Qbrexza® (glycopyrronium) Cloth	Topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older		1
Sofdra™ (sofpironium) Gel	Topical treatment of primary axillary hyperhidrosis in adults and pediatric patients 9 years of age and older		7

CLINICAL RATIONALE

Hyperhidrosis	Hyperhidrosis is defined as overactive sweating that can be up to four to five times more than necessary, causing embarrassment, discomfort, and anxiety.(5) There are two types of hyperhidrosis, primary and secondary. Primary focal hyperhidrosis refers to excessive sweating that is not caused by another medical condition and usually affects the axillae, palms, soles, face, and head. Secondary generalized hyperhidrosis is defined as excessive sweating caused by another medical condition or as a side effect of medication(s).(6)
	
	Diagnosis of primary focal hyperhidrosis should be made only after excluding secondary causes of excessive sweating.(2,3) The following are recommended diagnosis criteria for primary focal hyperhidrosis:(2,6)
	
	• Focal, visible, excessive sweating of at least 6 months duration without apparent cause with at least two of the following characteristics:
	  ○ Bilateral and relatively symmetric
	  ○ Impairs daily activities
	  ○ Frequency of at least one episode per week
	  ○ Age of onset less than 25 years
	  ○ Positive family history

	○ Cessation of focal sweating during sleep The first line therapy for axillary hyperhidrosis is topical antiperspirants.(2,4) Treatment with prescription antiperspirants (e.g., 20% aluminum chloride hexahydrate) may provide adequate therapy for individuals who have failed to respond to nonprescription antiperspirants, though "clinical strength" 20% aluminum zirconium trichlorohydrex products are now available over-the-counter.(4) Second line therapy includes botulinum toxin injection, topical glycopyrronium, and microwave thermolysis.(2,4) For patients who cannot be managed with first or second lines of therapy, alternative therapies (suction curettage, followed by systemic agents, then endoscopic thoracic sympathectomy) may be considered.(4) Glycopyrronium cloth was studied in two randomized, vehicle-controlled, multicenter trials involving 697 patients. The co-primary endpoints were the proportion of subjects having at least a 4-point improvement from baseline in the weekly mean Axillary Sweating Daily Diary (ASDD) item #2 (a patient reported outcome instrument scored from 0 [no sweating] to 10 [worst possible sweating]) score at Week 4 and the mean absolute change from baseline in gravimetrically measured sweat production at Week 4. Both trials found that more patients in the glycopyrronium tosylate groups achieved the specified ASDD measure of response than in the vehicle groups; pooled response rates were 60 versus 28 percent. In the second trial, patients in the glycopyrronium tosylate group had a greater mean absolute change in sweat production compared with the vehicle group.(1)
Safety	Qbrexza is contraindicated in patients with medical conditions that can be exacerbated by the anticholinergic effect of Qbrexza (e.g., glaucoma, paralytic ileus, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis, Sjogren's syndrome).(1) Sofdra is contraindicated in patients with medical conditions that can be exacerbated by the anticholinergic effect of Sofdra (e.g., glaucoma, paralytic ileus, unstable cardiovascular status in acute hemorrhage, severe ulcerative colitis, toxic megacolon complicating ulcerative colitis, myasthenia gravis, Sjogren's syndrome).(7)

REFERENCES

Number	Reference
1	Qbrexza prescribing information. Journey Medical Corporation. November 2022.
2	Hornberger J, Grimes K, Naumann M, et al. Recognition, Diagnosis, and Treatment of Primary Focal Hyperhidrosis. J Am Acad Dermatol. 2004 Aug;51(2):274-286.
3	Diagnosis Guidelines. International Hyperhidrosis Society: Official Site. Available at: https://www.sweathelp.org/about-hyperhidrosis/diagnosis-guidelines.html.
4	Primary Focal Axillary Hyperhidrosis Clinical Guideline. International Hyperhidrosis Society: Official Site. Available at: https://www.sweathelp.org/treatments-hcp/clinical-guidelines/primary-focal-hyperhidrosis/primary-focal-axillary.html.
5	Defining Hyperhidrosis. International Hyperhidrosis Society: Official Site. Available at: https://www.sweathelp.org/home/defining-hyperhidrosis.html.
6	Two Types of Hyperhidrosis. International Hyperhidrosis Society: Official Site. Available at: https://www.sweathelp.org/home/types-of-hyperhidrosis.html.
7	Sofdra prescribing information. Botanix SB Inc. June 2024.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of primary axillary hyperhidrosis defined by BOTH the following: A. Focal, visible, excessive sweating of at least 6 months duration without apparent cause **AND**

Module	Clinical Criteria for Approval
	B. TWO of the following characteristics: bilateral and relatively symmetric, impairs daily activities, frequency of at least one episode per week, age of onset less than 25 years, positive family history, cessation of focal sweating during sleep **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to 20% aluminum based topical antiperspirant (e.g., Drysol, OTC) **OR** B. The patient has an intolerance or hypersensitivity to 20% aluminum based topical antiperspirant **OR** C. The patient has an FDA labeled contraindication to 20% aluminum based topical antiperspirant **AND** 3. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 3 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. The prescriber has provided information in support of therapy with a higher dose for the requested indication **Length of Approval**: Initial: 3 months; Renewal: 12 months

Interstitial Lung Disease (ILD)

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Esbriet® (pirfenidone)* Tablet Capsule	Treatment of idiopathic pulmonary fibrosis (IPF)	* generic available	1
Ofev® (nintedanib) Capsule	Treatment of idiopathic pulmonary fibrosis (IPF) Slow the rate of decline in pulmonary function in patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD) Treatment of chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype		2

CLINICAL RATIONALE

Interstitial Lung Disease	Interstitial lung diseases (ILD) encompass a varied group of more than 200 lung disorders that affect the tissue and space around the alveoli. They are classified together because of similar physiologic, radiographic, clinical, or pathologic manifestations: respiratory symptoms such as shortness of breath and cough, specific chest radiographic abnormalities, typical changes on pulmonary function tests in which lung volume is decreased, and characteristic microscopic patterns of inflammation and fibrosis. Fibrosis is characterized by an increased amount and abnormal structure of the connective tissue, with lung biopsies with a predominance of fibrosis typically indicating advanced disease and poor prognosis.(11) The underlying causes of ILD can be classified into four categories: diseases associated with a condition that affects other parts of the body (e.g., autoimmune, collagen vascular disease), exposure to agents known to damage

	the lungs (e.g., medications, occupational exposures [e.g., asbestos, tobacco smoke]), genetic abnormalities (e.g., Hermansky-Pudlak syndrome), or idiopathic etiology (the most common form).(13)
Idiopathic Pulmonary Fibrosis (IPF)	Idiopathic pulmonary fibrosis (IPF) is a form of chronic, progressive fibrosing interstitial pneumonia of unknown origin occurring primarily in older adults and is limited to the lungs.(5,6) IPF is associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP).(4,6,17) IPF is characterized by fibroblast foci, featuring vigorous replication of mesenchymal cells and disposition of extracellular matrix. It is thought that repeated episodes of acute lung injury, due to unknown stimulus, leads to wound healing and fibrosis, with loss of lung function.(7) The natural progression can vary with some patients remaining stable for extended periods of time; some having steady, but rapid progression; and some patients experiencing acute exacerbations.(3) Historically, a diagnosis of IPF has been associated with a poor prognosis with many only living for 3-5 years post diagnosis. The estimated prevalence of IPF within the United States has been difficult to establish due to the historical lack of a uniform definition, evolving diagnostic criteria, and difference in case-finding methodologies and study designs. The range is between 14-63 per 100,000 population with an annual incidence of approximately 7-16 per 100,000 population.(4) Guidelines suggest that IPF be considered in adult patients presenting with unexplained chronic exertional dyspnea, cough, bibasilar inspiratory crackles, and/or finger clubbing.(4,6) An accurate diagnosis of IPF is a difficult and challenging process. The accuracy of the diagnosis increases with an integrated multidisciplinary approach. This includes dynamic discussion between pulmonologists, radiologists, and pathologists (when appropriate) who are experienced in the diagnosis of ILD.(3) The diagnosis of IPF requires exclusion of other known causes of ILD (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity), and either the presence of a UIP pattern on HRCT in patients not subjected to surgical lung biopsy (SLB) OR specific combinations of HRCT patterns and histopathological patterns in patients subjected to SLB.(3,6,17) The 2018 and updated 2022 guidelines provide a new diagnostic algorithm and schema for correlating histologic and radiologic findings in patients with suspected IPF. Aspects of this algorithm include criteria for four diagnostic categories for patterns of UIP based on HRCT findings (i.e., UIP, probable UIP, indeterminate for UIP, and alternative diagnosis), and four levels of certainty for

histopathologic diagnosis (i.e., UIP, probable UIP, indeterminate for UIP, and alternative diagnosis).(6,17)

UIP is characterized on HRCT by the presence of peripheral, basilar-predominant opacities associated with honeycombing and traction bronchiectasis-bronchiolectasis. In patients whose HRCT does not demonstrate a UIP pattern, the surgical lung biopsy may demonstrate UIP pattern on histopathology.(6,17) Table 1 below shows the algorithm for diagnosis with the updated guidelines.

Table 1. Idiopathic pulmonary fibrosis diagnosis based upon HRCT and biopsy patterns(6,17)

IPF Suspected*		Histopathology Pattern			
		UIP	**Probable UIP**	**Indeterminate for UIP (or biopsy not performed)**	**Alternative Diagnosis**
HRCT Pattern	**UIP**	IPF	IPF	IPF	Non-IPF diagnosis
	Probable UIP	IPF	IPF	IPF (likely)**	Non-IPF diagnosis
	Indeterminate	IPF	IPF (likely)**	Indeterminate***	Non-IPF diagnosis
	Alternative Diagnosis	IPF (likely)**	Indeterminate***	Non-IPF diagnosis	Non-IPF diagnosis

* ”Clinically suspected of having IPF” = unexplained patterns of bilateral pulmonary fibrosis on a chest radiography or chest CT, bibasilar inspiratory crackles, and age greater than 60 years. (Middle aged adults [greater than 40 years and less than 60 years], can rarely present with otherwise clinical features, especially in patients with features suggesting familial pulmonary fibrosis.)

** IPF is the likely diagnosis when any of the following features are present:

- Moderate-to-severe traction bronchiectasis and/or bronchiolectasis (defined as mild traction bronchiectasis and/or bronchiolectasis in four or more lobes, including the lingula as a lobe, or moderate to severe traction bronchiectasis in two or more lobes) in a man over age 50 years or in a woman over age 60 years

	• Extensive (greater than 30%) reticulation on HRCT and an age greater than 70 years • Increased neutrophils and/or absence of lymphocytosis in BAL fluid • Multidisciplinary discussion reaches a confident diagnosis of IPF *** Indeterminate for IPF • Without an adequate biopsy remains indeterminate • With an adequate biopsy may be reclassified to a more specific diagnosis after multidisciplinary discussion and/or additional consultation Prior to the simultaneous approvals of Esbriet (pirfenidone) and Ofev (nintedanib), there was no FDA approved pharmacologic therapy for idiopathic pulmonary fibrosis. The updated ATS/ERS/JRS/ALAT (American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society) clinical practice guidelines address nintedanib and pirfenidone treatment for IPF. The guidelines suggest that clinicians use nintedanib or pirfenidone in patients with IPF (conditional recommendation, moderate confidence in estimates of effects). As with other interventions, the available evidence focuses on patients with IPF with mild to moderate impairment in pulmonary function tests; it is unknown whether the therapeutic benefits would differ in patients with a more severe impairment in pulmonary function testing or those with other comorbidities. The evidence does not allow suggestions about the optimal duration of therapy, and it is unknown how long the treatment effect endures with ongoing drug therapy.(5,17) Currently, there are no head-to-head trials comparing the two agents. A retrospective cohort study assessed the clinical effectiveness of nintedanib and pirfenidone in the treatment of IPF. The primary outcome was all-cause mortality, which was seen reduced in the treated cohort versus the untreated cohort. This mortality benefit was only observed for the first two years of follow-up. No significant differences were noted in all-cause mortality between patients treated with nintedanib versus pirfenidone; however, pirfenidone had a slightly more favorable trend.(14) The possibility that combined therapy might be of greater benefit is under investigation, with results supporting further research into combination treatment with pirfenidone and nintedanib. An open-label, randomized trial (INJOURNEY) evaluating the safety and tolerability of nintedanib with add-on pirfenidone demonstrated a manageable safety and tolerability profile in patients with IPF, in line with the adverse event profiles of each

	drug.(15) Another trial, open-label, 24-week, single-arm, phase IV study, assessed safety and tolerability of treatment with pirfenidone and nintedanib in patients with IPF. Combined pirfenidone and nintedanib use for 24 weeks was tolerated by the majority of patients with IPF and associated with a similar pattern of adverse events expected for either treatment alone.(16)
Systemic Sclerosis (Scleroderma)-Associated Interstitial Lung Disease (SSc-ILD)	Systemic sclerosis is a connective tissue disease (CTD) that affects numerous organ systems, including skin, blood vessels, heart, lungs, kidneys, gastrointestinal, and musculoskeletal. Pulmonary disease is the leading cause of death in patients with systemic sclerosis, and ILD is a common manifestation that tends to occur early in the course of systemic sclerosis.(8) The American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) collaborated on classification criteria for the diagnosis of systemic sclerosis, in which they note that systemic sclerosis-associated ILD is diagnosed when there is radiographic evidence of diffuse parenchymal lung disease in patients with systemic sclerosis. The ACR/EULAR criteria note that ILD is defined as pulmonary fibrosis seen on HRCT or chest radiography, most pronounced in the basilar portions of the lungs.(10) The American College of Rheumatology (ACR) published a treatment algorithm for systemic sclerosis and related conditions. The ACR recommends the following treatment options for systemic sclerosis (scleroderma)-associated interstitial lung disease (SSc-ILD):(9) Induction therapy: • Mycophenolate mofetil (MMF) as first line therapy • IV cyclophosphamide as second line therapy • Rituximab as third line therapy • Lung transplant or hemopoietic stem cell transplant for select patients as fourth line therapy Maintenance therapy: • Mycophenolate mofetil (MMF) as first line therapy • Azathioprine as second line therapy • IV or oral cyclophosphamide as third line therapy
Chronic Fibrosing Interstitial Lung Disease with Progressive Phenotype	Patients that have a progressive fibrosing phenotype tend to be characterized by an increasing extent of fibrosis on HRCT, decreasing lung function, worsening of symptoms and quality of life, and early death despite treatment. The progressive

	phenotype is similar to IPF in clinical behavior and in many of the underlying pathogenic mechanisms, such as repeated chronic epithelial or vascular injuries leading to cell destruction and unregulated repair, that drive a self-sustaining process of pulmonary fibrosis.(12) There are currently no guidelines to define the management of patients with ILD with a progressive phenotype.(11)
Efficacy - Esbriet	ASCEND was a phase 3, randomized, double-blind, placebo-controlled, 52-week trial comparing pirfenidone 2403 mg/day (n=278) versus placebo (n=277) in patients with IPF. The primary endpoint was the change in FVC or death at week 52. In the pirfenidone group, there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percent predicted FVC or who died; there was also a relative increase of 132.5% in the proportion of patients with no decline in FVC (p less than 0.001). Pirfenidone reduced the decline in 6-minute walk distance (6MWD; p=0.04) and improved progression-free survival (PFS; p less than 0.001). There were no significant between-group differences in dyspnea scores (p=0.16), or in rates of death from any cause (p=0.10) or from IPF (p=0.23).(1) CAPACITY 004 and CAPACITY 006 were wo concurrent, phase 3, randomized, double-blind, placebo-controlled trials comparing pirfenidone and placebo in patient with IPF. The primary endpoint was the change in percent predicted FVC from baseline to week 72. In CAPACITY 004, patients were randomized 2:1:2 to pirfenidone 2403 mg/day (n=174), pirfenidone 1197 mg/day (n=87), or placebo (n=174). In CAPACITY 006, patients were randomized 1:1 to pirfenidone 2403 mg/day (n=171) or placebo (n=173).(1) In CAPACITY 004, pirfenidone reduced decline in FVC (p=0.001), mean FVC change at week 72 was -8.0% (SD 16.5) in the pirfenidone 2403 mg/day group, and −12.4% (18.5) in the placebo group (difference 4.4%, 95% CI 0.7-9.1); 35/174 (20%) vs. 60/174 (35%) patients, respectively, had a decline of at least 10%. A significant treatment effect was noted at all timepoints from week 24 and in an analysis over all study timepoints (p=0.0007). Mean change in percentage FVC in the pirfenidone 1197 mg/day group was intermediate to that in the pirfenidone 2403 mg/day and placebo groups.(1) In CAPACITY 006, the difference between groups in FVC change at week 72 was not significant (p=0.501). Mean change in FVC at week 72 was −9.0% (SD 19.6) in the pirfenidone group and −9.6% (19.1) in the placebo group, and the difference between groups in predicted FVC change at week 72 was not significant (0.6%, −3.5 to 4.7); however, a consistent pirfenidone effect was apparent until week 48 (p=0.005) and in an analysis of all study timepoints (p=0.007).(1)

Efficacy - Ofev	INPULSIS-1 and INPULSIS-2 were two replicate 52-week phase 3 trials that evaluated safety and efficacy of nintedanib twice daily compared to placebo in 1066 patients with IPF. Patients were randomized 3:2 to nintedanib or placebo. The primary endpoint was the annual rate of decline in FVC. In INPULSIS-1, the adjusted annual rate of change in FVC was −114.7 mL with nintedanib vs. −239.9 mL with placebo (difference, 125.3 mL; 95% CI, 77.7-172.8; p less than 0.001). There was no difference between groups in the time to the first acute exacerbation (HR with nintedanib, 1.15; 95% CI, 0.54-2.42; p=0.67). In INPULSIS-2, the adjusted annual rate of change in FVC was -113.6 mL with nintedanib vs. -207.3 mL with placebo (difference, 93.7 mL; 95% CI, 44.8-142.7; p less than 0.001). There was a significant benefit with nintedanib vs. placebo in the time to the first acute exacerbation (HR, 0.38; 95% CI, 0.19-0.77; p=0.005).(2) INBUILD was a randomized, double-blind, placebo-controlled trial evaluated the use of nintedanib in 663 patients with progressive fibrosing ILD. The primary endpoint was the annual rate of decline in FVC over 52 weeks. The two primary populations for analysis of the primary endpoint were the overall population and patients with a UIP-like fibrotic pattern. In the overall population, the adjusted rate of decline in FVC was -80.8 mL/year with nintedanib vs. -187.8 mL/year with placebo (treatment difference: 107.0 mL/year; 95% CI, 65.4-148.5; p less than 0.001). In patients with a UIP-like fibrotic pattern, the adjusted rate of decline in FVC was -82.9 mL/year with nintedanib vs. -211.1 mL/year with placebo (treatment difference: 128.2 mL/year; 95% CI, 70.8-185.6; p less than 0.001).(2) SENSCIS was a randomized, double-blind, placebo-controlled trial evaluated the use of nintedanib in 576 patients with SSc-ILD. The primary endpoint was the annual rate of decline in FVC over 52 weeks; key secondary endpoints were absolute changes from baseline in the modified Rodnan skin score and in the total score on the SGRQ at week 52. The adjusted annual rate of change in FVC was -52.4 mL/year with nintedanib vs. -93.3 mL/year with placebo (treatment difference: 41.0 mL/year; 95% CI, 2.9-79.0; p=0.04). Secondary endpoint measurements did not differ significantly between treatment arms.(2)
Safety	Neither Esbriet nor Ofev have any FDA labeled contraindications.(1,2)
Safety	Neither Esbriet nor Ofev have any FDA labeled contraindications.(1,2)

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1	Esbriet prescribing information. Genentech USA, Inc. February 2023.
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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of idiopathic pulmonary fibrosis (IPF) AND ALL of the following: 1. Other known causes of interstitial lung disease (ILD) have been excluded (e.g., domestic and occupational environmental exposures, connective tissue diseases, drug toxicities, alternative diagnoses, etc) **AND** 2. ONE of the following: A. The patient had a high-resolution computed tomography (HRCT) scan with results showing a pattern for usual interstitial pneumonia (UIP) **OR** B. The patient had a surgical lung biopsy with pathology confirming UIP **OR** C. The patient had a HRCT scan with results showing a pattern for probable UIP AND a surgical lung biopsy with pathology indicating probable UIP **OR** B. The patient has a diagnosis of systemic sclerosis-associated interstitial lung disease (SSc-ILD) AND ALL of the following:

Module	Clinical Criteria for Approval
	1. The requested agent is Ofev **AND** 2. The patient's diagnosis has been confirmed on high-resolution computed tomography (HRCT) or chest radiography scans **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response to ONE conventional agent (i.e., mycophenolate mofetil, cyclophosphamide, azathioprine) **OR** B. The patient has an intolerance or hypersensitivity to ONE conventional agent **OR** C. The patient has an FDA labeled contraindication to ALL conventional agents **OR** C. The patient has a diagnosis of chronic fibrosing interstitial lung disease (ILD) with a progressive phenotype AND ALL of the following: 1. The requested agent is Ofev **AND** 2. The patient has greater than 10% fibrotic features on HRCT **AND** 3. The patient presented with clinical signs of progression, defined by at least ONE of the following: A. FVC decline greater than or equal to 10% **OR** B. FVC decline greater than or equal to 5% and less than 10% with worsening symptoms or imaging **OR** C. Worsening symptoms and worsening imaging within the past 24 months **AND** 4. The patient has an FVC greater than or equal to 45% of predicted **AND** 5. The patient has a diffusion capacity of the lungs for carbon monoxide (DLCO) between 30% to less than 80% of predicted **AND** 6. The patient does NOT meet any of the following: A. A diagnosis of IPF B. Relevant airway obstructions (i.e., pre-bronchodilator FEV1/FVC less than 0.7) C. Significant pulmonary hypertension D. Greater than 1.5 times the upper limit of normal for ALT, AST, or bilirubin E. Known risk or predisposition to bleeding F. Receiving full dose anticoagulation treatment G. Recent history of MI or stroke **OR** D. The patient has another FDA approved indication for the requested agent **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., pathologist, pulmonologist, radiologist, rheumatologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**

Module	Clinical Criteria for Approval
	3. The patient will NOT be using the requested agent in combination with another agent included in this prior authorization program **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., pathologist, pulmonologist, radiologist, rheumatologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with another agent included in this prior authorization program **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. The prescriber has provided information in support of therapy with a higher dose for the requested indication **Length of Approval:** 12 months

Imcivree

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Imcivree® (setmelanotide) Subcutaneous injection	Chronic weight management in adult and pediatric patients 6 years of age or older with monogenic or syndromic obesity due to: • Pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) • Bardet-Biedl syndrome (BBS) Limitations of Use: Imcivree is not indicated for the treatment of patients with the following conditions as Imcivree would not be expected to be effective: • Obesity due to suspected POMC, PCSK1, or LEPR deficiency with POMC, PCSK1, or LEPR variants classified as benign or likely benign • Other types of obesity not related to POMC, PCSK1, or LEPR deficiency, or BBS, including obesity associated with other genetic syndromes and general (polygenic) obesity		1

CLINICAL RATIONALE

Monogenic Obesity Disorders	There is a strong genetic component to human obesity. Most genes that influence an individual's predisposition to gain weight are not yet known. However, a glimpse into the long-term regulation of body weight has come from

	studying extreme human obesity caused by single gene defects. These monogenic (single-gene) obesity disorders have confirmed that the hypothalamic leptin-melanocortin system is critical for energy balance in humans because disruption of these pathways causes the most severe obesity phenotypes. Approximately 20 different genes and at least 3 different mechanisms implicated in monogenic causes of obesity have been identified, however, they account for less than 5% of all severe obesity. Monogenic forms of obesity can be divided into three broad categories; the category further discussed in this program is that which is caused by mutations in genes that have a physiologic role in the hypothalamic Leptin-Melanocortin system of energy balance. Obesity due to leptin receptor mutations, proopiomelanocortin mutations, and proprotein convertase mutations will be addressed further here.(2,3) Congenital leptin (LEP) and leptin receptor (LEPR) deficiency are rare, autosomal recessive disorders associated with severe obesity from a very young age (before 2 years). The clinical phenotypes associated with congenital leptin and leptin receptor deficiencies are similar. Patients are born of normal birth weight but exhibit rapid weight gain in the first few months of life resulting in severe obesity. Affected subjects are characterized by intense hyperphagia with food seeking behavior and aggression when food is denied.(4) Leptin suppresses food intake in part by acting on hypothalamic neurons expressing pro-opiomelanocortin (POMC). People who are homozygous or compound heterozygous for loss of function mutations in the POMC gene are hyperphagic and develop early-onset obesity due to loss of melanocortin signaling at the MC4R in the hypothalamus. In the pituitary, POMC is the precursor for adrenocorticotropin (ACTH). As such, POMC deficiency presents in neonatal life with findings of secondary adrenal insufficiency: hypoglycemia, cholestatic jaundice, or other features of adrenal crisis requiring long-term corticosteroid replacement therapy.(2,4,5,6) Such children have pale skin, and white Caucasians have red hair, due to the lack of melanocortin function at melanocortin 1 receptors in the skin.(2,4,6) The prevalence of POMC is believed to be fewer than 10 patients worldwide.(2,3,5) Prohormone convertase-1 (PCSK1, also known as PC1/3) is an enzyme that acts upon a range of substrates including proinsulin, proglucagon, and POMC. Compound heterozygous or homozygous mutations in PCSK1 cause neonatal small bowel enteropathy, glucocorticoid deficiency (secondary to ACTH deficiency), hypogonadotropic hypogonadism and postprandial hypoglycemia due to impaired processing of proinsulin to insulin as well as severe, early onset

	obesity.(4) The prevalence of PCSK1 deficiency is believed to be fewer than 20 patients worldwide.(3) Rhythm Pharmaceuticals has started a registry for patients with certain rare genetic disorders of obesity, and their "Uncovering Rare Obesity Program" offers free genetic testing in the United States for patients of all ages.
Syndromic Obesity Disorders	Syndromic obesity corresponds to severe obesity associated with additional phenotypes (e.g., mental retardation, dysmorphic features, and organ-specific developmental abnormalities). Prader-Willi (PWS) and Bardet-Biedl (BBS) syndromes are the two syndromes most frequently linked with obesity, though many other syndromes are now associated with obesity.(3) BBS is a rare autosomal recessive ciliopathy characterized by retinal dystrophy, obesity, post-axial polydactyly, renal dysfunction, learning difficulties, and hypogonadism.(2,3,4,8) Diagnosis is based on clinical findings; four primary features OR three primary and two secondary features are required to make a clinical diagnosis.(8,9) Molecular genetic testing is also available and currently 16 genes are known to be associated with Bardet–Biedl syndrome (BBS); this accounts for approximately 80% of those clinically diagnosed with BBS.(8)
Efficacy	Setmelanotide is an MC4 receptor agonist with 20-fold less activity at the melanocortin 3 (MC3) and melanocortin 1 (MC1) receptors. MC4 receptors in the brain are involved in regulation of hunger, satiety, and energy expenditure.(1,5) In patients with obesity due to POMC, PCSK1, and LEPR deficiency associated with insufficient activation of the MC4 receptor, setmelanotide may re-establish MC4 receptor pathway activity to reduce hunger and promote weight loss through decreased caloric intake and increased energy expenditure.(1,6) The safety and efficacy of setmelanotide for chronic weight management in patients with obesity due to POMC, PCSK1, and LEPR deficiency were assessed in 2 identically designed, 1-year, open-label studies, each with an 8-week, double-blind withdrawal period. Study 1 (NCT02896192) enrolled patients aged 6 years and above with obesity and genetically confirmed or suspected POMC or PCSK1 deficiency, and Study 2 (NCT03287960) enrolled patients aged 6 years and above with obesity and genetically confirmed or suspected LEPR deficiency. The studies enrolled patients with bi-allelic, homozygous, or presumed compound heterozygous pathogenic, likely pathogenic variants, or VUS for either the POMC or PCSK1 genes (Study 1) or the LEPR gene (Study 2). Patients with double heterozygous variants in 2 different genes were not eligible for treatment. In both studies, adult patients had a body mass index (BMI) of greater than or equal to

	30 kg/m^2.(1,7) Weight in pediatric patients was greater than or equal to 95th percentile using growth chart assessments.(1) In Study 1, 80% of patients with obesity due to POMC or PCSK1 deficiency met the primary endpoint, achieving a greater than or equal to 10% weight loss after 1 year of treatment. In Study 2, 46% of patients with obesity due to LEPR deficiency achieved a greater than or equal to 10% weight loss after 1 year of treatment.(1,7) The safety and efficacy of setmelanotide for chronic weight management in adult and pediatric patients aged 6 years and older with obesity and a clinical diagnosis of Bardet-Biedl syndrome (BBS) were assessed in a 66-week clinical study, which included a 14-week randomized, doubleblind, placebo-controlled period and a 52-week open-label period (Study 3 [NCT03746522]). The study enrolled patients aged 6 years and above with obesity and a clinical diagnosis of BBS. Adult patients had a BMI of greater than or equal to 30 kg/m^2 and pediatric patients had weight greater than or equal to 97th percentile using growth chart assessments.(1,9) Clinical diagnosis of BBS in study participants required four primary features OR three primary and two secondary features.(9) In Study 3, 38.7% of patients with obesity due to BBS met the primary endpoint, achieving a greater than or equal to 10% weight loss after 1 year of treatment.(1)
Safety	Imcivree is contraindicated in patients with a severe hypersensitivity reaction to setmelanotide or any of the excipients in Imcivree.(1)

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Number	Reference
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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient's benefit plan covers the requested agent **AND** 2. ONE of the following: A. ALL of the following: 1. The patient has a diagnosis of monogenic obesity due to pro-opiomelanocortin (POMC) deficiency, proprotein convertase subtilisin/kexin type 1 (PCSK1) deficiency, or leptin receptor (LEPR) deficiency **AND** 2. Genetic testing with an FDA-approved test has confirmed variants in POMC, PCSK1, or LEPR genes (medical records required) **AND**

Module	Clinical Criteria for Approval
	3. The patient's genetic status is bi-allelic, homozygous, or compound heterozygous (NOT double heterozygous) **AND** 4. The patient's genetic variant is interpreted as pathogenic, likely pathogenic, OR of uncertain significance (VUS) **AND** 5. The patient's genetic variant is NOT classified as benign or likely benign **OR** B. BOTH of the following: 1. The patient has a diagnosis of syndromic obesity due to Bardet-Biedl syndrome (BBS) **AND** 2. The patient's diagnosis has been clinically confirmed by four primary features OR three primary and two secondary features (medical records required) (i.e., primary features [rod-cone dystrophy, polydactyly, obesity, genital anomalies, renal anomalies, learning difficulties]; secondary features [speech delay, developmental delay, diabetes mellitus, dental anomalies, congenital heart disease, bracydactyly/syndactyly, ataxia/poor coordination, anosmia/hyposmia]) **AND** 3. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 4. ONE of the following: A. For adult patients, the body mass index (BMI) is greater than or equal to 30 kg/m^2 **OR** B. For pediatric patients, weight is greater than or equal to 95th percentile (for POMC, PCSK1, or LEPR) or 97th percentile (for BBS) using growth chart assessments **AND** 5. ONE of the following: A. The patient is newly starting therapy **OR** B. ONE of the following: 1. For patients with obesity due to POMC, PCSK1, or LEPR deficiency, ONE of the following: A. The patient is currently being treated and has received less than 16 weeks (4 months) of therapy **OR** B. The patient has received at least 16 weeks of therapy, and has achieved a weight loss of ONE of the following: 1. Weight loss of greater than or equal to 5% of baseline body weight (prior to the initiation of the requested agent) **OR** 2. For patients with continued growth potential, weight loss of greater than or equal to 5% of baseline BMI (prior to the initiation of the requested agent) **OR** 2. For patients with obesity due to BBS, ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient is currently being treated and has received less than one year of therapy **OR** B. The patient has received at least one year of therapy, and has achieved a weight loss of ONE of the following: 1. Weight loss of greater than or equal to 5% of baseline body weight (prior to the initiation of the requested agent) **OR** 2. For patients aged less than 18 years, weight loss of greater than or equal to 5% of baseline BMI (prior to the initiation of the requested agent) **AND** 6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist, metabolic disorders) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 4 months for POMC, PCSK1, or LEPR deficiency; 12 months for BBS NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient's benefit plan covers the requested agent **AND** 3. ONE of the following: A. For adult patients, the patient has achieved and maintained weight loss of greater than or equal to 5% of baseline body weight (prior to the initiation of the requested agent) **OR** B. ONE of the following: 1. For patients with POMC, PCSK1, or LEPR deficiency AND continued growth potential, the patient has achieved and maintained weight loss of greater than or equal to 5% of baseline BMI (prior to the initiation of the requested agent) **OR** 2. For patients with BBS AND are aged less than 18 years, the patient has achieved and maintained weight loss of greater than or equal to 5% of baseline BMI (prior to the initiation of the requested agent) **AND**

Module	Clinical Criteria for Approval
	4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist, metabolic disorders) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** Initial - up to 4 months for POMC, PCSK1, or LEPR deficiency; up to 12 months for BBS Renewal - up to 12 months

Insomnia Agents

Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
AMBIEN® (zolpidem)*^ Tablet	Short-term treatment of insomnia characterized by difficulties with sleep initiation	*Hypnotics classified as Schedule IV controlled substances ^generic available	2
AMBIEN CR® (zolpidem CR)*^ Tablet	Short-term treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance	*Hypnotics classified as Schedule IV controlled substances ^generic available	1
Belsomra® (suvorexant)* Tablet	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance	*Hypnotics classified as Schedule IV controlled substances	3
DAYVIGO® (lemborexant)* Tablet	Treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance	*Hypnotics classified as Schedule IV controlled substances	13
EDLUAR®	Short-term treatment of insomnia characterized by difficulties with sleep initiation	*Hypnotics classified as Schedule IV	4

Agent(s)	FDA Indication(s)	Notes	Ref#
(zolpidem)* Sublingual tablet		controlled substances	
Lunesta® (eszopiclone)*^ Tablet	Treatment of insomnia	*Hypnotics classified as Schedule IV controlled substances ^generic available	6
QUVIVIQ® (daridorexant)* Tablet	Treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance	*Hypnotics classified as Schedule IV controlled substances	14
Rozerem® (ramelteon)^ Tablet	Treatment of insomnia characterized by difficulty with sleep onset	^generic available	7
Silenor® (doxepin)^ Tablet	Treatment of insomnia characterized by difficulty with sleep maintenance	^generic available	8
Zolpidem Tartrate* Capsule	Short-term treatment of transient insomnia characterized by difficulties with sleep initiation in adults younger than age 65 years of age	*Hypnotics classified as Schedule IV controlled substances	16
Zolpidem	Treatment of insomnia when a middle-of-the-night awakening is followed by difficulty returning to sleep	*Hypnotics classified as	5

Agent(s)	FDA Indication(s)	Notes	Ref#
Sublingual tablet		Schedule IV controlled substances	
ZolpiMist (zolpidem)* Oral spray	Short-term treatment of insomnia characterized by difficulties with sleep initiation	*Hypnotics classified as Schedule IV controlled substances	9

CLINICAL RATIONALE

Insomnia	Insomnia is the most prevalent sleep disorder and can be associated with numerous adverse effects on function, health, and quality of life. (10,11) The American Academy of Sleep Medicine and the American College of Physicians created clinical guidelines for the management (psychological/behavioral and pharmacological).(10,11,15) The guidelines indicate psychological/behavioral interventions are first line and as effective as pharmacologic therapies. Initial approaches to treatment should include at least one behavioral intervention such as stimulus control therapy or relaxation therapy, or the combination of cognitive therapy, stimulus control therapy, sleep restriction therapy with or without relaxation therapy, otherwise known as cognitive behavioral therapy for insomnia (CBT-I). Short-term hypnotic therapy should be supplemented with behavioral and cognitive therapies.(10,15) The guidelines recommend these general sequence of medication trials for patients with primary insomnia:(15) • Short-intermediate acting benzodiazepine receptor agonists (BZD or newer BzRAs) or ramelteon: examples of these medications include zolpidem, eszopiclone, zaleplon, and temazepam • Alternate short-intermediate acting BzRAs or ramelteon if the initial agent has been unsuccessful • Sedating antidepressants, especially when used in conjunction with treating comorbid depression/anxiety: examples of these include trazodone, amitriptyline, doxepin, and mirtazapine • Combined BzRA or ramelteon and sedating antidepressant

	• Other sedating agents: examples include anti-epilepsy medications (gabapentin, tiagabine) and atypical antipsychotics (quetiapine and olanzapine) The guidelines also provide recommendations regarding the management of chronic insomnia with all prescription medications:(15) • Pharmacological treatment should be accompanied by patient education regarding: 1. treatment goals and expectations 2. safety concerns 3. potential side effects and drug interactions 4. other treatment modalities (cognitive and behavioral treatments) 5. potential for dosage escalation 6. rebound insomnia • Patients should be followed on a regular basis, every few weeks in the initial period of treatment when possible, to assess for effectiveness, possible side effects, and the need for ongoing medication. • Efforts should be made to employ the lowest effective maintenance dosage of medication and to taper medication when conditions allow. ○ Medication tapering and discontinuation are facilitated by cognitive behavioral therapy for insomnia. • Chronic hypnotic medication may be indicated for long-term use in those with severe or refractory insomnia or chronic comorbid illness. Whenever possible, patients should receive an adequate trial of cognitive behavioral treatment during long-term pharmacotherapy. ○ Long-term prescribing should be accompanied by consistent follow-up, ongoing assessment of effectiveness, monitoring for adverse effects, and evaluation for new onset or exacerbation of existing comorbid disorders. ○ Long-term administration may be nightly, intermittent (e.g., three nights per week), or as needed. Over-the-counter antihistamine or antihistamine/analgesic type drugs (OTC “sleep aids”) as well as herbal and nutritional substances (e.g., valerian and melatonin) are not recommended in the treatment of chronic insomnia due to the relative lack of efficacy and safety data.(15)
Safety	AMBIEN, AMBIEN CR, EDLUAR, Zolpidem sublingual tablet, Zolpidem capsule, and ZolpiMist have boxed warnings regarding complex sleep behaviors:(1,2,4,5,9,16)

	Complex sleep behaviors including sleep-walking, sleep-driving, and engaging in other activities while not fully awake may occur following use of AMBIEN, AMBIEN CR, EDLUAR, Zolpidem sublingual tablet, Zolpidem capsule, and ZolpiMist. Some of these events may result in serious injuries, including death. Discontinue AMBIEN, AMBIEN CR, EDLUAR, Zolpidem sublingual tablet, Zolpidem capsule, and ZolpiMist immediately if a patient experiences a complex sleep behavior. AMBIEN, AMBIEN CR, EDLUAR, Zolpidem sublingual tablet, Zolpidem capsule, and ZolpiMist are contraindicated in the following: (1,2,4,5,9,16) • Patient who have experienced complex sleep behaviors taking zolpidem • Known hypersensitivity to zolpidem Belsomra, DAYVIGO, and QUVIVIQ are contraindicated in patients with narcolepsy.(3,13,14) Lunesta is contraindicated in the following:(6) • Patient who have experienced complex sleep behaviors taking eszopiclone • Known hypersensitivity to eszopiclone Rozerem is contraindicated in the following:(7) • Patient who develop angioedema after treatment with ramelteon • In combination with fluvoxamine Silenor is contraindication in the following:(8) • Known hypersensitivity to doxepin, any of the inactive ingredients, or other dibenzoxepines • Coadministration or use within the past 14 days with a monoamine oxidase inhibitor (MAOI) • In patients with untreated narrow angle glaucoma or severe urinary retention
Use in the Elderly	Every three years, the American Geriatrics Society (AGS) revises the list of Potentially Inappropriate Medications for use in individuals over the age of 65, which is known as the Beers Criteria. The Beers Criteria provides recommendations for medications that should be avoided in this population.(12)

	Zolpidem, zaleplon, and eszopiclone are all included in the Beers Criteria. Benzodiazepine-receptor agonist hypnotics (i.e., Z drugs) have adverse events similar to benzodiazepines in older adults (e.g., delirium, falls, fractures); increased emergency room visits and hospitalizations; motor vehicle crashes; minimal improvement in sleep latency and duration. Beers provides a strong recommendation that eszopiclone, zaleplon, and zolpidem drugs be avoided in persons over the age of 65.(12) Doxepin doses that are less than or equal to 6 mg have demonstrated side effect profile that are similar to a placebo. But doses greater 6 mg have been found to be highly anticholinergic and associated with orthostatic hypotension and increased sedation. Based on the side effect profile, the AGS recommends that doxepin doses greater than 6 mg should be avoided in persons over the age of 65.(12)

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Number	Reference
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4	EDLUAR prescribing information. Meda Pharmaceuticals Inc. August 2022.
5	Zolpidem sublingual tablet prescribing information. Par Pharmaceuticals. October 2019.
6	Lunesta prescribing information. Sunovian Pharmaceuticals, Inc. August 2019.
7	Rozerem prescribing information. Takeda Pharmaceuticals America, Inc. November 2021.
8	Silenor prescribing information. Currax Pharmaceuticals LLC. December 2022.
9	ZolpiMist prescribing information. Magna Pharmaceuticals. August 2019.
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Number	Reference
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11	Sateia, Michael J, MD, et al. Clinical Practice Guidelines for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of Clinical Sleep Medicine*. 2017. 13 (2): 307-349.
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13	DAYVIGO prescribing information. Eisai Inc. June 2022.
14	QUVIVIQ prescribing information. Idorsia Pharmaceuticals LTD. October 2023.
15	Schutte-Rodin S, Broch L, Buysse D, et al. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med. 2008;4(5): 487-504.
16	Zolpidem Tartrate Capsules prescribing information. Almatica Pharma LLC. May 2023

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Insulin Combination Agents (Soliqua, Xultophy)

Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Soliqua® 100/33 (insulin glargine/lixisenatide) Injection	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Limitations of use: • Has not been studied in patients with a history of pancreatitis Consider other antidiabetic therapies in patients with a history of pancreatitis. • Not recommended for use in combination with any other product containing lixisenatide or another GLP-1 receptor agonist • Not indicated for use in patients with type 1 diabetes mellitus or diabetic ketoacidosis. • Not recommended in patients with gastroparesis. • Has not been studied in combination with prandial insulin.		1
Xultophy® 100/3.6 (insulin degludec/liraglutide) Injection	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of use: • Not recommended as first-line therapy for patients inadequately controlled on diet and exercise. • Not recommended for use in combination with any other product containing liraglutide or another GLP-1 receptor agonist.		2

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis. • Has not been studied in combination with prandial insulin		

CLINICAL RATIONALE

Guidelines	The American Diabetes Association (ADA) states that first-line therapy for type 2 diabetes depends on comorbidities, patient-centered treatment factors, and management needs but will generally include metformin and comprehensive lifestyle modification. When A1c is greater than or equal to 1.5% above the glycemic target, many patients will require dual combination therapy to achieve their target A1c level. Insulin has the advantage of being effective where other agents are not and should be considered as part of any combination regimen when hyperglycemia is severe, especially if catabolic features are present. If basal insulin has been titrated to an acceptable fasting blood glucose level (or if the dose is greater than 0.5 units/kg/day with indications of need for other therapy) and A1c remains above target, consider advancing to combination injectable therapy. This approach can use a GLP-1 added to basal insulin or multiple doses of insulin. The combination of basal insulin and GLP-1 has potent glucose-lowering actions and less weight gain and hypoglycemia compared with intensified insulin regimens. For patients with established atherosclerotic cardiovascular disease (ASCVD) or indicators of high ASCVD risk (such as patients greater than or equal to 55 years of age with coronary, carotid, or lower-extremity artery stenosis greater than 50% or left ventricular hypertrophy), heart failure, or chronic kidney disease, an SGLT2 inhibitor or GLP-1 with demonstrated CVD benefit is recommended as part of the glucose-lowering regimen independent of the A1C, independent of metformin use, and in consideration of other patient-specific factors.(3) Basal with or without prandial insulin treatment may be needed as initial therapy if the A1C is >10% and/or glucose values are >300 mg/dL, combined with catabolic symptoms, such as weight loss. If symptomatic hyperglycemia is present, a GLP-1 RA alone is not recommended as it requires titration and may delay glucose control. The goal of initial intensive insulin therapy for symptomatic hyperglycemia is to reduce glucose levels safely and promptly. After improved glycemic control is achieved with short-term insulin therapy,

	especially with a new diagnosis of DM, a role for noninsulin antihyperglycemic agents could be considered. For most persons who need intensification of glycemic control and who are already undergoing 3 to 4 oral therapies, a GLP-1 RA or GIP/GLP-1 RA should be the initial choice, if not already in use. If glycemic targets are not achieved with these therapies, basal insulin should be added alone or as a basal insulin/GLP-1 RA combination injection. Stepwise addition of prandial insulin at 1 to 3 meals is recommended if additional glycemic control is required. The dose of basal insulin can be based on A1C levels at the time of initiation. For an A1C <8%, basal insulin can be started at 0.1 to 0.2 U/kg/day and for an A1C >8%, 0.2 to 0.3 U/kg/day can be considered. Analog insulins, including detemir, glargine, or degludec are preferred over human insulins such as neutral protamine Hagedorn (NPH) to reduce hypoglycemia.(4)
Safety (1,2)	Xultophy carries a black box warning. Liraglutide, one of the components of Xultophy, causes thyroid C-cell tumors at clinically relevant expression in both genders of rats and mice. It is unknown whether Xultophy causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.(2) Xultophy has the following contraindications:(2) • Patients with a personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 • During episodes of hypoglycemia • Patients with a serious hypersensitivity reaction to insulin degludec, liraglutide, or any of the excipients in Xultophy Soliqua has the following contraindications:(1) • During episodes of hypoglycemia • Serious hypersensitivity to insulin glargine, lixisenatide, or any of the excipients in Soliqua

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1	Soliqua prescribing information. Sanofi-Aventis US LLC. June 2022.

Number	Reference
2	Xultophy prescribing information. Novo Nordisk Inc. July 2023.
3	American Diabetes Association. Standards of medical care in diabetes-2022. Available at: https://diabetesjournals.org/care/issue/45/Supplement_1.
4	American Diabetes Association, 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023. Diabetes Care 1 January 2023; 46 (Supplement_1): S140–S157. https://doi.org/10.2337/dc23-S009.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Insulin Pumps

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Omnipod DASH® System Infusion disposable pump kit	For subcutaneous delivery of insulin at set and variable rates for the management of diabetes mellitus in persons requiring insulin.		8
Omnipod GO® Infusion disposable pump kit	For the subcutaneous infusion of insulin at a preset basal rate in one 24-hour time period for 3 days (72 hours) in adults with type 2 diabetes.		12
Omnipod® 5 G6* Infusion disposable pump supplies	For subcutaneous delivery of insulin at set and variable rates for the management of diabetes mellitus in persons requiring insulin.	*The Omnipod 5 System is designed to work with the Dexcom G6 Continuous Glucose Monitor (CGM)	11
Omnipod® 5 G7 Infusion disposable pump supplies	For subcutaneous delivery of insulin at set and variable rates for the management of diabetes mellitus in persons requiring insulin.		11
Omnipod® Infusion disposable pump kit	For subcutaneous delivery of insulin at set and variable rates for the management of diabetes mellitus in persons requiring insulin.		7
V-Go® Infusion disposable pump kit	For continuous subcutaneous infusion of either 20 Units of insulin (0.83 U/hr), 30 Units of insulin (1.25 U/hr) or 40 Units of insulin (1.67 U/hr) in one 24-hour time		10

Agent(s)	FDA Indication(s)	Notes	Ref#
	period and on-demand bolus dosing in 2 Unit increments (up to 36 Units per one 24-hour time period) in adults requiring insulin.		

CLINICAL RATIONALE

Diabetes	The American Diabetes Association recommends that most people with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or subcutaneous insulin infusion. In addition, many patients with type 2 diabetes eventually require insulin therapy for both prandial and basal blood glucose control.(4) The purpose of insulin pumps is to mimic the pancreas' normal release of insulin.(5) Since insulin pumps only use short-acting insulin, frequent blood glucose checks for safety are required. Most diabetes providers will require a patient to check their blood glucose at least four times daily before using an insulin pump. There are technical aspects to using a pump; using a pump can be more complicated than injections in some ways.(6) Insulin pump therapy is not recommended for people who are unable to perform at least four blood glucose checks per day, are unable to maintain contact with their healthcare provider, or are unable to use the system according to instructions.(1) The Omnipod is a small device that is filled with insulin by the patient and worn on the body. Up to 200 units of insulin can be injected into the Pod. Omnipod is designed for use with U-100 rapid-acting insulin. NovoRapid, Humalog, and Apidra are safe to use in the Omnipod, but only Humalog and Apidra are compatible for up to 72 hours. The Pod should be changed when either 200 Units of insulin has been delivered or 72 hours has elapsed. Once applied, the patient uses a Personal Diabetes Manager (PDM) wireless device to control the rate and amount of insulin delivered by the pod. Insulin can be delivered at a basal rate as well as a bolus (such as would be used at mealtime). The PDM also contains a FreeStyle blood glucose meter. Information from the PDM can be uploaded to data management software for review.(7) The Omnipod DASH system uses the DASH PDM with a smart-phone like device with a touchscreen and connected to the Pod via Bluetooth. The Omnipod system and the Omnipod DASH system are not compatible; Pods from one

	system cannot be used with the other.(8) The manufacturer warranties the PDM for a period of 4 years from initial purchase.(2) Omnipods are packaged in boxes of 10. Omnipod DASH pods are packaged in boxes of 5.(9) The Omnipod 5 system is integrated with the Dexcom G6 Continuous Glucose Monitor. The Pod can be adjusted by using the Omnipod 5 App on a compatible smartphone, or with an included wireless controller.(11) The Omnipod GO insulin delivery device is intended for the subcutaneous infusion of insulin at a preset basal rate in one 24-hour time period for 3 days (72 hours) in adults with type 2 diabetes. It comes in 7 different models: 10, 15, 20, 25, 30, 35, and 40 units per day. There is no ability to deliver a bolus dose of insulin using the Omnipod GO.(12) The V-Go system is a device that is applied to the skin like a patch that delivers insulin to the patient. Three types of V-Go devices are available, delivering 20, 30, or 40 units of insulin over 24 hours. A U-100 fast acting insulin should be used with V-Go. Humalog, and NovoLog have been found to be safe for use in V-Go. The device delivers insulin at the basal rate over 24 hours specified by which device is selected. The device can also deliver a bolus of 2 units to the patient by clicking a button on the device. Up to 36 units (18 clicks) of insulin can be delivered via bolus per device. V-Go devices are packaged as a kit containing 30 V-Go devices and a filling accessory. They are to be dispensed as a full kit; kits are not to be broken apart.(10)
Safety	The Omnipod 5 System is NOT recommended for people who are:(1,2) • Unable to monitor glucose as recommended by their healthcare provider are • Unable to maintain contact with their healthcare provider are • Unable to use the Omnipod 5 System according to instructions are • Taking hydroxyurea as it could lead to falsely elevated CGM values and result in over-delivery of insulin that can lead to severe hypoglycemia • Do NOT have adequate hearing and/or vision to allow recognition of all functions of the Omnipod 5 System, including alerts, alarms, and reminders • Device components including the Pod, CGM transmitter, and CGM sensor must be removed before Magnetic Resonance Imaging (MRI), Computed Tomography (CT) scan, or diathermy treatment. In addition, the Controller and smartphone should be placed outside of the procedure room. Exposure to MRI, CT, or diathermy treatment can damage the components.

	Insulin pump therapy is NOT recommended for people who are:(1,2) • Unable to perform at least four (4) blood glucose tests per day • Unable to maintain contact with their healthcare provider • Unable to use the any system according to instructions

REFERENCES

Number	Reference
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2	Omnipod DASH System User Guide. Insulet Corporation. 2018-2023. Available at: https://www.omnipod.com/safety.
3	V-Go Health Care Provider website. Mankind Corporation. July 2023. Available at: https://www.go-vgo.com/hcp/.
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5	Device Technology. American Diabetes Association. Available at: https://www.diabetes.org/diabetes/device-technology
6	Who Should Use a Pump? American Diabetes Association. Available at: https://www.diabetes.org/diabetes/device-technology/who-should-use-a-pump.
7	Podder's Handbook Omnipod User's Guide. Available at: https://www.myomnipod.com/en-gb/eros-user-guide.
8	Omnipod Dash Insulin Management System Frequently Asked Questions. Available at: https://www.myomnipod.com/en-gb/faq-dash.

Number	Reference
9	Diabetic Warehouse e-commerce site. Available at: https://www.diabeticwarehouse.org/pages/search-results-page?q=omnipod.
10	V-Go Product Website. Available at: https://www.go-vgo.com/.
11	Omnipod 5 Information. Available at: https://www.omnipod.com/what-is-omnipod/omnipod-5.
12	Omnipod GO marketing approval letter and Form 3881 https://www.accessdata.fda.gov/cdrh_docs/pdf22/K223372.pdf.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when BOTH of the following are met: 1. ONE of the following: A. The patient has been using the requested product within the past 90 days **OR** B. The prescriber states the patient has been using the requested product within the past 90 days AND is at risk if therapy is changed **OR** C. ALL of the following: 1. The patient has diabetes mellitus AND requires insulin therapy **AND** 2. The patient is on an insulin regimen of 3 or more injections per day **AND** 3. The patient performs 4 or more blood glucose tests per day or is using Continuous Glucose Monitoring (CGM) **AND** 4. The patient has completed a comprehensive diabetes education program **AND** 5. The patient has demonstrated willingness and ability to play an active role in diabetes self-management **AND** 6. The patient has had ONE of the following while compliant on an optimized multiple daily insulin injection regimen: A. Glycosylated hemoglobin level (HbA1C) greater than 7% **OR** B. History of recurring hypoglycemia **OR** C. Wide fluctuations in blood glucose before mealtime **OR** D. Dawn phenomenon with fasting blood sugars frequently exceeding 200 mg/dL **OR** E. History of severe glycemic excursions **AND** 2. ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient's age is within the manufacturer recommendations for the requested indication for the requested product **OR** B. There is support for using the requested product for the patient's age **Length of Approval:** 12 months

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Interleukin (IL)-1 Inhibitors

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Arcalyst® (rilonacept) Subcutaneous injection	Treatment of Cryopyrin Associated Periodic Syndrome (CAPS), including Familial Cold Auto-Inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS) in adults and children 12 years and older Maintenance of remission of deficiency of interleukin-1 receptor antagonist (DIRA) in adults and pediatric patients weighing at least 10 kg Treatment of recurrent pericarditis (RP) and reduction in risk of recurrence in adults and pediatric patients 12 years and older		1

CLINICAL RATIONALE

Cryopyrin-Associated Periodic Syndromes (CAPS)	Cryopyrin-associated periodic syndrome (CAPS) is a rare autosomal dominant hereditary autoimmune disorder associated with a defect in the cryopyrin protein. CAPS syndrome is caused by a gain of function mutation in the NLRP3 gene leading to over secretion of fever causing cytokine IL-1B. The CAPS spectrum includes mild, moderate, and severe phenotypes. The mild phenotype is called familial cold autoinflammatory syndrome (FCAS), the moderate phenotype is also known as Muckle-Wells syndrome (MWS), the neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurologic cutaneous articular syndrome (CINCA) describes the severe phenotype. CAPS is diagnosed clinically and genetically. There are more than 240 sequence variants of the NLRP3 gene and mutations in this gene are not inclusive of a CAPS diagnosis. The diagnostic criteria of CAPS recognize that all but a few patients with CAPS have detectable systemic inflammation and use unique CPS-specific clinical features along the whole disease spectrum to achieve reasonable specificity and sensitivity to aid clinicians in making the CAPS diagnosis. These diagnostic criteria do not include genetic confirmation, and therefore can be applied in places where genetic testing is not available. The diagnostic criteria for CAPS are as follows:(6)

	• Raised inflammatory markers (CRP/SAA)
	• The presence of at least two of the following signs/symptoms:
	  ○ Urticaria-like rash
	  ○ Cold/stress triggered episodes
	  ○ Sensorineural hearing loss
	  ○ Musculoskeletal symptoms of arthralgia/arthritis/myalgia
	  ○ Chronic aseptic meningitis
	  ○ Skeletal abnormalities of epiphyseal overgrowth/frontal bossing
	
	FCAS is characterized by episodes of rash, fever. and joint pain following generalized exposure to cold. Attacks usually occur 1-2 hours after exposure and last less than 24.(2) Patients experience urticaria, arthralgia, fever with chills, severe thirst, red-eyes, and headache after a general cold exposure, including air conditioning. In MWS, inflammation can occur spontaneously as well as from triggers, such as stress, cold, or exercise, with episodes lasting from one to three days. MWS shares the same characteristics as FCAS, but is also characterized by renal amyloidosis, sensorineural hearing loss, and conjunctivitis. Hearing loss, partial or complete, often develop by teenage years.(3)
	
	NOMID is a rare chronic inflammatory disease. NOMID is characterized by fever, urticarial rash, aseptic meningitis, deforming arthropathy, hearing loss, and intellectual disability. An urticaria-like rash develops within the first six weeks of life, and a characteristic bony overgrowth predominantly involving the knees develops in most affected children. Therapies are aimed at suppressing inflammation and have included high-dose corticosteroids, disease-modifying antirheumatic drugs, and biologic agent targeting tumor necrosis factor (TNF). Selective blockade of interleukin-1B is effective in the pathophysiology and organ-specific manifestations of NMOSD, in particular the CNS manifestations of the disease.(5)
	
	Treatment aims are to suppress systemic inflammation, to improve functionality, to prevent organ damage, and to increase patients' quality of life. To achieve these aims, cytokine targeting drugs are important and evidence-based treatment. Since IL-1 plays a central role in CAPS pathogenesis, the anti-IL1 treatments (anakinra, canakinumab, and rilonacept) are recommended for the whole CAPS spectrum.(6)

Deficiency of the IL-1 Receptor Antagonist (DIRA)	Systemic autoinflammatory diseases (SAIDs) are a group of multisystem immunodysregulatory disorders caused primarily by the dysfunction of the innate immune system. Currently, SAIDs are comprised of a wide range of disorders with systemic and organ-specific inflammation in the absence of infections or autoimmunity. In a subset of genetically defined SAIDs, the pathogenesis is

	driven by increased release or signaling of the pro-inflammatory cytokine IL-1.(7) Patients with DIRA present with early-onset pustular rashes that can be triggered by mechanical stress (pathergy), with sterile osteomyelitis, and nail changes (onychomadesis). Although inflammatory markers are typically highly elevated, fever may be absent. Vertebral involvement can include odontoid osteomyelitis resulting in destruction and neck instability, vertebral block formation and gibbus-like spinal changes that need to be screened for by MRI or CT. The differential diagnosis for DIRA includes chronic recurrent multifocal osteomyelitis (CRMO), synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome and pustular psoriasis. Genetic testing for monogenic defects with overlapping clinical features should include *LPIN2, FGR, FBLIM1* for CRMO*, CARD14* for CARD14-Mediated Psoriasis (CAMPS)*, IL36RN* for Deficiency of IL-36 Receptor Antagonist (DITRA)*, AP1S3* for other pustular psoriasis and *MEFV f*or Pyrin-Associated Autoinflammation with Neutrophilic Dermatosis (PAAND).(7) Aims of therapy are early control of disease activity, prevention of disease and treatment related damage, and optimal health-related quality of life. The ultimate goal of a treat-to-target approach is complete remission. In absence of a consensus definition of remission or minimal disease activity for these diseases, remission has been defined for clinical studies and clinical monitoring as an absence of clinical symptoms and normal inflammatory markers. Anakinra and rilonacept both block IL-1α and IL-1β and should be used for DIRA patients.(7)
Recurrent Pericarditis	Pericarditis is inflammation of the pericardial layers around the heart and is the most common form of pericardial disease. Pericarditis may be caused infections, post-cardiac injury syndrome, or pericarditis may be idiopathic. Pericarditis is categorized into four types, acute, incessant, recurrent, and chronic. These categories are based on the length of time of the attack and the presentation. Acute pericarditis is an event lasting 4 weeks or less, incessant is an event lasting more than 4 weeks without a remission, recurrent pericarditis is new signs and symptoms of pericarditis after a symptom-free interval of 4 to 6 weeks, and chronic is an event lasting more than 3 months. Roughly 20% to 30% of patients that develop acute pericarditis will have recurrences, and 50% of patients that have a recurrence will experience more recurrences.(9) The treatment algorithm for therapeutic management of patients with recurrent pericarditis is as follows:(10)

	• First line therapy: Aspirin or other nonsteroidal anti-inflammatory drug (NSAID) for 1-2 weeks plus colchicine for 6-12 months and exercise restrictions • Second line therapy: Low dose corticosteroids for 1 week plus colchicine • Third line: Aspirin or other NSAID plus colchicine plus corticosteroids triple therapy • Fourth line: IL-1 inhibitors (anakinra, rilonacept) for inflammatory phenotype and azathioprine, IVIG for non-inflammatory phenotype • Fifth line: Pericardiectomy The American College of Cardiology note that mycophenolate mofetil and methotrexate have also been shown to be effective in the treatment of recurrent pericarditis that are not responsive to corticosteroids, corticosteroid dependent, or intolerant to corticosteroids.(9)
Safety	Arcalyst does not have any FDA labeled contraindications.(1)

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2	Hoffman HM, Wanderer AA, Broide DH. Familial cold autoinflammatory syndrome: phenotype and genotype of an autosomal dominant periodic fever. J Allergy Clin Immunol. 2001 Oct;108(4):615-20. doi: 10.1067/mai.2001.118790. PMID: 11590390; PMCID: PMC4321996.
3	Yu, J. R., & Leslie, K. S. (2010). Cryopyrin-associated periodic syndrome: an update on diagnosis and treatment response. *Current allergy and asthma reports*, *11*(1), 12-20.
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Number	Reference
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10	Andreis A, Imazio M, Casula M, Avondo S, Brucato A. Recurrent pericarditis: an update on diagnosis and management. Intern Emerg Med. 2021 Apr;16(3):551-558. doi: 10.1007/s11739-021-02639-6. Epub 2021 Feb 28. PMID: 33641044; PMCID: PMC7914388.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** All target agents are eligible for continuation of therapy

Module	Clinical Criteria for Approval
	1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. ONE of the following A. BOTH of the following: 1. The patient has ONE of the following indications: A. Cryopyrin Associated Periodic Syndrome (CAPS) **OR** B. Familial Cold Auto-Inflammatory Syndrome (FCAS) **OR** C. Muckle-Wells Syndrome (MWS) **AND** 2. BOTH of the following: A. The patient has elevated pretreatment serum inflammatory markers (C-reactive protein/serum amyloid A) **AND** B. The patient has at least TWO symptoms typical for CAPS (i.e., urticaria-like rash, cold/stress triggered episodes, sensorineural hearing loss, musculoskeletal symptoms of arthralgia/arthritis/myalgia, chronic aseptic meningitis, skeletal abnormalities of epiphyseal overgrowth/frontal bossing) **OR** B. BOTH of the following: 1. The patient has a diagnosis of deficiency of interleukin-1 receptor antagonist **AND** 2. The requested agent is being used for maintenance of remission **OR** C. The patient has a diagnosis of recurrent pericarditis AND ONE of the following 1. BOTH of the following: A. The patient has tried and had an inadequate response to at least a 6-month trial of colchicine **AND** B. ONE of the following: 1. Colchicine was used concomitantly with at least a 1 week trial of a non-steroidal anti-inflammatory drug (NSAID) AND a corticosteroid **OR** 2. The patient has an intolerance or hypersensitivity to BOTH an NSAID AND a corticosteroid **OR**

Module	Clinical Criteria for Approval
	3. The patient has an FDA labeled contraindication to ALL NSAIDs AND ALL corticosteroids **OR** 2. The patient has an intolerance or hypersensitivity to colchicine **OR** 3. The patient has an FDA labeled contraindication to colchicine **OR** 4. The patient has tried and had an inadequate response to an oral immunosuppressant (i.e., azathioprine, methotrexate, mycophenolate) used in the treatment of recurrent pericarditis **OR** 5. The patient has an intolerance or hypersensitivity to oral immunosuppressants used in the treatment of recurrent pericarditis **OR** 6. The patient has an FDA labeled contraindication to oral immunosuppressants used in the treatment of recurrent pericarditis **OR** D. The patient has another FDA approved indication for the requested agent **AND** 2. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **OR** C. The patient has another indication that is supported in compendia for the requested agent **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist, pediatrician, cardiologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. ONE of the following (Please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (copy of support required, e.g., clinical trials, phase III studies, guidelines) **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent

Module	Clinical Criteria for Approval
	Compendia Allowed: AHFS or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in area of the patient's diagnosis (e.g., allergist, immunologist, pediatrician, cardiologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. ONE of the following (Please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for use of combination therapy (copy of support required, e.g., clinical trials, phase III studies, guidelines) **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met:

Module	Clinical Criteria for Approval
	1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

CONTRAINDICATION AGENTS

Contraindicated as Concomitant Therapy
Agents NOT to be used Concomitantly Abrilada (adalimumab-afzb) Actemra (tocilizumab) Adalimumab Adbry (tralokinumab-ldrm) Amjevita (adalimumab-atto) Arcalyst (rilonacept) Avsola (infliximab-axxq) Benlysta (belimumab) Bimzelx (bimekizumab-bkzx) Cibinqo (abrocitinib) Cimzia (certolizumab) Cinqair (reslizumab) Cosentyx (secukinumab) Cyltezo (adalimumab-adbm) Dupixent (dupilumab) Enbrel (etanercept) Entyvio (vedolizumab)

Contraindicated as Concomitant Therapy
Fasenra (benralizumab)
Hadlima (adalimumab-bwwd)
Hulio (adalimumab-fkjp)
Humira (adalimumab)
Hyrimoz (adalimumab-adaz)
Idacio (adalimumab-aacf)
Ilaris (canakinumab)
Ilumya (tildrakizumab-asmn)
Inflectra (infliximab-dyyb)
Infliximab
Kevzara (sarilumab)
Kineret (anakinra)
Leqselvi (deuruxolitinib)
Litfulo (ritlecitinib)
Nemluvio (nemolizumab-ilto)
Nucala (mepolizumab)
Olumiant (baricitinib)
Omvoh (mirikizumab-mrkz)
Opzelura (ruxolitinib)
Orencia (abatacept)
Otezla (apremilast)
Pyzchiva (ustekinumab-ttwe)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rinvoq (upadacitinib)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Saphnelo (anifrolumab-fnia)
Selarsdi (ustekinumab-aekn)
Siliq (brodalumab)
Simlandi (adalimumab-ryvk)
Simponi (golimumab)
Simponi ARIA (golimumab)
Skyrizi (risankizumab-rzaa)
Sotyktu (deucravacitinib)
Spevigo (spesolimab-sbzo) subcutaneous injection
Stelara (ustekinumab)

Contraindicated as Concomitant Therapy
Taltz (ixekizumab)
Tezspire (tezepelumab-ekko)
Tofidence (tocilizumab-bavi)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tyenne (tocilizumab-aazg)
Tysabri (natalizumab)
Velsipity (etrasimod)
Wezlana (ustekinumab-auub)
Xeljanz (tofacitinib)
Xeljanz XR (tofacitinib extended release)
Xolair (omalizumab)
Yuflyma (adalimumab-aaty)
Yusimry (adalimumab-aqvh)
Zeposia (ozanimod)
Zymfentra (infliximab-dyyb)

Interleukin-4 (IL-4) Inhibitor

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Dupixent® (dupilumab) Injection for subcutaneous use	Treatment of adult and pediatric patients aged 6 months and older with moderate-to-severe atopic dermatitis (AD) whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent can be used with or without topical corticosteroids Add-on maintenance treatment of adult and pediatric patients aged 6 years and older with moderate-to-severe asthma characterized by an eosinophilic phenotype or with oral corticosteroid dependent asthma • Limitation of Use: Not indicated for the relief of acute bronchospasm or status asthmaticus Add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP) Treatment of adult and pediatric patients aged 1 years and older, weighing at least 15 kg, with eosinophilic esophagitis (EoE) Treatment of adult patients with prurigo nodularis (PN)		1

CLINICAL RATIONALE

Atopic Dermatitis	Atopic dermatitis (AD), also known as atopic eczema, is a chronic, pruritic inflammatory dermatosis affecting up to 25% of children and 1-5% of adults. AD follows a relapsing course and is associated with elevated serum immunoglobulin (IgE) levels and a personal or family history of type I allergies,

	allergic rhinitis, and/or asthma. Onset is most common between 3 and 6 months of age, with approximately 60% of patients developing the eruption in the first year of life and 90% by age 5. While the majority of affected individuals have resolution of disease by adulthood, 10 to 30% do not, and a smaller percentage first develop symptoms as adults. AD has a complex pathogenesis involving genetic, immunologic, and environmental factors, which lead to a dysfunctional skin barrier and dysregulation of the immune system. Clinical findings include erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and lichenification. These clinical findings vary by patient age and chronicity of lesions. Pruritus is a hallmark of the condition that is responsible for much of the disease burden borne by patients and their families. Typical patterns include facial, neck and extensor involvement in infants and children; flexure involvement in any age group, with sparing of groin and axillary regions.(2) Goals of treatment are to reduce symptoms (pruritus and dermatitis), prevent exacerbations, and minimize therapeutics risks.(13) Despite its relapsing and remitting nature, the majority of patients with AD can achieve clinical improvement and disease control with topical emollient/moisturizer use and conventional topical therapies (including corticosteroids and calcineurin inhibitors).(5,13) Moisturizers reduce signs, symptoms, and inflammation in AD, and can improve severity while also increasing time between flares. Moisturizers are considered generally safe and are strongly recommended to be used as part of a treatment regimen for AD, either as monotherapy or as concurrent use with pharmacologic treatments.(4) Topical therapies remain the mainstay of treatment due to their proven track record and generally favorable safety profile. They can be utilized individually or in combination with other topical, physical, and/or systemic treatments; as different classes of treatment have different mechanisms of action, combining therapies allows for the targeting of AD via multiple disease pathways. The American Academy of Dermatology (AAD) strongly recommends the following topical agents:(4) • Topical corticosteroids (TCS) • Calcineurin inhibitors (TCIs) (e.g., tacrolimus, pimecrolimus) • Topical PDE-4 inhibitors (e.g., crisaborole) [mild to moderate AD] • Topical JAK inhibitors (e.g., ruxolitinib) [mild to moderate AD] TCS are the most commonly utilized FDA-approved therapies in AD and are commonly used as first-line treatment for mild-to severe dermatitis in all skin regions. TCS target a variety of immune cells and suppress the release of proinflammatory cytokines. High to very high (super) potency TCS can be used to

	control flares and treat severe disease, while medium potency TCS are utilized for longer courses and as maintenance therapy. Lower potency TCS may be used, and it is important to consider the anatomical site (i.e., using lower potency agents on the face, neck, genitals, and body folds) and severity of the disease when choosing a steroid potency. Most studies of TCS in AD management involve twice daily application, but some studies (particularly for potent TCS) suggest once daily use may be sufficient. Traditionally, TCS were stopped once AD signs and symptoms of an AD flare were controlled. Maintenance in between AD flares with once to twice weekly use of TCS is another approach.(4) TCIs are a safe anti-inflammatory option for mild-to-severe AD, particularly when there is concern for adverse events secondary to corticosteroid use. Both tacrolimus and pimecrolimus have been shown to be effective in treating AD, but pimecrolimus may be more appropriate for patients who have milder disease or are sensitive to local reactions.(4) Prescribing information for pimecrolimus cream and tacrolimus ointment indicate evaluation after 6 weeks if symptoms of AD do not improve for adults and pediatrics.(6,12). When AD is more severe or refractory to topical treatment, advanced treatment with phototherapy or systemic medications can be considered. Phototherapy is conditionally recommended by the AAD as a treatment for AD based on low certainty evidence. The AAD strongly recommends the following systemic therapies:(5) • Monoclonal antibodies (biologics) (e.g., dupilumab, tralokinumab) • JAK inhibitors (e.g., upadacitinib, abrocitinib, baricitinib) In a change from the 2014 AAD AD guidelines, the use of systemic antimetabolites such as methotrexate, immunosuppressants such as systemic corticosteroids, mycophenolate mofetil, azathioprine, and cyclosporine are now conditionally recommended for AD only in a small number of select patients due to low or very low certainty of evidence and need for monitoring. The most favored first-line systemic is dupilumab.(5) There is no clear consensus on how to operationalize a definition of the FDA indication for treatment of patients with "moderate to severe" AD. The severity of AD can vary substantially over time and, from a patient's perspective, can include a complex combination of intensity of itch, location, body surface area (BSA) involvement, and degree of skin impairment. Given the variability of patient phenotype and lack of familiarity among clinicians with scoring systems used in

	clinical trials, it is advisable to create a broad clinically relevant definition inclusive of multiple specific measures of disease intensity for example:(26) One of the following: • Affected BSA greater than or equal to 10% • Investigator Global Assessment (IGA) greater than or equal to 3 • Eczema Area and Severity Index (EASI) greater than or equal to 16 OR One of the following: • Affected BSA greater than or equal to 10% • Involvement of body sites that are difficult to treat with prolonged topical corticosteroid therapy (e.g., hands, feet, face, neck, scalp, genitals/groin, skin folds) • Severe itch that has been unresponsive to topical therapies
Asthma	Asthma is a chronic inflammatory disorder of the airways.(9,11) It is characterized by variable and recurring clinical symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation.(9) Symptoms of asthma include wheezing, coughing, recurrent difficulty breathing, shortness of breath, and chest tightness. Generally, these symptoms will occur or worsen with exposure to allergens and irritants, infections, exercise, changes in weather, stress, or menstrual cycles. Guidelines recommend the use of detailed medical history, physical examination, and spirometry to make a diagnosis of asthma.(9,11) The Global Initiative for Asthma (GINA) guidelines recommend a stepwise approach for managing asthma. Long-term goals for asthma management are to achieve good control of symptoms, maintain normal activity level, and to minimize the future risk of exacerbations, fixed airflow limitation, and side-effects. IgE is the antibody responsible for activation of allergic reactions and is important to the pathogenesis of allergic asthma and the development and persistence of inflammation. GINA guidelines define moderate asthma as that which is well controlled with Step 3 or Step 4 treatment (e.g., low- or medium-dose inhaled corticosteroids [ICS] in combination with a long-acting beta agonist [LABA] in either treatment track). Severe asthma is defined as asthma that remains uncontrolled despite optimized treatment with high-dose ICS-LABA, or that requires high-dose ICS-LABA to prevent it from becoming uncontrolled. Severe asthma must be distinguished from asthma that is difficult to treat due to

	inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity, as they need very different treatment compared with if asthma is relatively refractory to high-dose ICS-LABA or even oral corticosteroids (OCS). Early initiation of low dose ICS in patients with asthma has led to greater improvement in lung function than initiation of ICS after symptoms have been present for more than 2 to 4 years. The 2023 GINA guidelines recommend every adult and adolescent with asthma should receive ICS-containing controller medication to reduce the risk of serious exacerbation, even in patients with infrequent symptoms.(11)
	
	2023 GINA STEP recommendations for adults and adolescents (12 years of age and over) are intended to reduce the risk of serious exacerbations and are broken into two tracks based on reliever therapy.
	
	Track 1 is the preferred approach recommended by GINA, because using low dose ICS-formoterol as the reliever reduces the risk of exacerbations compared with regimens with short-acting β2-agonist (SABA) as the reliever, and is a simpler regimen:(11)
	
	• Step 1:
	  ○ As-needed-only low dose ICS-formoterol
	• Step 2:
	  ○ As-needed-only low dose ICS-formoterol
	• Step 3: address and treat modifiable risk factors (e.g., adherence, technique) before considering step up
	  ○ Controller: low dose ICS-formoterol
	  ○ Reliever: as-needed low dose ICS-formoterol
	• Step 4:
	  ○ Controller: medium dose ICS-formoterol
	  ○ Reliever: as-needed low dose ICS-formoterol
	• Step 5: patients with uncontrolled symptoms and/or exacerbations despite Step 4 treatment should be assessed for contributory factors, have their treatment optimized, and be referred for expert assessment including severe asthma phenotype, and potential add on treatment
	  ○ Controller: at least medium dose ICS-formoterol; consider high dose ICS-formoterol
	  ○ Reliever: as-needed low dose ICS-formoterol
	  ○ Refer for phenotypic assessment +/- biologic therapy
	  ○ Add-on treatments include:
	  ▪ Long-acting muscarinic antagonist (LAMA) for patients greater than or equal to 18 years (greater than or equal to 6 years for tiotropium) in separate or combination inhalers

	▪ Anti-IgE (subcutaneous (SC) omalizumab in patients greater than or equal to 6 years) for severe allergic asthma ▪ Anti-interleukin (IL) 5 or anti-IL5R or anti-IL4R for severe eosinophilic/Type 2 asthma • Anti-IL5: SC mepolizumab for patients greater than or equal to 6 years OR intravenous (IV) reslizumab for patients greater than or equal to 18 years of age • Anti-IL5R: SC benralizumab for patients greater than or equal to 12 years • Anti-IL4R: SC dupilumab for patients greater than or equal to 6 years ▪ Anti-thymic stromal lymphopoietin (TSLP) for severe asthma (SC tezepelumab for patients greater than or equal to 12 years) ▪ Add-on azithromycin three days/week reduces exacerbations, but increases antibiotic resistance ○ Maintenance oral corticosteroids (OCS) should be used only as last resort, because short-term and long-term systemic side-effects are common and serious • Note, ICS-formoterol should not be used as the reliever by patients taking any other (non-formoterol) ICS-LABA or ICS-LABA-LAMA **Track 2** is an alternative approach if Track 1 is not possible or is not preferred by a patient with no exacerbations on their current therapy. Before considering a regimen with SABA reliever, the clinician should consider whether the patient is likely to be adherent with their controller therapy; if not, they will be exposed to the higher risk of exacerbations with SABA-only treatment:(11) • Step 1: ○ Take ICS whenever SABA taken ○ Reliever: as-needed ICS-SABA or as needed SABA • Step 2: ○ Controller: low dose ICS ○ Reliever: as-needed ICS-SABA or as-needed SABA ○ Alternative options with limited indications, or less evidence for efficacy and/or safety: ▪ Low dose ICS whenever SABA taken ▪ Daily leukotriene receptor antagonist (LTRA). These are less effective than daily ICS, particularly for preventing exacerbations, and there is a US FDA boxed warning about the risk of serious mental health effects with montelukast

	▪ Daily low-dose ICS-LABA as initial therapy leads to faster improvement in symptoms and FEV1 than ICS alone but is costlier, and the reduction in exacerbations compared with SABA is similar to that with ICS ▪ For adults with rhinitis who are allergic to house dust mite and have FEV1 > 70% predicted, consider adding sublingual immunotherapy (SLIT) • Step 3: address and treat modifiable risk factors (e.g., adherence, technique) before considering step up o Controller: low dose ICS-LABA o Reliever: as-needed ICS-SABA or as-needed SABA o Alternative options: ▪ Medium dose ICS ▪ Low-dose ICS plus LTRA ▪ For adults with rhinitis who are allergic to house dust mite and have FEV1 > 70% predicted, consider adding SLIT • Step 4: o Controller: medium/high dose ICS-LABA o Reliever: as-needed ICS-SABA or as-needed SABA o Alternative options: ▪ Add-on LAMA for patients greater than or equal to 18 years (greater than or equal to 6 years for tiotropium) in separate or combination inhalers. Before considering add-on LAMA for patients with exacerbations, increase ICS dose to at least medium ▪ Add-on LTRA or low-dose sustained-release theophylline to a medium or high-dose ICS ▪ For adults with rhinitis who are allergic to house dust mite and have FEV1 > 70% predicted, consider adding sublingual immunotherapy (SLIT) • Step 5: patients with uncontrolled symptoms and/or exacerbations despite Step 4 treatment should be assessed for contributory factors, have their treatment optimized, and be referred for expert assessment including severe asthma phenotype, and potential add on treatment o Controller: medium/high dose ICS-LABA o Reliever: as-needed ICS-SABA or as-needed SABA o Refer for phenotypic assessment +/- biologic therapy o Add-on treatments include: ▪ Long-acting muscarinic antagonist (LAMA) for patients greater than or equal to 18 years (greater than or equal to 6 years for tiotropium) in separate or combination inhalers

	▪ Anti-IgE (SC omalizumab in patients greater than or equal to 6 years) for severe allergic asthma ▪ Anti-interleukin (IL) 5 or anti-IL5R or anti-IL4R for severe eosinophilic/Type 2 asthma • Anti-IL5: SC mepolizumab for patients greater than or equal to 6 years OR IV reslizumab for patients greater than or equal to 18 years of age • Anti-IL5R: SC benralizumab for patients greater than or equal to 12 years • Anti-IL4R: SC dupilumab for patients greater than or equal to 6 years ▪ Anti-thymic stromal lymphopoietin (TSLP) for severe asthma (SC tezepelumab for patients greater than or equal to 12 years) ▪ Add-on azithromycin three days/week reduces exacerbations, but increases antibiotic resistance o Maintenance oral corticosteroids (OCS) should be used only as last resort, because short-term and long-term systemic side-effects are common and serious 2023 GINA STEP recommendations for children (6 to 11 years of age) are intended to reduce the risk of serious exacerbations:(11) • Step 1: o Low dose ICS taken whenever SABA taken o Reliever: as-needed SABA • Step 2 o Preferred Controller: daily low dose ICS o Reliever: as-needed SABA o Alternative options: ▪ Low-dose ICS whenever SABA is taken using separate inhalers ▪ Daily LTRA is less effective for exacerbation reduction. Advise parents about US FDA warning on montelukast • Step 3: check inhaler technique and adherence, and treat modifiable risk factors before considering step up: o Preferred options: ▪ Medium-dose ICS maintenance plus as-needed SABA ▪ Low-dose ICS-LABA maintenance plus as-needed SABA ▪ Maintenance and reliever therapy (MART) with a very low dose of budesonide-formoterol dry powder inhaler (DPI)

	○ Alternative option: Low dose ICS plus LTRA. The FDA boxed warning for montelukast also applies to children • Step 4: Individual children's responses vary, so each of the Step 3 options may be tried before considering a step-up to Step 4. ○ Preferred options: ▪ Medium dose ICS-LABA plus as-needed SABA • If asthma is not well controlled on medium-dose ICS, refer for expert assessment and advice. ▪ Low dose ICS-formoterol MART ○ Alternative options: ▪ High dose ICS-LABA plus as-needed SABA ▪ Add-on tiotropium ▪ Add-on LTRA • Step 5: ○ Refer for phenotypic assessment ○ Controller: Continue controller from step 4 or consider higher dose ICS-LABA ○ Reliever: as needed SABA (or ICS-formoterol reliever for MART) ○ Add on treatments include: ▪ Therapy with anti-IgE, anti-IL4R, or anti-IL5 ▪ As a last resort consider add on low dose OCS but consider side effects **Severe Asthma Phenotype and Eosinophilic Asthma Subphenotype** Roughly 3% to 10% of adults with asthma have severe asthma as defined by the GINA 2023 guidelines.(11) The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014; updated 2020) and the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group mirror the GINA definition of severe asthma.(9,25) The ERS/ATS definition uncontrolled asthma for adult and pediatric patients 6 years of age and over:(10) • Frequent severe exacerbations (i.e., two or more bursts of systemic corticosteroids within the past 12 months) • Serious exacerbations (i.e., at least one hospitalization, intensive care unit stay, or mechanical ventilation in the past 12 months) • Airflow limitation (i.e., FEV1 less than 80% predicted) • Asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids

	A specialist, preferably in a multidisciplinary severe asthma clinic (if available) performs further assessment, which includes the patient's inflammatory phenotype (i.e., Type 2 or non-Type 2).(11)
	
	Type 2 inflammation is characterized by the presence of cytokines such as interleukin (IL)-4, IL-5, and IL-13, which are often produced by the adaptive immune system on recognition of allergens. It is also characterized by eosinophilia or increased fraction of exhaled nitric oxide (FeNO) and may be accompanied by atopy. In many patients with asthma, Type 2 inflammation rapidly improves when ICS are taken regularly and correctly; this is classified as mild or moderate asthma. In severe asthma, Type 2 inflammation may be relatively refractory to high dose ICS. Type 2 inflammation is considered refractory if any of the following are found while the patient is taking high dose ICS or daily OCS:(11)
	
	• Blood eosinophils greater than or equal to 150 cells/microliter
	• FeNO greater than or equal to 20 ppb
	• Sputum eosinophils greater than or equal to 2%
	• Asthma is clinically allergen-driven
	
	Biologic agents should be considered as add-on therapy for patients with refractory Type 2 inflammation with exacerbations or poor symptom control despite taking at least high dose ICS/LABA, and who have allergic or eosinophilic biomarkers or need maintenance OCS. 2023 GINA recommends the biologics below based on patient eligibility factors:(11)
	
	• Anti-IgE (omalizumab):
	  ○ Sensitization on skin prick testing or specific IgE
	  ○ Total serum IgE and weight within dosage range
	  ○ Exacerbations in the last year
	• Anti-IL5/Anti-IL5R (benralizumab, mepolizumab, reslizumab):
	  ○ Exacerbations in the last year
	  ○ Blood eosinophils greater than or equal to 150 cells/microliter (for benralizumab and mepolizumab) or greater than or equal to 300 cells/microliter (for reslizumab)
	• Anti-IL4R (dupilumab):
	  ○ Exacerbations in the last year
	  ○ Blood eosinophil greater than or equal to 150 cells/microliter but less than or equal to 1500 cells/microliter, or FeNO greater than or equal to 25 ppb, or taking maintenance OCS
	• Anti-TSLP (tezepelumab):

	○ Exacerbations in the last year Patient response should be evaluated 4 months after initiating therapy and follow up should occur every 3 to 6 months thereafter. 2023 GINA recommends the following step-down therapy process in patients responding well to targeted biologic therapy:(11) • Reevaluate the need for each asthma medication every 3 to 6 months, but inhaled therapy should not be completely stopped • Oral treatments: gradually decreased starting with OCS due to significant adverse effects • Inhaled treatments: consider reducing ICS dose after 3 to 6 months, but do not completely stop inhaled therapy. Continue at least medium dose ICS and remind patients of the importance of continued inhaled controller therapy • Biologic treatments: trial withdrawal after 12 months of treatment and only if patient's asthma remains well controlled on medium dose ICS, and for allergic asthma, there is no further exposure to a previous allergic trigger
Chronic Rhinosinusitis with Nasal Polyps	Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory condition affecting the paranasal sinuses.(16) The exact cause of CRSwNP is unknown, but biopsies of nasal polyps have shown elevated levels of eosinophils. Sinus computed tomography (CT) and/or nasal endoscopy are needed to determine the presence of sinonasal inflammation and nasal polyps.(15) The International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR-RS) indicates that the diagnostic criteria for CRSwNP consist of ALL the following:(24) • Symptoms greater than or equal to 12 weeks • Two of the following symptoms: ○ Nasal discharge (rhinorrhea or post-nasal drainage) ○ Nasal obstruction or congestion ○ Hyposmia (loss or decreased sense of smell) ○ Facial pressure or pain • One or more of the following findings: ○ Evidence of inflammation on nasal endoscopy or computed tomography ○ Evidence of purulence coming from paranasal sinuses or ostiomeatal complex

	• Presence of nasal polyps Topical saline irrigation and intranasal corticosteroids (INCS) are recommended in the guidelines as initial treatment for CRSwNP.(16,18,24) Nasal saline irrigation used as adjunct treatment with other therapies improves symptoms and quality of life (QoL) outcomes and is considered an important aspect of management of CRSwNP. Saline irrigation can improve nasal mucosa function through the mechanical clearance of thick mucus and inflammatory mediators, including eosinophilic mucin.(18,24) INCS can have a positive impact on the disease and improve symptoms, reduce nasal polyp size, and improve sense of smell.(18,24) The ICAR-RS strongly recommends INCS before or after sinus surgery.(24) INCS are well tolerated and long term treatment is effective and safe. Many different INCS have been used in the treatment of CRSwNP, including triamcinolone, mometasone, fluticasone, and budesonide, but no differences were shown to recommend a specific formulation.(18) For patients using INCS for at least 4 weeks and who continue to have high disease burden, biologics may be considered and preferred over other medical treatment choices.(16) Oral systemic corticosteroids (OCS), used as a short course, can result in a significant reduction in symptoms and nasal polyps for up to three months after the start of treatment. Up to 2 courses per year, taken in addition to INCS, can be useful for patients with partially or uncontrolled disease.(18) The ICAR-RS strongly recommends the use of OCS in the short term management of CRSwNP, but does not recommend longer term use due to the increased risk of adverse effects.(24) Endoscopic sinus surgery (ESS) is aimed at improving symptoms and creating better conditions for local treatment. Sinus surgery should be considered when disease is refractory and remains symptomatic despite trial of primary medical therapy (e.g., nasal sinus irrigation, INCS, oral corticosteroids). Based on current evidence, delaying surgical intervention can be detrimental to symptom improvement and outcomes.(18,24) After surgery, patients need to continue other treatments due to the chronic nature of the disease and nasal polyps potentially reoccurring despite surgery.(15,18) INCS can help to prevent nasal polyp recurrence.(18,24) Biologics can be considered in patients where their disease remains uncontrolled despite appropriate medical treatment and sinus surgery. (16,27) Biologics vary in their magnitude of benefits and harms and certainty of evidence across outcomes. Dupilumab and omalizumab are the most beneficial for most patient

	important outcomes when comparing with other biologics, followed by mepolizumab.(16)
Eosinophilic Esophagitis	Eosinophilic Esophagitis (EoE) is an allergen/immune-mediated disease characterized by symptoms of esophageal dysfunction and marked eosinophilic inflammation of the esophageal mucosa in the absence of secondary causes. EoE has dramatically increased in prevalence over the years. EoE is characterized by symptoms related to esophageal dysfunction and histologically with eosinophil-predominant inflammation (a peak count of greater than or equal to 15 eosinophils per high-power field on esophageal biopsy). Atopic and allergic inflammatory conditions commonly occur concomitantly with EoE.(19) The symptoms of EoE are age dependent. Young children may refuse to eat, have decreased appetite, recurring abdominal pain, trouble swallowing, and vomiting. Young adults and adults have the same symptoms, but often struggle to swallow dry or dense, solid foods due to inflammation. Food impaction is a common cause for emergency room visits in patients with EoE. Patients may also have concurrent gastroesophageal reflux disease (GERD). EoE is a progressive disease if left untreated. The chronic inflammation can lead to tissue fibrosis and strictures in the esophagus that require esophageal dilation.(20) The diagnosis of EoE is suspected on the basis of chronic symptoms such as dysphagia, food impaction, food refusal, failure to progress with food introduction, heartburn, regurgitation, vomiting, chest pain, odynophagia, abdominal pain, and malnutrition. Due to the wide range of chronic symptoms, the diagnosis should be highly considered in the presence of concomitant atopic conditions and if there are endoscopic findings. Endoscopic findings associated with EoE include esophageal rings, longitudinal furrows, exudates, edema, strictures, or narrow caliber esophagus. Assessment of non-EoE disorders and esophageal biopsy are required to confirm the diagnosis of EoE, with at least 15 eosinophils (eos)/ high-power field (hpf) present on esophageal biopsy.(21) Nonpharmacological treatment of EoE includes dilation and diet. Dilation is only conditionally recommended for patients with dysphagia associated with strictures due to EoE, noting that the dilation does not address the underlying inflammation.(22) Both elemental and elimination diets have been shown to be effective, however, barriers of adherence and cost make this treatment modality feasible only for select patients.(3,22) Proton pump inhibitors (PPIs) are a first line treatment option for patients with EoE, and PPI monotherapy is widely used in practice. PPIs have a longstanding safety profile and have shown to be effective based on symptom response and

	histological remission. The 2020 American Gastroenterological Association (AGA) and the Joint Task Force on Allergy-Immunology Practice Parameters (JTF) guidelines conditionally recommend their use while the 2022 British Society of Gastroenterology (BSG) and British Society of Pediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN) guidelines strongly recommend their use.(3,22) The AGA/JTF and BSG/BSPGHAN both strongly recommend the use of topical glucocorticoids for the treatment of EoE. Studies showed that topical (swallowed) budesonide or topical fluticasone induced histological remission significantly better than placebo and had similar adverse events to placebo. Due to the chronic nature of the disease and the risk of progression, topical corticosteroids may be continued as maintenance therapy after remission with short term use. A clinical review of the patient should guide this decision based on preference to avoid long term adverse effects of topical steroids, or to prevent undesirable outcomes of the disease itself.(3,22)
Prurigo Nodularis	Prurigo nodularis (PN) is a skin disorder that is defined by the presence of chronic pruritus and multiple elevated, firm, and nodular lesions. PN is more common in older adults but can occur in children. The underlying cause of PN is unknown, but it appears neural and immunologic processes both play a role in its development. The nodules form in a subset of patients that have chronic pruritus, with the nodules forming in areas with continuous scratching over prolonged periods of time. There is significant disease burden associated with PN including sleep disruption, anxiety, and depression. The nodules are typically firm, dome-shaped, and itchy and range in size from millimeters to several centimeters. The nodules can range in color from flesh tones to brown/black and can range in number from a few to hundreds. The pruritis associated with PN can range from sporadic to continuous and generally the underlying cause is unknown. There are a number of conditions, both dermatologic and other diseases, that are associated with PN, such as atopic dermatitis, kidney disease, diabetes, and HIV.(23) The diagnosis of PN is generally one of exclusion. The American Academy of Dermatology (AAD) indicates that the diagnostic workup should include a clinical examination with a complete review of systems and assessment of PN severity, which should include both disease burden (e.g., quality of life, sleep disturbances) and pruritis intensity. The AAD notes three core features associated with PN:(23) • Presence of firm, nodular lesions • Pruritus that lasts for at least 6 weeks

	• History and/or signs of repeated scratching, picking, or rubbing Management requires a multifaceted approach with a focus on controlling the underlying pruritis. Topical therapies are initial therapy for limited disease. Topical therapies include topical and intralesional corticosteroids.(23) The International Forum for the Study of Itch (IFSI) 2020 guideline on chronic prurigo including prurigo nodularis strongly recommends moderate to very potent topical corticosteroids on lesional skin.(17) Topical calcineurin inhibitors and topical calcipotriol have been used but have not been adequately studied. Phototherapy is used in patients with more widespread and refractory PN. Systemic oral therapies include cyclosporine and methotrexate and are generally used in patients with widespread, refractory disease that does not respond to phototherapy.(23)
Efficacy	**Atopic Dermatitis(1,7,8)** Dupilumab was FDA approved through two randomized, double-blind, placebo-controlled phase 3 trials (SOLO 1 and SOLO 2). All patients in both trials were at least 18 years old, had chronic AD (according to American Academy of Dermatology Consensus Criteria Eichenfield 2014) that had been present for at least 3 years, and had greater than or equal to 10% body surface area (BSA) involvement at the screening and baseline visits. Additionally, all patients had a documented recent history (within 6 months before the screening visit) of inadequate response to treatment with topical medications (defined as failure to achieve and maintain remission or a low disease activity state despite treatment with a daily regimen of topical corticosteroids of medium to higher potency applied for greater than or equal to 28 days or for the maximum duration recommended by the product prescribing information [e.g., 14 days for super-potent topical corticosteroids], whichever is shorter), or whom topical treatments are otherwise medically inadvisable. The primary outcome measure in both trials was proportion of patients with both IGA (Investigator Global Assessment) 0 to 1 (on a 5-point scale) and a reduction from baseline of greater than or equal to 2 points at week 16. There were several secondary endpoints included. Some examples include: proportion of patients with Eczema Area and Severity Index (EASI) -75 (greater than or equal to 75% improvement from baseline) at week 16, percent change from baseline to week 16 in pruritus numerical rating scale (NRS), change from baseline to week 16 in % BSA, and changes in quality of life, anxiety, and depression. The manufacturer reports the following results from SOLO 1 and SOLO 2. In SOLO 1, the primary outcome (an IGA of 0-1 and a reduction of greater than or equal to 2 points from baseline at week 16) occurred in 85 patients (38%) who

	received dupilumab every other week and in 83 (37%) who received dupilumab weekly, as compared with 23 (10%) who received placebo (P less than 0.001 for both comparisons with placebo). The results were similar in SOLO 2, with the primary outcome occurring in 84 patients (36%) who received dupilumab every other week and in 87 (36%) who received dupilumab weekly, as compared with 20 (8%) who received placebo (P less than 0.001 for both comparisons). In addition, in the two trials, an improvement from baseline to week 16 of at least 75% on the Eczema Area and Severity Index was reported in significantly more patients who received each regimen of dupilumab than in patients who received placebo (P less than 0.001 for all comparisons). Dupilumab was also associated with improvement in other clinical end points, including reduction in pruritus and symptoms of anxiety or depression and improvement in quality of life. The efficacy and safety of Dupixent monotherapy in adolescent subjects was evaluated in a multicenter, randomized, double-blind, placebo-controlled trial in 251 adolescent subjects 12 to 17 years of age, with moderate-to-severe AD and a minimum BSA involvement of greater than or equal to 10%. Eligible subjects enrolled into this trial had previous inadequate response to topical medication. Subjects in the Dupixent group with baseline weight of less than 60 kg received an initial dose of 400 mg at Week 0, followed by 200 mg every 2 weeks for 16 weeks. Subjects with baseline weight of greater than or equal to 60 kg received an initial dose of 600 mg at Week 0, followed by 300 mg every 2 weeks for 16 weeks. Subjects were permitted to receive rescue treatment at the discretion of the investigator. Subjects who received rescue treatment were considered non-responders. The primary endpoint was the proportion of subjects with an IGA 0 (clear) or 1 (almost clear) and at least a 2-point improvement from baseline to Week 16. Other evaluated outcomes included the proportion of subjects with EASI-75 or EASI-90 (improvement of at least 75% or 90% in EASI from baseline, respectively), and reduction in itch as measured by the Peak Pruritus NRS (greater than or equal to 4-point improvement). The efficacy results at Week 16 were as follows: • IGA 0 or 1: 24% for Dupixent and 2% for placebo • EASI-75: 42% for Dupixent and 8% for placebo • EASI-90: 23% for Dupixent and 2% for placebo • Peak Pruritus NRS (greater than or equal to 4-point improvement): 37% for Dupixent and 5% for placebo **Asthma(1)**

	The asthma development program included three randomized, double-blind, placebo controlled, parallel-group, multi-center trials (AS Trials 1, 2, and 3) of 24 to 52 weeks in treatment duration which enrolled a total of 2888 subjects (12 years of age and older). Subjects enrolled in AS Trials 1 and 2 were required to have a history of 1 or more asthma exacerbations that required treatment with systemic corticosteroids or emergency department visit or hospitalization for the treatment of asthma in the year prior to trial entry. Subjects enrolled in AS Trial 3 required dependence on daily oral corticosteroids in addition to regular use of high-dose inhaled corticosteroids plus an additional controller(s). In all 3 trials, subjects were enrolled without requiring a minimum baseline blood eosinophil count. In AS Trials 2 and 3 subjects with screening blood eosinophil level of greater than 1500 cells/mcL (less than 1.3%) were excluded. Dupixent was administered as add-on to background asthma treatment. Subjects continued background asthma therapy throughout the duration of the studies, except in AS Trial 3 in which OCS dose was tapered as described below. AS Trial 1 was a 24-week dose-ranging study which included 776 subjects (18 years of age and older). Dupixent compared with placebo was evaluated in adult subjects with moderate to severe asthma on a medium or high-dose inhaled corticosteroid and a long acting beta agonist. Subjects were randomized to receive either 200 mg (N equal to 150) or 300 mg (N equal to 157) Dupixent every other week (Q2W) or 200 mg (N equal to 154) or 300 mg (N equal to 157) Dupixent every 4 weeks following an initial dose of 400 mg, 600 mg or placebo (N equal to 158), respectively. The primary endpoint was mean change from baseline to Week 12 in FEV1 (L) in subjects with baseline blood eosinophils greater than or equal to 300 cells/mcL. Other endpoints included percent change from baseline in FEV1 and annualized rate of severe asthma exacerbation events during the 24-week placebo controlled treatment period. Results were evaluated in the overall population and subgroups based on baseline blood eosinophil count (greater than or equal to 300 cells/mcL and less than 300 cells/mcL. Additional secondary endpoints included responder rates in the patient reported Asthma Control Questionnaire (ACQ-5) and Asthma Quality of Life Questionnaire, Standardized Version (AQLQ(S)) scores. AS Trial 2 was a 52-week study which included 1902 subjects (12 years of age and older). Dupixent compared with placebo was evaluated in 107 adolescents and 1795 adult subjects with moderate-to-severe asthma on a medium or high-dose inhaled corticosteroid (ICS) and a minimum of one and up to two additional controller medications. Subjects were randomized to receive either 200 mg (N=631) or 300 mg (N=633) Dupixent Q2W (or matching placebo for either 200 mg [N equal to 317] or 300 mg [N equal to 321] Q2W) following an initial dose of 400 mg, 600 mg or placebo respectively. The primary endpoints were the

	annualized rate of severe exacerbation events during the 52-week placebo controlled period and change from baseline in pre-bronchodilator FEV1 at Week 12 in the overall population (unrestricted by minimum baseline blood eosinophils count). Additional secondary endpoints included annualized severe exacerbation rates and FEV1 in patients with different baseline levels of blood eosinophils as well as responder rates in the ACQ-5 and AQLQ(S) scores. AS Trial 3 was a 24-week oral corticosteroid-reduction study in 210 subjects with asthma who required daily oral corticosteroids in addition to regular use of high dose inhaled corticosteroids plus an additional controller. After optimizing the OCS dose during the screening period, subjects received 300 mg Dupixent (N=103) or placebo (N=107) once Q2W for 24 weeks following an initial dose of 600 mg or placebo. Subjects continued to receive their existing asthma medicine during the study; however, their OCS dose was reduced every 4 weeks during the OCS reduction phase (Week 4-20), as long as asthma control was maintained. The primary endpoint was the percent reduction of oral corticosteroid dose at Weeks 20 to 24 compared with the baseline dose, while maintaining asthma control in the overall population (unrestricted by minimum baseline blood eosinophils count). Additional secondary endpoints included the annualized rate of severe exacerbation events during treatment period and responder rate in the ACQ-5 and AQLQ(S) scores. AS Trials 1 and 2 evaluated the frequency of severe asthma exacerbations defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or hospitalization or emergency room visit due to asthma that required systemic corticosteroids. In the primary analysis population (subjects with baseline blood eosinophil count of greater than or equal to 300 cells/mcL in AS Trial 1 and the overall population in AS Trial 2), subjects receiving either Dupixent 200 mg or 300 mg Q2W had significant reductions in the rate of asthma exacerbations compared to placebo. In the overall population in AS Trial 2, the rate of severe exacerbations was 0.46 and 0.52 for Dupixent 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo rates of 0.87 and 0.97. The rate ratio of severe exacerbations compared to placebo was 0.52 (95% CI: 0.41, 0.66) and 0.54 (95% CI: 0.43, 0.68) for Dupixent 200 mg Q2W and 300 mg Q2W, respectively. Prespecified subgroup analyses of AS Trials 1 and 2 demonstrated that there were greater reductions in severe exacerbations in subjects with higher baseline blood eosinophil levels. In AS Trial 2, reductions in exacerbations were significant in the subgroup of subjects with baseline blood eosinophils greater than or equal to 150 cells/mcL. In subjects with baseline blood eosinophil count

	less than 150 cells/mcL, similar severe exacerbation rates were observed between Dupixent and placebo. Significant increases in pre-bronchodilator FEV1 were observed at Week 12 for AS Trials 1 and 2 in the primary analysis populations (subjects with baseline blood eosinophil count of greater than or equal to 300 cells/mcL in AS Trial 1 and the overall population in AS Trial 2). In the overall population in AS Trial 2, the FEV1 LS mean change from baseline was 0.32 L (21%) and 0.34 L (23%) for Dupixent 200 mg Q2W and 300 mg Q2W, respectively, compared to matched placebo means of 0.18 L (12%) and 0.21 L (14%). The mean treatment difference versus placebo was 0.14 L (95% CI: 0.08, 0.19) and 0.13 L (95% CI: 0.08, 0.18) for Dupixent 200 mg Q2W and 300 mg Q2W, respectively. Subgroup analysis of AS Trials 1 and 2 demonstrated greater improvement in subjects with higher baseline blood eosinophils. **CRSwNP(1)** Two randomized, double-blind, parallel-group, multicenter, placebo-controlled studies (CSNP Trial 1 and CSNP Trial 2) evaluated Dupixent in CRSwNP. There were 724 subjects aged 18 years and older on background intranasal corticosteroids (INCS) included in the trials. These studies included subjects with CRSwNP despite prior sinonasal surgery or treatment with, or who were ineligible to receive or were intolerant to, systemic corticosteroids in the past 2 years. Patients with chronic rhinosinusitis without nasal polyposis were not included in these trials. Rescue with systemic corticosteroids or surgery was allowed during the studies at the investigator's discretion. In CSNP Trial 1, a total of 276 subjects were randomized to receive either 300 mg Dupixent (N=143) or placebo (N=133) every other week for 24 weeks. In CSNP Trial 2, 448 subjects were randomized to receive either 300 mg Dupixent (N=150) every other week for 52 weeks, 300 mg Dupixent (N=145) every other week until week 24 followed by 300 mg Dupixent every 4 weeks until week 52, or placebo (N=153). All subjects had evidence of sinus opacification on the Lund Mackay (LMK) sinus CT scan and 73% to 90% of subjects had opacification of all sinuses. Subjects were stratified based on their histories of prior surgery and co-morbid asthma/nonsteroidal anti-inflammatory drug exacerbated respiratory disease (NSAID-ERD). A total of 63% of subjects reported previous sinus surgery, with a mean number of 2.0 prior surgeries, 74% used systemic corticosteroids in the previous 2 years with a mean number of 1.6 systemic corticosteroid courses in the previous 2 years, 59% had co-morbid asthma, and 28% had NSAID-ERD. The co-primary efficacy endpoints were change from baseline to Week 24 in bilateral endoscopic nasal polyps score (NPS; 0-8 scale) as graded by central

	blinded readers and change from baseline to Week 24 in nasal congestion/obstruction score averaged over 28 days (NC; 0-3 scale), as determined by subjects using a daily diary. In both studies, key secondary end-points at Week 24 included change from baseline in: LMK sinus CT scan score, daily loss of smell, and 22-item sinonasal outcome test (SNOT-22). In the pooled efficacy results, the reduction in the proportion of subjects rescued with systemic corticosteroids and/or sinonasal surgery (up to Week 52) were evaluated. Statistically significant efficacy was observed in CSNP Trial 2 with regard to improvement in bilateral endoscopic NPS score at week 24 and week 52. Similar results were seen in CSNP Trial 1 at Week 24. In the post-treatment period when subjects were off Dupixent, the treatment effect diminished over time. In both studies, significant improvements in nasal congestion were observed as early as the first assessment at Week 4. A significant decrease in the LMK sinus CT scan score was observed. Dupilumab significantly improved the loss of smell compared to placebo. In both studies, significant improvements in daily loss of smell severity were observed as early as the first assessment at Week 4. Dupilumab significantly decreased sinonasal symptoms as measured by SNOT-22 compared to placebo. In the pre-specified multiplicity-adjusted pooled analysis of two studies, treatment with Dupixent resulted in significant reduction of systemic corticosteroid use and need for sinonasal surgery versus placebo (HR of 0.24; 95% CI: 0.17, 0.35). The proportion of subjects who required systemic corticosteroids was reduced by 74% (HR of 0.26; 95% CI: 0.18, 0.38). The total number of systemic corticosteroid courses per year was reduced by 75% (RR of 0.25; 95% CI: 0.17, 0.37). The proportion of subjects who required surgery was reduced by 83% (HR of 0.17; 95% CI: 0.07, 0.46). The effects of Dupixent on the primary endpoints of NPS and nasal congestion and the key secondary endpoint of LMK sinus CT scan score were consistent in patients with prior surgery and without prior surgery. **EoE(1)** A single randomized, double-blind, parallel-group, multicenter, placebo-controlled trial, including two 24-week treatment periods (Parts A and B), was conducted in adult and pediatric subjects 12 to 17 years of age, weighing at least 40 kg, with EoE (NCT03633617). In both parts, subjects were randomized to receive 300 mg Dupixent every week or placebo. Eligible subjects had greater than or equal to 15 intraepithelial eosinophils per high-power field (eos/hpf) following a treatment

	course of a proton pump inhibitor (PPI) either prior to or during the screening period and symptoms of dysphagia as measured by the Dysphagia Symptom Questionnaire (DSQ). At baseline, 43% of subjects in Part A and 37% of subjects in Part B had a history of prior esophageal dilations. The coprimary efficacy endpoints in Parts A and B were the (1) proportion of subjects achieving histological remission defined as peak esophageal intraepithelial eosinophil count of less than or equal to 6 eos/hpf at week 24; and (2) the absolute change in the subject reported DSQ score from baseline to week 24. In Parts A and B, a greater proportion of subjects randomized to Dupixent achieved histological remission (peak esophageal intraepithelial eosinophil count less than or equal to 6 eos/hpf) compared to placebo (Part A: 25% vs 2%; Part B: 47% vs 5%). Treatment with Dupixent also resulted in a significant improvement in LS mean change in DSQ score compared to placebo at week 24 (Part A: -21.9 vs -9.6; Part B -23.8 vs -13.9). The results of the anchor-based analyses that incorporated the subjects' perspectives indicated that the observed improvement in dysphagia from Parts A and B is representative of a clinically meaningful within-subject improvement. **PN(1,14)** The prurigo nodularis (PN) development program included two 24-week randomized, double-blind, placebo-controlled, multicenter, parallel-group trials (PRIME [NCT04183335] and PRIME 2 [NCT04202679]) in 311 adult subjects 18 years of age and older with pruritus (WINRS greater than or equal to 7 on a scale of 0 to 10) and greater than or equal to 20 nodular lesions. PRIME and PRIME 2 assessed the effect of Dupixent on pruritus improvement as well as its effect on PN lesions. In these two trials, subjects received either subcutaneous Dupixent 600 mg (two 300 mg injections) on day 1, followed by 300 mg once every other week (Q2W) for 24 weeks, or matching placebo. At baseline, the mean Worst Itch-Numeric Rating Scale (WI-NRS) was 8.5, 66% had 20 to 100 nodules (moderate), and 34% had greater than 100 nodules (severe). Patients were required to have failed at least a 2-week trial of a medium to super potent topical corticosteroid or topical corticosteroids were not medically advised. The WI-NRS is comprised of a single item, rated on a scale from 0 (no itch) to 10 (worst imaginable itch). Subjects were asked to rate the intensity of their worst pruritus (itch) over the past 24 hours using this scale. The Investigator's Global Assessment for Prurigo Nodularis-Stage (IGA PN-S) is a

	scale that measures the approximate number of nodules using a 5-point scale from 0 (clear) to 4 (severe). Efficacy was assessed with the proportion of subjects with improvement (reduction) in WI-NRS by greater than or equal to 4 points, the proportion of subjects with IGA PN-S 0 or 1 (the equivalent of 0-5 nodules), and the proportion of subjects who achieved a response in both WI-NRS and IGA PN-S per the criteria described above. Overall, patients treated with Dupixent saw improvement in all endpoints over placebo.
Safety	Dupilumab is contraindicated in patients who have a known hypersensitivity to dupilumab or any excipients of Dupixent.(1)

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27	Fokkens WJ, Viskens A, Backer V, et al. EPOS/EUFOREA update on indication and evaluation of Biologics in Chronic Rhinosinusitis with Nasal Polyps 2023. *Rhinology*. 2023;0(0):194-202. doi:10.4193/rhin22.489

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** All target agents are eligible for continuation of therapy 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. ONE of the following: A. The patient has a diagnosis of moderate-to-severe atopic dermatitis (AD) AND ALL of the following: 1. ONE of the following: A. The patient has at least 10% body surface area involvement **OR** B. The patient has involvement of body sites that are difficult to treat with prolonged topical corticosteroid therapy (e.g., hands, feet, face, neck, scalp, genitals/groin, skin folds) **OR** C. The patient has an Eczema Area and Severity Index (EASI) score greater than or equal to 16 **OR** D. The patient has an Investigator Global Assessment (IGA) score greater than or equal to 3 **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to at least a medium-potency topical corticosteroid used in the treatment of AD after at least a 4-week duration of therapy **OR**

Module	Clinical Criteria for Approval
	B. The patient has an intolerance or hypersensitivity to at least a medium-potency topical corticosteroid used in the treatment of AD **OR** C. The patient has an FDA labeled contraindication to ALL medium-, high-, and super-potency topical corticosteroids used in the treatment of AD **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response to a topical calcineurin inhibitor (e.g., Elidel/pimecrolimus, Protopic/tacrolimus) used in the treatment of AD after at least a 6-week duration of therapy **OR** B. The patient has an intolerance or hypersensitivity to a topical calcineurin inhibitor used in the treatment of AD **OR** C. The patient has an FDA labeled contraindication to ALL topical calcineurin inhibitors used in the treatment of AD **AND** 4. The prescriber has documented the patient's baseline (prior to therapy with the requested agent) pruritus and other symptom severity (e.g., erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and/or lichenification) **OR** B. The patient has a diagnosis of moderate to severe asthma AND BOTH of the following: 1. ONE of the following: A. The patient has eosinophilic type asthma AND ONE of the following: 1. The patient has a baseline (prior to therapy with the requested agent) blood eosinophilic count of 150 cells/microliter or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids **OR** 2. The patient has a fraction of exhaled nitric oxide (FeNO) of 20 parts per billion or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids **OR** 3. The patient has sputum eosinophils 2% or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids **OR**

Module	Clinical Criteria for Approval
	B. The patient has oral corticosteroid dependent type asthma **AND** 2. The patient has a history of uncontrolled asthma while on asthma control therapy as demonstrated by ONE of the following: A. Frequent severe asthma exacerbations requiring two or more courses of systemic corticosteroids (steroid burst) within the past 12 months **OR** B. Serious asthma exacerbations requiring hospitalization, mechanical ventilation, or visit to the emergency room or urgent care within the past 12 months **OR** C. Controlled asthma that worsens when the doses of inhaled and/or systemic corticosteroids are tapered **OR** D. The patient has baseline (prior to therapy with the requested agent) Forced Expiratory Volume (FEV1) that is less than 80% of predicted **OR** C. The patient has a diagnosis of chronic rhinosinusitis with nasal polyps (CRSwNP) AND ALL of the following: 1. The patient has at least TWO of the following symptoms consistent with chronic rhinosinusitis (CRS): A. Nasal discharge (rhinorrhea or post-nasal drainage) B. Nasal obstruction or congestion C. Loss or decreased sense of smell (hyposmia) D. Facial pressure or pain **AND** 2. The patient has had symptoms consistent with chronic rhinosinusitis (CRS) for at least 12 consecutive weeks **AND** 3. The patient's diagnosis was confirmed by ONE of the following: A. Anterior rhinoscopy or endoscopy **OR** B. Computed tomography (CT) of the sinuses **AND** 4. ONE of the following: A. ONE of the following: 1. The patient had an inadequate response to sinonasal surgery **OR** 2. The patient is NOT a candidate for sinonasal surgery **OR** B. ONE of the following: 1. The patient has tried and had an inadequate response to oral systemic corticosteroids **OR**

Module	Clinical Criteria for Approval
	2. The patient has an intolerance or hypersensitivity to therapy with oral systemic corticosteroids **OR** 3. The patient has an FDA labeled contraindication to ALL oral systemic corticosteroids **AND** 5. ONE of the following: A. The patient has tried and had an inadequate response to intranasal corticosteroids (e.g., fluticasone, Sinuva) after at least a 4-week duration of therapy **OR** B. The patient has an intolerance or hypersensitivity to therapy with intranasal corticosteroids (e.g., fluticasone, Sinuva) **OR** C. The patient has an FDA labeled contraindication to ALL intranasal corticosteroids **OR** D. The patient has a diagnosis of eosinophilic esophagitis (EoE) AND BOTH of the following: 1. The patient's diagnosis was confirmed by ALL of the following: A. Chronic symptoms of esophageal dysfunction **AND** B. Greater than or equal to 15 eosinophils per high-power field on esophageal biopsy **AND** C. Other causes that may be responsible for or contributing to symptoms and esophageal eosinophilia have been ruled out **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to ONE standard corticosteroid therapy used in the treatment of EoE (i.e., budesonide oral suspension, swallowed budesonide nebulizer suspension, swallowed fluticasone MDI) **OR** B. The patient has an intolerance or hypersensitivity to standard corticosteroid therapy used in the treatment of EoE **OR** C. The patient has an FDA labeled contraindication to ALL standard corticosteroid therapies used in the treatment of EoE **OR** D. The patient has tried and had an inadequate response to ONE proton pump inhibitor (PPI) used in the treatment of EoE **OR** E. The patient has an intolerance or hypersensitivity to PPI therapy used in the treatment of EoE **OR**

Module	Clinical Criteria for Approval
	F. The patient has an FDA labeled contraindication to ALL PPI therapies used in the treatment of EoE **OR** E. The patient has a diagnosis of prurigo nodularis (PN) and BOTH of the following: 1. The patient has ALL of the following features associated with PN: A. Presence of firm, nodular lesions **AND** B. Pruritus that has lasted for at least 6 weeks **AND** C. History and/or signs of repeated scratching, picking, or rubbing **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to at least a medium-potency topical corticosteroid used in the treatment of PN after at least a 2-week duration of therapy **OR** B. The patient has an intolerance or hypersensitivity to therapy with at least a medium-potency topical corticosteroid used in the treatment of PN **OR** C. The patient has an FDA labeled contraindication to ALL medium-, high-, and super-potency topical corticosteroids used in the treatment of PN **OR** F. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **OR** C. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has a diagnosis of moderate-to-severe atopic dermatitis (AD), then BOTH of the following: A. The patient is currently treated with topical emollients and practicing good skin care **AND** B. The patient will continue the use of topical emollients and good skin care practices in combination with the requested agent **AND** 3. If the patient has a diagnosis of chronic rhinosinusitis with nasal polyps (CRSwNP) BOTH of the following:

Module	Clinical Criteria for Approval
	A. The patient is currently treated with standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids) **AND** B. The patient will continue standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids) in combination with the requested agent **AND** 4. If the patient has a diagnosis of moderate to severe asthma, ALL of the following: A. ONE of the following: 1. The patient is NOT currently being treated with the requested agent AND is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **OR** 2. The patient is currently being treated with the requested agent AND ONE of the following: A. Is currently treated with an inhaled corticosteroid for at least 3 months that is adequately dosed to control symptoms **OR** B. Is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **OR** 3. The patient has an intolerance or hypersensitivity to inhaled corticosteroid therapy **OR** 4. The patient has an FDA labeled contraindication to ALL inhaled corticosteroids **AND** B. ONE of the following: 1. The patient is currently being treated for at least 3 months with ONE of the following: A. A long-acting beta-2 agonist (LABA) **OR** B. Long-acting muscarinic antagonist (LAMA) **OR** C. A leukotriene receptor antagonist (LTRA) **OR** D. Theophylline **OR** 2. The patient has an intolerance or hypersensitivity to therapy with long-acting beta-2 agonists (LABA), long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonist (LTRA), or theophylline **OR** 3. The patient has an FDA labeled contraindication to ALL long-acting beta-2 agonists (LABA) AND long-acting muscarinic antagonists (LAMA) **AND** C. The patient will continue asthma control therapy (e.g., ICS, ICS/LABA, LTRA, LAMA, theophylline) in combination with the requested agent **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., atopic dermatitis - dermatologist, allergist, immunologist; asthma -allergist, immunologist, pulmonologist; CRSwNP -otolaryngologist, allergist, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. ONE of the following (please refer to "Agents NOT to be used Concomitantly" table):

Module	Clinical Criteria for Approval
	A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (submitted copy of clinical trials, phase III studies, guidelines required) **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 6 months Note: Initial loading dose is allowed for asthma, atopic dermatitis, or prurigo nodularis only and may require a Quantity Limit review. The loading dose plus maintenance dose may be approved for 1 month, followed by maintenance dosing for the remainder of the length of approval. NOTE: If Quantity Limit applies, please refer to Quantity Limit criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. ONE of the following: A. The patient has a diagnosis of moderate-to-severe atopic dermatitis (AD) AND BOTH of the following: 1. The patient has had a reduction or stabilization from baseline (prior to therapy with the requested agent) of ONE of the following: A. Affected body surface area **OR** B. Flares **OR** C. Pruritus, erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and/or lichenification **OR** D. A decrease in the Eczema Area and Severity Index (EASI) score **OR** E. A decrease in the Investigator Global Assessment (IGA) score **AND**

Module	Clinical Criteria for Approval
	2. The patient will continue standard maintenance therapies (e.g., topical emollients, good skin care practices) in combination with the requested agent **OR** B. The patient has a diagnosis of moderate to severe asthma AND BOTH of the following: 1. The patient has had improvements or stabilization with the requested agent from baseline (prior to therapy with the requested agent) as indicated by ONE of the following: A. The patient has had an increase in percent predicted Forced Expiratory Volume (FEV1) **OR** B. The patient has had a decrease in the dose of inhaled corticosteroids required to control the patient's asthma **OR** C. The patient has had a decrease in need for treatment with systemic corticosteroids due to exacerbations of asthma **OR** D. The patient has had a decrease in number of hospitalizations, need for mechanical ventilation, or visits to urgent care or emergency room due to exacerbations of asthma **AND** 2. The patient is currently treated and is compliant with asthma control therapy [e.g., inhaled corticosteroids, ICS/long-acting beta-2 agonist (LABA), leukotriene receptor antagonist (LTRA), long-acting muscarinic antagonist (LAMA), theophylline] **OR** C. The patient has a diagnosis of chronic rhinosinusitis with nasal polyps (CRSwNP) AND BOTH of the following: 1. The patient has had clinical benefit with the requested agent **AND** 2. The patient will continue standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids) in combination with the requested agent **OR** D. The patient has a diagnosis other than moderate-to-severe atopic dermatitis (AD), moderate to severe asthma, or chronic rhinosinusitis with nasal polyps (CRSwNP) AND has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., atopic dermatitis - dermatologist, allergist, immunologist; asthma -allergist, immunologist, pulmonologist; CRSwNP -otolaryngologist, allergist, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. ONE of the following (please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following:

Module	Clinical Criteria for Approval
	1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for use of combination therapy (submitted copy of clinical trials, phase III studies, guidelines required) **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months Note: If approving initial loading dose, please approve initial loading dose for asthma, atopic dermatitis, or prurigo nodularis only. The loading dose plus maintenance dose may be approved for 1 month, followed by maintenance dosing for the remainder of the length of approval.

CONTRAINDICATION AGENTS

Contraindicated as Concomitant Therapy
Agents NOT to be used Concomitantly Abrilada (adalimumab-afzb) Actemra (tocilizumab) Adalimumab Adbry (tralokinumab-ldrm) Amjevita (adalimumab-atto) Arcalyst (rilonacept) Avsola (infliximab-axxq) Benlysta (belimumab) Bimzelx (bimekizumab-bkzx) Cibinqo (abrocitinib) Cimzia (certolizumab) Cinqair (reslizumab) Cosentyx (secukinumab) Cyltezo (adalimumab-adbm) Dupixent (dupilumab) Enbrel (etanercept) Entyvio (vedolizumab) Fasenra (benralizumab) Hadlima (adalimumab-bwwd) Hulio (adalimumab-fkjp) Humira (adalimumab) Hyrimoz (adalimumab-adaz) Idacio (adalimumab-aacf) Ilaris (canakinumab) Ilumya (tildrakizumab-asmn) Inflectra (infliximab-dyyb) Infliximab Kevzara (sarilumab) Kineret (anakinra) Leqselvi (deuruxolitinib) Litfulo (ritlecitinib) Nemluvio (nemolizumab-ilto) Nucala (mepolizumab) Olumiant (baricitinib) Omvoh (mirikizumab-mrkz) Opzelura (ruxolitinib)

Contraindicated as Concomitant Therapy
Orencia (abatacept)
Otezla (apremilast)
Pyzchiva (ustekinumab-ttwe)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rinvoq (upadacitinib)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Saphnelo (anifrolumab-fnia)
Selarsdi (ustekinumab-aekn)
Siliq (brodalumab)
Simlandi (adalimumab-ryvk)
Simponi (golimumab)
Simponi ARIA (golimumab)
Skyrizi (risankizumab-rzaa)
Sotyktu (deucravacitinib)
Spevigo (spesolimab-sbzo) subcutaneous injection
Stelara (ustekinumab)
Taltz (ixekizumab)
Tezspire (tezepelumab-ekko)
Tofidence (tocilizumab-bavi)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tyenne (tocilizumab-aazg)
Tysabri (natalizumab)
Velsipity (etrasimod)
Wezlana (ustekinumab-auub)
Xeljanz (tofacitinib)
Xeljanz XR (tofacitinib extended release)
Xolair (omalizumab)
Yuflyma (adalimumab-aaty)
Yusimry (adalimumab-aqvh)
Zeposia (ozanimod)
Zymfentra (infliximab-dyyb)

Interleukin-5 (IL-5) Inhibitors

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Fasenra® (benralizumab) Injection for subcutaneous use	Add-on maintenance treatment of patients with severe asthma aged 12 years and older, and with an eosinophilic phenotype Limitations of use: • Treatment of other eosinophilic conditions • Relief of acute bronchospasm or status asthmaticus		2
Nucala® (mepolizumab) Injection for subcutaneous use	Add-on maintenance treatment of patients aged 6 years and older with severe asthma and with an eosinophilic phenotype Treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA) Treatment of adult and pediatric patients aged 12 years and older with hypereosinophilic syndrome (HES) for greater than or equal to 6 months without an identifiable non-hematologic secondary cause Add-on maintenance treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in adult patients 18 years of age and older with inadequate response to nasal corticosteroids Limitation of use: • Not for relief of acute bronchospasm or status asthmaticus		1

CLINICAL RATIONALE

Asthma	Asthma is a chronic inflammatory disorder of the airways.(3,5) It is characterized by variable and recurring clinical symptoms, airflow obstruction, bronchial

	hyperresponsiveness, and underlying inflammation.(3) Symptoms of asthma include wheezing, coughing, recurrent difficulty breathing, shortness of breath, and chest tightness. Generally, these symptoms will occur or worsen with exposure to allergens and irritants, infections, exercise, changes in weather, stress, or menstrual cycles. Guidelines recommend the use of detailed medical history, physical examination, and spirometry to make a diagnosis of asthma.(3,5) The Global Initiative for Asthma (GINA) guidelines recommend a stepwise approach for managing asthma. Long-term goals for asthma management are to achieve good control of symptoms, maintain normal activity level, and to minimize the future risk of exacerbations, fixed airflow limitation, and side-effects.(5) IgE is the antibody responsible for activation of allergic reactions and is important to the pathogenesis of allergic asthma and the development and persistence of inflammation. GINA guidelines define moderate asthma as that which is well controlled with Step 3 or Step 4 treatment (e.g., low- or medium-dose inhaled corticosteroids [ICS] in combination with a long-acting beta agonist [LABA] in either treatment track). Severe asthma is defined as asthma that remains uncontrolled despite optimized treatment with high-dose ICS-LABA, or that requires high-dose ICS-LABA to prevent it from becoming uncontrolled. Severe asthma must be distinguished from asthma that is difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity, as they need very different treatment compared with if asthma is relatively refractory to high-dose ICS-LABA or even oral corticosteroids (OCS). Early initiation of low dose ICS in patients with asthma has led to greater improvement in lung function than initiation of ICS after symptoms have been present for more than 2 to 4 years. The 2023 GINA guidelines recommend every adult and adolescent with asthma should receive ICS-containing controller medication to reduce the risk of serious exacerbation, even in patients with infrequent symptoms.(5) 2023 GINA STEP recommendations for adults and adolescents (12 years of age and over) are intended to reduce the risk of serious exacerbations and are broken into two tracks based on reliever therapy. **Track 1** is the preferred approach recommended by GINA, because using low dose ICS-formoterol as reliever reduces the risk of exacerbations compared with regimens with short-acting β2-agonist (SABA) as reliever, and is a simpler regimen. Note ICS-formoterol should not be used as the reliever by patients taking any other (non-formoterol) ICS-LABA or ICS-LAMA:(5) • Step 1:

	○ As-needed low dose ICS-formoterol • Step 2: ○ As-needed low dose ICS-formoterol • Step 3: address and treat modifiable risk factors (e.g., adherence, technique) before considering step up ○ Maintenance: low dose ICS-formoterol ○ Reliever: as-needed low dose ICS-formoterol • Step 4: ○ Maintenance: medium dose ICS-formoterol ○ Reliever: as-needed low dose ICS-formoterol • Step 5: patients with uncontrolled symptoms and/or exacerbations despite Step 4 treatment should be assessed for contributory factors, have their treatment optimized, and be referred for expert assessment including severe asthma phenotype, and potential add on treatment ○ Maintenance: consider high dose ICS-formoterol ○ Reliever: as-needed low dose ICS-formoterol ○ Add-on LAMA for patients greater than or equal to 18 years (greater than or equal to 6 years for tiotropium) in separate or combination inhalers ○ Refer for phenotypic assessment +/- biologic therapy ▪ Add-on anti-IgE for severe allergic asthma • SC omalizumab in patients greater than or equal to 6 years ▪ Add-on anti-interleukin (IL)5 or anti-IL5R or anti-IL4R for severe eosinophilic/Type 2 asthma • Anti-IL5: SC mepolizumab for patients greater than or equal to 6 years OR IV reslizumab for patients greater than or equal to 18 years of age • Anti-IL5R: SC benralizumab for patients greater than or equal to 12 years • Anti-IL4R: SC dupilumab for patients greater than or equal to 6 years ▪ Add-on anti-thymic stromal lymphopoietin (TSLP) for severe asthma • SC tezepelumab for patients greater than or equal to 12 years ○ Add-on azithromycin three days/week reduces exacerbations, but increases antibiotic resistance ○ Maintenance oral corticosteroids (OCS) should be used only as last resort, because short-term and long-term systemic side-effects are common and serious

	Track 2 is an alternative approach if Track 1 is not possible or is not preferred by a patient with no exacerbations on their current therapy. Before considering a regimen with SABA reliever, the clinician should consider whether the patient is likely to be adherent with their controller therapy; if not, they will be exposed to the higher risk of exacerbations with SABA-only treatment:(5)
	
	• Step 1:
	  ○ Take ICS whenever SABA taken
	  ○ Reliever: as-needed ICS-SABA or as needed SABA
	• Step 2:
	  ○ Preferred maintenance: low dose ICS
	  ○ Preferred reliever: as-needed ICS-SABA or as-needed SABA
	  ○ Alternative options with limited indications, or less evidence for efficacy and/or safety:
	  ▪ Low dose ICS whenever SABA taken
	  ▪ Daily LTRA. These are less effective than daily ICS, particularly for preventing exacerbations and there is a US FDA boxed warning about the risk of serious mental health effects with montelukast
	  ▪ Daily low-dose ICS-LABA as initial therapy leads to faster improvement in symptoms and FEV1 than ICS alone but is costlier, and the reduction in exacerbations compared with SABA is similar to that with ICS
	  ▪ For adults with rhinitis who are allergic to house dust mite and have FEV1 > 70% predicted, consider adding sublingual immunotherapy (SLIT)
	• Step 3: address and treat modifiable risk factors (e.g., adherence, technique) before considering step up
	  ○ Preferred maintenance: low dose ICS-LABA
	  ○ Preferred reliever: as-needed ICS-SABA or as-needed SABA
	  ○ Alternative options:
	  ▪ Medium dose ICS
	  ▪ Low-dose ICS plus LTRA but review US FDA boxed warning
	  ▪ For adults with rhinitis who are allergic to house dust mite and have FEV1 > 70% predicted, consider adding SLIT
	• Step 4:
	  ○ Preferred maintenance: medium/high dose ICS-LABA
	  ○ Preferred reliever: as-needed ICS-SABA or as-needed SABA
	  ○ Alternative options:
	  ▪ Add-on LAMA for patients greater than or equal to 18 years (greater than or equal to 6 years for tiotropium my mist inhaler)

	• Before considering add-on LAMA for patients with exacerbations, increase ICS dose to at least medium ▪ For adults with rhinitis who are allergic to house dust mite and have FEV1 > 70% predicted, consider adding sublingual immunotherapy (SLIT) • Step 5: patients with uncontrolled symptoms and/or exacerbations despite Step 4 treatment should be assessed for contributory factors, have their treatment optimized, and be referred for expert assessment including severe asthma phenotype, and potential add on treatment ○ Maintenance: medium/high dose ICS-LABA ○ Reliever: as-needed ICS-SABA or as-needed SABA ○ Add-on LAMA for patients greater than or equal to 18 years (greater than or equal to 6 years for tiotropium) in separate or combination inhalers ○ Refer for phenotypic assessment +/- biologic therapy ▪ Add-on anti-IgE for severe allergic asthma • SC omalizumab in patients greater than or equal to 6 years ▪ Add-on anti-interleukin (IL)5 or anti-IL5R or anti-IL4R for severe eosinophilic/Type 2 asthma • Anti-IL5: SC mepolizumab for patients greater than or equal to 6 years OR IV reslizumab for patients greater than or equal to 18 years of age • Anti-IL5R: SC benralizumab for patients greater than or equal to 12 years • Anti-IL4R: SC dupilumab for patients greater than or equal to 6 years ▪ Add-on anti-thymic stromal lymphopoietin (TSLP) for severe asthma • SC tezepelumab for patients greater than or equal to 12 years ○ Add-on azithromycin three days/week reduces exacerbations, but increases antibiotic resistance ○ Maintenance OCS should only be used as last resort, because short-term and long-term systemic side-effects are common and serious 2023 GINA STEP recommendations for children (6 to 11 years of age) are intended to reduce the risk of serious exacerbations:(5) • Step 1:

	○ Low dose ICS taken whenever SABA taken ○ Reliever: as needed SABA • Step 2: ○ Preferred: daily low dose ICS ○ Preferred reliever: as needed SABA ○ Alternative options: ▪ Low-dose ICS whenever SABA is taken using separate inhalers ▪ Daily LTRA are less effective for exacerbation reduction. Advise parents about US FDA warning on montelukast • Step 3: after checking inhaler technique and adherence, and treating modifiable risk factors (any of the following): ○ Medium-dose ICS maintenance plus as-needed SABA ○ Low-dose ICS-LABA maintenance plus as-needed SABA ○ Maintenance and reliever therapy (MART) with a very low dose of budesonide-formoterol DPI • Step 4: Individual children's responses vary, so each of the Step 3 options may be tried before considering a step-up to Step 4. Refer for expert advice ○ Preferred: medium dose ICS-LABA plus as-needed SABA ○ Preferred: low dose ICS-formoterol MART plus as-needed low-dose ICS-formoterol ○ Alternative options: ▪ Add-on tiotropium ▪ Add-on LTRA • Step 5: ○ Refer for phenotypic assessment with or without higher dose ICS-LABA ○ Reliever: as needed SABA (or ICS-formoterol reliever for MART) ○ Add on therapy with anti-IgE or anti-IL4R, anti-IL5 ○ As a last resort consider add on low dose OCS but consider side effects **Severe Asthma Phenotype and Eosinophilic Asthma Subphenotype** Roughly 3% to 10% of adults with asthma have severe asthma as defined by the GINA 2023 guidelines.(5) The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014; updated 2020) and the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group mirror the GINA definition of severe asthma, and defined

	uncontrolled asthma for adult and pediatric patients 5 years of age and over:(3,19)
	
	• Frequent severe exacerbations (i.e., two or more bursts of systemic corticosteroids within the past 12 months)
	• Serious exacerbations (i.e., at least one hospitalization, intensive care unit stay, or mechanical ventilation in the past 12 months)
	• Airflow limitation (i.e., FEV1 less than 80% predicted)
	• Asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids
	
	A specialist, preferably in a multidisciplinary severe asthma clinic (if available) performs further assessment, which includes the patient's inflammatory phenotype (i.e., Type 2 or non-Type 2).(5)
	
	Type 2 inflammation is characterized by the presence of cytokines such as interleukin (IL)-4, IL-5, and IL-13, which are often produced by the adaptive immune system on recognition of allergens. It is also characterized by eosinophilia or increased fraction of exhaled nitric oxide (FeNO) and may be accompanied by atopy. In many patients with asthma, Type 2 inflammation rapidly improves when ICS are taken regularly and correctly; this is classified as mild or moderate asthma. In severe asthma, Type 2 inflammation may be relatively refractory to high dose ICS. Type 2 inflammation is considered refractory if any of the following are found while the patient is taking high dose ICS or daily OCS:(5)
	
	• Blood eosinophils greater than or equal to 150 cells/microliter
	• FeNO greater than or equal to 20 ppb
	• Sputum eosinophils greater than or equal to 2%
	• Asthma is clinically allergen-driven
	
	Biologic agents should be considered as add-on therapy for patients with refractory Type 2 inflammation with exacerbations or poor symptom control despite taking at least high dose ICS/LABA, and who have allergic or eosinophilic biomarkers or need maintenance OCS.(5) 2023 GINA recommends the biologics below based on patient eligibility factors:
	
	• Anti-IgE (omalizumab):
	  ○ Sensitization on skin prick testing or specific IgE
	  ○ Total serum IgE and weight within dosage range
	  ○ Exacerbations in the last year
	• Anti-IL5/Anti-IL5R (benralizumab, mepolizumab, reslizumab):

	○ Exacerbations in the last year ○ Blood eosinophils greater than or equal to 150 cells/microliter (for benralizumab and mepolizumab) or greater than or equal to 300 cells/microliter (for reslizumab) • Anti-IL4R (dupilumab): ○ Exacerbations in the last year ○ Blood eosinophil greater than or equal to 150 cells/microliter but less than or equal to 1500 cells/microliter, or FeNO greater than or equal to 25 ppb, or taking maintenance OCS • Anti-TSLP (tezepelumab): ○ Exacerbations in the last year Patient response should be evaluated 4 months after initiating therapy and follow up should occur every 3 to 6 months thereafter. 2023 GINA recommends the following step-down therapy process in patients responding well to targeted biologic therapy:(5) • Reevaluate the need for each asthma medication every 3 to 6 months, but inhaled therapy should not be completely stopped • Oral treatments: gradually decreased starting with OCS due to significant adverse effects. • Inhaled treatments: consider reducing ICS dose after 3 to 6 months, but do not completely stop inhaled therapy. Continue at least medium dose ICS and remind patients of the importance of continued inhaled controller therapy • Biologic treatments: trial withdrawal after 12 months of treatment and only if patient's asthma remains well controlled on medium dose ICS, and for allergic asthma, there is no further exposure to a previous allergic trigger
Eosinophilic Granulomatosis with Polyangiitis (EGPA)	Eosinophilic granulomatosis with polyangiitis (EGPA), formally known as Churg-Strauss Syndrome, is a rare small-vessel vasculitis that occurs in patients with asthma and eosinophilia and is histologically characterized by tissue eosinophilia, necrotizing vasculitis and eosinophil-rich granulomatous inflammation. EGPA is an anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, characterized by asthma, eosinophilia and granulomatous or vasculitic involvement of several organs. Current practice relies on recommendations and guidelines addressing the management of ANCA-associated vasculitis and not specifically developed for EGPA.(20) The main clinical features of EGPA are late-onset allergic rhinitis and asthma, increased blood eosinophil count, and vasculitis manifestations, some of which can be life

	threatening. Once EGPA is suspected based on clinical findings of asthma with eosinophilia, asthma with systemic manifestations, or even eosinophilia with extrapulmonary disease, a biopsy demonstrating small or medium sized vessel vasculitis strongly supports the diagnosis of EGPA. Skin, nerve, and muscle are among the most common biopsied tissues, but endomyocardial, renal, and gastrointestinal biopsies may also be useful. Antineutrophil cytoplasm antibody (ANCA) testing is also recommended. ANCA positivity is highly suggestive of EGPA, but ANCA negative results do not rule out its diagnosis.(6) The clinical phenotype of EGPA is quite heterogeneous and the diagnosis is not always straightforward. Anti-neutrophil cytoplasmic antibodies (ANCA), usually against myeloperoxidase (MPO), are detectable in approximately 40% of the cases and are associated with a different frequency of clinical manifestations: features of vasculitis, particularly glomerulonephritis, peripheral neuropathy and purpura, occur more often in ANCA-positive patients, whereas the so-called eosinophilic features such as cardiac involvement and gastroenteritis are more frequent in ANCA-negative patients.(20) There are two types of classifications used for the diagnosis of EGPA. The first and most commonly used classification is by the American College of Rheumatology (ACR). ACR has established six criteria for the classification of EGPA in a patient with documented vasculitis. The presence of four or more of these criteria can establish a diagnosis of EGPA:(7) • Asthma (a history of wheezing or diffuse high-pitched rales on expiration) • Eosinophilia (greater than 10% eosinophils on white blood cell differential count) • Mononeuropathy (including multiplex), multiple mononeuropathies, or polyneuropathy attributed to a systemic vasculitis • Migratory or transient pulmonary infiltrates detected radiographically • Paranasal sinus abnormality • Biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas The Lanham criteria is also used for the diagnosis of EGPA. The Lanham criteria requires the patient to have all three of the following: asthma, peak peripheral blood eosinophilia in excess of 1500 cells/microliter, and systemic vasculitis involving two or more extra-pulmonary organs.(7,8) The American College of Rheumatology/European Alliance of Associations for Rheumatology developed classification criteria for EGPA broken into clinical

criteria as well as laboratory and biopsy criteria. Considerations when applying these criteria(20)

- These classification criteria should be applied to classify a patient as having EGPA when a diagnosis of small- or medium-vessel vasculitis has been made
- Alternate diagnoses mimicking vasculitis should be excluded prior to applying the criteria

	points
Clinical Criteria	
Obstructive airway disease	+3
Nasal Polyps	+3
Mononeuritis multiplex	+1
Laboratory and Biopsy Criteria	
Blood eosinophil count greater than or equal to 1 X 10^9/liter	+5
Extravascular eosinophilic-predominant inflammation on biopsy	+2
Positive test for cytoplasmic antineutrophil cytoplasmic antibodies (cANCA)	-3
Hematuria	-1

Sum the scores for the 7 items, if present. A score of greater than or equal to 6 is needed for classification of EGPA

The Five-Factor Score (FFS) predicts the risk of mortality in patients with an established diagnosis of EGPA, as well as polyarteritis nodosa microscopic polyangiitis or GPA. It includes five factors associated with shortened overall survival, namely, renal insufficiency (serum creatinine > 1.58 mg/dl), proteinuria > 1 g per day, cardiomyopathy, gastrointestinal involvement

	and central nervous system (CNS) involvement. The FFS considers clinical manifestations only at the time of diagnosis, the appearance of new manifestations during follow-up should also be taken into account when choosing remission-induction regimens for disease flares. New-onset active EGPA is considered severe if FFS is greater than or equal to 1 or there is presence of peripheral neuropathy, alveolar hemorrhage or other organ-or life-threatening manifestations. For relapsing EGPA severe disease consists of severe systemic relapse and non-severe is respiratory relapse alone or non-severe systemic relapse.(20) For remission induction in patients with new-onset, active EGPA, glucocorticoids should be administered as initial therapy. In patients with severe disease cyclophosphamide or rituximab and/or disease modifying anti-rheumatic drugs (DMARDs) should be added to glucocorticoid therapy. Remission maintenance for non-severe disease guidelines recommend glucocorticoids plus mepolizumab. Remission maintenance for severe disease guidelines recommend glucocorticoids plus rituximab and/or mepolizumab and or DMARDs. Although the evidence supporting the use of traditional immunosuppressants for remission maintenance in non-severe EGPAS is scarce, these agents are often used in routine clinical practice.(20) Treatment for relapsing EGPA in non-severe disease glucocorticoids alone or glucocorticoids plus mepolizumab along with optimization of inhaled therapies. Treatment of relapsing severe disease high-dose oral glucocorticoids plus cyclophosphamide or rituximab is recommended.(20) Refractory EGPA is defined as unchanged or increased disease activity after 4 weeks of appropriate remission-induction therapy. The persistence or worsening of systemic manifestations should be distinguished from that of respiratory manifestations. Mepolizumab in combination with glucocorticoids is recommended to induce remission in patients with relapsing-refractory EGPA without organ-or life-threatening manifestations. Mepolizumab can also be used for remission maintenance, particularly in patients requiring a daily prednisone greater than or equal to 7.5 mg for the control of their respiratory manifestations.(20)
Hypereosinophilic Syndrome (HES)	The eosinophilias encompass a broad range of non-hematologic (secondary or reactive) and hematologic (primary or clonal) disorders with potential for end-organ damage. Hypereosinophilia (HE) has generally been defined as peripheral blood eosinophil count greater than 1500 cells/microliter, OR pathologic confirmation of tissue HE by at least one of the following: percentage of eosinophils in bone marrow section exceeds 20% of all nucleated cells, marked

	deposition of eosinophil granule proteins is found, or tissue infiltration by eosinophils is extensive in the opinion of the pathologist.(12) To establish a diagnosis of HES, all three of the following criteria must be met:(11,12,13) • Criteria for HE fulfilled • Evidence of HE-related organ damage (e.g., fibrosis of lung, heart, digestive tract, skin, etc; thrombosis with or without thromboembolism; cutaneous erythema, edema/angioedema, ulceration, pruritis, or eczema; peripheral or central neuropathy with chronic or recurrent neurologic deficit; other organ system involvement such as liver, pancreas, kidney) • Exclusion of secondary (non-hematologic) causes of eosinophilia (e.g., infection, allergy/atopy, medications, collagen vascular disease, metabolic [e.g., adrenal insufficiency], solid tumor/lymphoma) Although the clinical manifestations can be similar irrespective of the cause of the eosinophilia, the choice of the initial therapeutic agent(s) for a given patient depends mainly on whether the patient has clinical features consistent with a myeloid disorder. Patients with myeloid variants of HES (e.g., PDGFRA-positive HES) often have an aggressive course with disabling complications and high mortality in the absence of treatment, and are treated initially with imatinib; those with other types of HES are treated with an initial trial of glucocorticoids.(11,12,13,14) Oral corticosteroids have been used for decades in the treatment of HES and, with the exception of imatinib for PDGFRA-associated HES as noted above, remain the first-line treatment for most patients. Hydroxyurea is a typical second-line agent, whether used as monotherapy or in conjunction with corticosteroids. Additional immunomodulatory and cytotoxic agent options include interferon-α, azathioprine, cyclosporine, methotrexate, and tacrolimus.(12,13,14) Despite the wide variety of commercially available immunomodulatory and cytotoxic agents, a significant proportion of patients with HES are treatment-refractory or experience treatment-related toxicity. Monoclonal anti–IL-5 antibody therapy for HES has a number of unique advantages related to the specificity of IL-5 for the eosinophil lineage.(12,13,14)
Chronic Rhinosinusitis with Nasal Polyposis	Chronic rhinosinusitis with nasal polyposis (CRSwNP) is an inflammatory condition affecting the paranasal sinuses. The International Consensus Statement on allergy and rhinology: Rhinosinusitis indicates that the diagnostic criteria for chronic rhinosinusitis (CRS) consist of ALL the following:(18) • Symptoms greater than or equal to 12 weeks

	• Two of the following symptoms:
	  ○ Nasal discharge (rhinorrhea or post-nasal drainage)
	  ○ Nasal obstruction or congestion
	  ○ Hyposmia (loss or decreased sense of smell)
	  ○ Facial pressure or pain
	• One or more of the following findings:
	  ○ Evidence of inflammation on nasal endoscopy or computed tomography
	  ○ Evidence of purulence coming from paranasal sinuses or ostiomeatal complex
	
	Sinus computed tomography (CT) and/or nasal endoscopy are needed to determine the presence of sinonasal inflammation and nasal polyps. The exact cause of CRSwNP is unknown, but biopsies of nasal polyps have shown elevated levels of eosinophils.(15)
	
	Intranasal corticosteroids (INCS) are recommended in the guidelines for CRSwNP. There are several formulations of INCS and it is recommended that clinicians must help each patient arrive at a management decision consistent with that patient's values and preferences as no formulation is recommended over another. For patients using INCS for at least 4 weeks and who continue to have high disease burden, biologics are preferred over other medical treatment choices. Biologics vary in their magnitude of benefits and harms and certainty of evidence across outcomes. For outcomes most important to patient care, dupilumab and omalizumab are the most beneficial, followed by mepolizumab. Other management options for CRSwNP that patients and their caregivers could consider include saline rinse, surgery, antibiotics, and for people with aspirin (non-steroidal anti-inflammatory)-exacerbated respiratory disease consider using aspirin therapy after desensitization.(16)

Efficacy	**Asthma** **Fasenra** Benralizumab was approved through 3 confirmatory clinical trials. Trial 1 and Trial 2 were exacerbation trials in patients 12 years of age and older. All subjects continued their background asthma therapy throughout the duration of the trials. The primary endpoint was the rate of asthma exacerbations in patients who were taking high-dose ICS and LABA. Asthma exacerbation was defined as a worsening of asthma requiring use of oral/systemic corticosteroids for at least 3 days, and/or emergency department visits requiring use of oral/systemic corticosteroids and/or hospitalization. For patients on maintenance oral

	corticosteroids, an asthma exacerbation requiring oral corticosteroids was defined as a temporary increase in stable oral/systemic corticosteroids for at least 3 days or a single depo-injectable dose of corticosteroids. In Trial 1, 35% of patients receiving benralizumab experienced an asthma exacerbation compared to 51% on placebo. In Trial 2, 40% of patients receiving benralizumab experienced an asthma exacerbation compared to 51% on placebo.(2) Trial 3 was a randomized OCS reduction trial in asthma patients. Patients were required to be treated with daily OCS (7.5 to 40 mg per day) in addition to regular use of high-dose ICS and LABA with or without additional controller(s). The trial included an 8-week run-in period during which the OCS was titrated to the minimum effective dose without losing asthma control. For the purposes of the OCS dose titration, asthma control was assessed by the investigator based on a patient's FEV1, peak expiratory flow, nighttime awakenings, short-acting bronchodilator rescue medication use or any other symptoms that would require an increase in OCS dose. Fasenra achieved greater reductions in daily maintenance OCS dose while maintaining asthma control compared to placebo (median reduction of 75% for Fasenra vs 25% for placebo).(2) **Nucala** The efficacy of mepolizumab for the treatment of severe eosinophilic asthma was established in three double-blind, randomized, placebo-controlled trials: A dose-ranging and exacerbation reduction trial (trial 1) and two confirmatory trials (trial 2 and 3). All subjects continued their background asthma therapy throughout the duration of the trials. Trial 1 enrolled subjects with uncontrolled asthma despite use of high dose inhaled corticosteroids (ICS) plus additional controller(s), with or without OCS. Trial 2 was a placebo- and active-controlled trial in subjects with asthma not adequately controlled on high-dose inhaled corticosteroids plus additional controller(s) with or without OCS. The primary end point for trial 1 and 2 was frequency of asthma exacerbations. Compared to placebo, subjects receiving mepolizumab experienced significantly fewer exacerbations and had a longer time to first exacerbation.(1) Trial 3 was an OCS-reduction study in asthma patients who required daily OCS in addition to regular controller medications. The primary end point was percent reduction of OCS dose during weeks 20 to 24 without loss of asthma control. The baseline mean oral corticosteroid use was similar between the Nucala and placebo group. Overall, mepolizumab achieved greater reduction in oral corticosteroid use while maintaining asthma control when compared to placebo.

	However, the difference between the mepolizumab and placebo groups was not statistically significant.(1) **EGPA** **Nucala** A total of 136 subjects with EGPA were evaluated in a randomized, placebo-controlled, multicenter, 52-week trial. Subjects enrolled had a diagnosis of EGPA for at least 6 months prior to enrollment with a history of relapsing or refractory disease and were on a stable dosage of oral prednisolone or prednisone of greater than or equal to 7.5 mg/day (but not greater than 50 mg/day) for at least 4 weeks prior to enrollment. Subjects received 300 mg of mepolizumab or placebo administered subcutaneously once every 4 weeks while continuing their stable OCS therapy. Starting at Week 4, OCS was tapered during the treatment period at the discretion of the investigator. The co-primary endpoints were the total accrued duration of remission over the 52-week treatment period, defined as Birmingham Vasculitis Activity Score (BVAS) = 0 (no active vasculitis) plus prednisolone or prednisone dose less than or equal to 4 mg/day, and the proportion of subjects in remission at both Week 36 and Week 48 of treatment. The BVAS is a clinician-completed tool to assess clinically active vasculitis that would likely require treatment, after exclusion of other causes.(1) A significantly higher proportion of subjects receiving mepolizumab achieved remission at both Week 36 and Week 48 compared with placebo. In addition, significantly more subjects receiving mepolizumab achieved remission within the first 24 weeks and remained in remission for the remainder of the 52-week study treatment period compared with placebo (19% for mepolizumab versus 1% for placebo; OR 19.7; 95% CI: 2.3, 167.9).(1) The time to first relapse (defined as worsening related to vasculitis, asthma, or sino-nasal symptoms requiring an increase in dose of corticosteroids or immunosuppressive therapy or hospitalization) was significantly longer for subjects receiving mepolizumab compared with placebo with a hazard ratio of 0.32 (95% CI: 0.21, 0.5). Additionally, subjects receiving mepolizumab had a reduction in rate of relapse compared with subjects receiving placebo (rate ratio 0.50; 95% CI: 0.36, 0.70 for mepolizumab compared with placebo). The incidence and number of relapse types (vasculitis, asthma, sino-nasal) were numerically lower with mepolizumab compared with placebo.(1)

	Subjects receiving mepolizumab had a significantly greater reduction in average daily OCS dose compared with subjects receiving placebo during Weeks 48 to 52.(1) **HES** **Nucala** A total of 108 adult and adolescent patients aged 12 years and older with HES for at least 6 months were evaluated in a randomized, double-blind, placebo-controlled, multicenter, 32-week trial (NCT #02836496). Patients with non-hematologic secondary HES (e.g., drug hypersensitivity, parasitic helminth infection, HIV infection, non-hematologic malignancy) or FIP1L1-PDGFRα kinase-positive HES were excluded from the trial. Patients received 300 mg of Nucala or placebo subcutaneously once every 4 weeks while continuing their stable HES therapy. Patients entering the trial had experienced at least 2 HES flares within the past 12 months and a blood eosinophil count of 1,000 cells/microliter or higher during screening. Historical HES flares for the trial entry criteria were defined as HES-related worsening of clinical symptoms or blood eosinophil counts requiring an escalation in therapy. Patients must have been on stable background HES therapy for a minimum of 4 weeks prior to randomization; existing HES therapy was maintained throughout the treatment period unless there was symptom worsening that required a dose increase. HES therapy could include chronic or episodic oral corticosteroids (OCS), immunosuppressive, and/or cytotoxic therapy.(1,10) The efficacy of Nucala in HES was established based upon the proportion of patients who experienced a HES flare during the 32-week treatment period. A HES flare was defined as worsening of clinical signs and symptoms of HES or increasing eosinophils (on at least 2 occasions), resulting in the need to increase OCS or increase/add cytotoxic or immunosuppressive HES therapy. Over the 32-week treatment period, the incidence of HES flare over the treatment period was 56% for the placebo group and 28% for the group treated with Nucala (50% reduction).(1,10) **CRSwNP** **Nucala** A randomized, double-blind, multicenter, placebo-controlled 52-week trial (NCT03085797) evaluated Nucala in patients with CRSwNP. The trial inclusion requirements included adult patients on background intranasal corticosteroids

	(INCS), with recurrent and symptomatic CRSwNP despite at least 1 surgery for the removal of nasal polyps within the previous 10 years. A total of 407 subjects were randomized to receive either 100 mg Nucala (N=206) or placebo (N=201) every 4 weeks for 52 weeks (13 doses). All study participants received mometasone furoate 400 mcg (intolerant participants received 200mcg) daily along with Nucala or placebo. Participants were not required to have sinus CT scans, but were required to have endoscopic confirmation of diagnosis.(1) The co-primary efficacy endpoints were change from baseline to Week 52 in total endoscopic nasal polyps score (NPS; 0-8 scale) as graded by independent blinded assessors and change from baseline in nasal visual analog scale (VAS; 0-10 scale) during weeks 49 to 52.(1) Statistically significant efficacy was observed regarding improvement (decrease) in bilateral endoscopic NPS score at week 52, and nasal obstruction VAS score from weeks 49 to 52. Total endoscopic NPS significantly improved at week 52 from baseline with mepolizumab versus placebo (adjusted difference in medians -0.73, 95% CI -1.11 to -0.34; p less than 0.001) and nasal obstruction VAS score during weeks 49–52 also significantly improved (-3.14, -4.09 to -2.18; p less than 0.001).(1) Treatment with Nucala resulted in significant reduction of systemic corticosteroid use and need for sinonasal surgery versus placebo. The proportion of subjects who required surgery was reduced by 57% (HR of 0.43; 95% CI: 0.25, 0.76). Treatment with Nucala also significantly reduced the need for systemic steroids for nasal polyps versus placebo.(1)
Safety	• Fasenra (benralizumab) is contraindicated in those with known hypersensitivity to benralizumab or excipients.(2) • Nucala (mepolizumab) is contraindicated in patients with history of hypersensitivity to mepolizumab or excipients in the formulation.(1) Benralizumab and mepolizumab have not been studied for use in combination with Xolair (omalizumab).

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy**

Module	Clinical Criteria for Approval
	All Target Agents are Eligible for Continuation of Therapy 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. ONE of the following A. The patient has a diagnosis of severe eosinophilic asthma and BOTH of the following: 1. The patient's diagnosis has been confirmed by ONE of the following: A. The patient has a baseline (prior to therapy with the requested agent) blood eosinophilic count of 150 cells/microliter or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids **OR** B. The patient has a fraction of exhaled nitric oxide (FeNO) of 20 parts per billion or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids **OR** C. The patient has sputum eosinophils 2% or higher while on high-dose inhaled corticosteroids or daily oral corticosteroids **AND** 2. The patient has a history of uncontrolled asthma while on asthma control therapy as demonstrated by ONE of the following: A. Frequent severe asthma exacerbations requiring two or more courses of systemic corticosteroids (steroid burst) within the past 12 months **OR** B. Serious asthma exacerbations requiring hospitalization, mechanical ventilation, or visit to the emergency room or urgent care within the past 12 months **OR** C. Controlled asthma that worsens when the doses of inhaled and/or systemic corticosteroids are tapered **OR** D. The patient has baseline (prior to therapy with the requested agent) Forced Expiratory Volume (FEV1) that is less than 80% of predicted **OR**

Module	Clinical Criteria for Approval
	B. The patient has a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) and ALL of the following: 1. The requested agent is Nucala **AND** 2. The patient has had a diagnosis of EGPA for at least 6 months with a history of relapsing or refractory disease **AND** 3. The patient's diagnosis of EGPA was confirmed by ONE of the following: A. The patient meets 4 of the following: 1. Asthma (history of wheezing or diffuse high-pitched rales on expiration) 2. Eosinophilia (greater than 10% eosinophils on white blood cell differential count) 3. Mononeuropathy (including multiplex), multiple mononeuropathies, or polyneuropathy attributed to a systemic vasculitis 4. Migratory or transient pulmonary infiltrates detected radiographically 5. Paranasal sinus abnormality 6. Biopsy containing a blood vessel showing the accumulation of eosinophils in extravascular areas **OR** B. The patient meets ALL of the following: 1. Medical history of asthma **AND** 2. Peak peripheral blood eosinophilia greater than 1000 cells/microliter **AND** 3. Systemic vasculitis involving two or more extra-pulmonary organs **AND** 4. ONE of the following: A. The patient is currently on maximally tolerated oral corticosteroid therapy **OR** B. The patient has an intolerance or hypersensitivity to oral corticosteroid therapy **OR** C. The patient has an FDA labeled contraindication to ALL oral corticosteroids **AND** 5. ONE of the following: A. The patient has tried and had an inadequate response to ONE non-corticosteroid immunosuppressant (e.g., azathioprine, cyclophosphamide, methotrexate, mycophenolate mofetil, rituximab) **OR**

Module	Clinical Criteria for Approval
	B. The patient has an intolerance or hypersensitivity to ONE non-corticosteroid immunosuppressant **OR** C. The patient has an FDA labeled contraindication to ALL of the following immunosuppressants 1. Azathioprine 2. Cyclophosphamide 3. Methotrexate 4. Mycophenolate mofetil **OR** C. The patient has a diagnosis of hypereosinophilic syndrome (HES) and ALL of the following: 1. The requested agent is Nucala **AND** 2. BOTH of the following: A. The patient has had a diagnosis of HES for at least 6 months **AND** B. The patient has a history of at least 2 HES flares within the past 12 months (i.e., worsening of clinical symptoms and/or blood eosinophil counts requiring an escalation in therapy) **AND** 3. The patient's diagnosis of HES was confirmed by BOTH of the following: A. ONE of the following: 1. The patient has a peripheral blood eosinophil count greater than 1000 cells/microliter **OR** 2. The patient has a percentage of eosinophils in bone marrow section exceeding 20% of all nucleated cells **OR** 3. The patient has marked deposition of eosinophil granule proteins found **OR** 4. The patient has tissue infiltration by eosinophils that is extensive in the opinion of a pathologist **AND** B. ALL of the following: 1. Secondary (reactive, non-hematologic) causes of eosinophilia have been excluded (e.g., infection, allergy/atopy, medications, collagen vascular disease, metabolic [e.g., adrenal insufficiency], solid tumor/lymphoma) **AND** 2. There has been evaluation of of hypereosinophilia-related organ involvement (e.g.,

Module	Clinical Criteria for Approval
	fibrosis of lung, heart, digestive tract, skin; thrombosis with or without thromboembolism; cutaneous erythema, edema/angioedema, ulceration, pruritis, or eczema; peripheral or central neuropathy with chronic or recurrent neurologic deficit; other organ system involvement such as liver, pancreas, kidney) **AND** 3. The patient does NOT have FIP1L1-PDGFRA-positive disease **OR** D. The patient has a diagnosis of chronic rhinosinusitis with nasal polyposis (CRSwNP) AND ALL of the following: 1. The requested agent is Nucala **AND** 2. The patient has at least TWO of the following symptoms consistent with chronic rhinosinusitis (CRS): A. Nasal discharge (rhinorrhea or post-nasal drainage) B. Nasal obstruction or congestion C. Loss or decreased sense of smell (hyposmia) D. Facial pressure or pain **AND** 3. The patient has had symptoms consistent with chronic rhinosinusitis (CRS) for at least 12 consecutive weeks **AND** 4. The patient's diagnosis was confirmed by ONE of the following: A. Anterior rhinoscopy or endoscopy **OR** B. Computed tomography (CT) of the sinuses **AND** 5. ONE of the following: A. ONE of the following: 1. The patient had an inadequate response to sinonasal surgery **OR** 2. The patient is NOT a candidate for sinonasal surgery **OR** B. ONE of the following: 1. The patient has tried and had an inadequate response to oral systemic corticosteroids **OR** 2. The patient has an intolerance or hypersensitivity to therapy with oral systemic corticosteroids **OR** 3. The patient has an FDA labeled contraindication to ALL oral systemic corticosteroids **AND** 6. ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient has tried and had an inadequate response to intranasal corticosteroids (e.g., fluticasone, Sinuva) after at least a 4-week duration of therapy **OR** B. The patient has an intolerance or hypersensitivity to therapy with intranasal corticosteroids (e.g., fluticasone, Sinuva) **OR** C. The patient has an FDA labeled contraindication to ALL intranasal corticosteroids **OR** E. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **OR** C. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has a diagnosis of severe eosinophilic asthma, then ALL of the following: A. ONE of the following: 1. The patient is NOT currently being treated with the requested agent AND is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **OR** 2. The patient is currently being treated with the requested agent AND ONE of the following: A. Is currently treated with an inhaled corticosteroid for at least 3 months that is adequately dosed to control symptoms **OR** B. Is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **OR** 3. The patient has an intolerance or hypersensitivity to inhaled corticosteroid therapy **OR** 4. The patient has an FDA labeled contraindication to ALL inhaled corticosteroids **AND** B. ONE of the following: 1. The patient is currently being treated for at least 3 months with ONE of the following: A. A long-acting beta-2 agonist (LABA) **OR** B. Long-acting muscarinic antagonist (LAMA) **OR** C. A leukotriene receptor antagonist (LTRA) **OR** D. Theophylline **OR**

Module	Clinical Criteria for Approval
	2. The patient has an intolerance or hypersensitivity to therapy with long-acting beta-2 agonists (LABA), long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonists (LTRA) or theophylline **OR** 3. The patient has an FDA labeled contraindication to ALL long-acting beta-2 agonists (LABA) AND long-acting muscarinic antagonists (LAMA) **AND** C. The patient will continue asthma control therapy (e.g., ICS, ICS/LABA, LTRA, LAMA, theophylline) in combination with the requested agent **AND** 3. If the patient has a diagnosis of hypereosinophilic syndrome (HES), ALL of the following: A. ONE of the following: 1. The patient is currently being treated with maximally tolerated oral corticosteroid (OCS) **OR** 2. The patient has an intolerance or hypersensitivity to oral corticosteroid (OCS) therapy **OR** 3. The patient has an FDA labeled contraindication to ALL oral corticosteroids **AND** B. ONE of the following: 1. The patient is currently being treated with ONE of the following: A. Hydroxyurea **OR** B. Interferon-a **OR** C. Another immunosuppressive agent (e.g., azathioprine, cyclosporine, methotrexate, tacrolimus) **OR** 2. The patient has an intolerance or hypersensitivity to therapy with hydroxyurea, interferon-a, or immunosuppressive agents (e.g., azathioprine, cyclosporine, methotrexate, tacrolimus) **OR** 3. The patient has an FDA labeled contraindication to hydroxyurea, interferon-a, and ALL immunosuppressive agents (e.g., azathioprine, cyclosporine, methotrexate, tacrolimus) **AND** C. The patient will continue existing HES therapy (e.g., OCS, hydroxyurea, interferon-a, immunosuppressants) in combination with the requested agent **AND** 4. If the patient has a diagnosis of chronic rhinosinusitis with nasal polyposis (CRSwNP), BOTH of the following: A. The patient is currently treated with standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids) **AND** B. The patient will continue standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids) in combination with the requested agent **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist, otolaryngologist, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. ONE of the following (Please refer to "Agents NOT to be used Concomitantly" table):

Module	Clinical Criteria for Approval
	A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (copy of support required, e.g., clinical trials, phase III studies, guidelines) **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 6 months for severe eosinophilic asthma; 12 months for EGPA, HES, CRSwNP, and all other FDA approved or or compendia supported indications For Fasenra, approve loading dose for new starts and the maintenance dose for the remainder of the 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. ONE of the following: A. The patient has a diagnosis of severe eosinophilic asthma AND BOTH of the following: 1. The patient has had improvements or stabilization with the requested agent from baseline (prior to therapy with the requested agent) as indicated by ONE of the following: A. Increase in percent predicted Forced Expiratory Volume (FEV1) **OR** B. Decrease in the dose of inhaled corticosteroids required to control the patient's asthma **OR** C. Decrease in need for treatment with systemic corticosteroids due to exacerbations of asthma **OR**

Module	Clinical Criteria for Approval
	D. Decrease in number of hospitalizations, need for mechanical ventilation, or visits to urgent care or emergency room due to exacerbations of asthma **AND** 2. The patient is currently treated and is compliant with asthma control therapy (i.e., inhaled corticosteroids [ICS], ICS/long-acting beta-2 agonist [ICS/LABA], leukotriene receptor antagonist [LTRA], long-acting muscarinic antagonist [LAMA], theophylline) **OR** B. The patient has a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA) AND ALL of the following: 1. The requested agent is Nucala **AND** 2. The patient has had improvements or stabilization with the requested agent from baseline (prior to therapy with the requested agent) as indicated by ONE of the following: A. Remission achieved with the requested agent **OR** B. Decrease in oral corticosteroid maintenance dose required for control of symptoms related to EGPA **OR** C. Decrease in hospitalization due to symptoms of EGPA **OR** D. Dose of maintenance corticosteroid therapy and/or immunosuppressant therapy was not increased **AND** 3. ONE of the following: A. The patient is currently treated and is compliant with maintenance therapy with oral corticosteroids **OR** B. The patient has an intolerance or hypersensitivity to oral corticosteroid therapy **OR** C. The patient has an FDA labeled contraindication to ALL oral corticosteroids **OR** C. The patient has a diagnosis of hypereosinophilic syndrome (HES) AND ALL of the following: 1. The requested agent is Nucala **AND** 2. The patient has had improvements or stabilization with the requested agent from baseline (prior to therapy with the requested agent) as indicated by ONE of the following: A. Decrease in incidence of HES flares **OR** B. Escalation of therapy (due to HES-related worsening of clinical symptoms or increased blood eosinophil counts) has not been required **AND** 3. ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient is currently treated and is compliant with oral corticosteroid and/or other maintenance therapy (e.g., hydroxyurea, interferon-a, azathioprine, cyclosporine, methotrexate, tacrolimus) **OR** B. The patient has an intolerance or hypersensitivity to therapy with oral corticosteroids or other maintenance agents (e.g., hydroxyurea, interferon-a, azathioprine, cyclosporine, methotrexate, tacrolimus) **OR** C. The patient has an FDA labeled contraindication to ALL oral corticosteroids AND maintenance agents (e.g., hydroxyurea, interferon-a, azathioprine, cyclosporine, methotrexate, tacrolimus) **OR** D. The patient has a diagnosis of chronic rhinosinusitis with nasal polyposis (CRSwNP) AND ALL of the following: 1. The requested agent is Nucala **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The patient will continue standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids) in combination with the requested agent **OR** E. The patient has another FDA labeled indication for the requested agent and route of administration AND has had clinical benefit with the requested agent **OR** F. The patient has another indication that is supported in compendia for the requested agent and route of administration AND has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist, otolaryngologist, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. ONE of the following (Please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (copy of support required, e.g., clinical trials, phase III studies, guidelines) **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **Length of Approval:** Initial: up to 6 months for severe eosinophilic asthma; up to 12 months for EGPA, HES, CRSwNP, and all other FDA approved or compendia supported indications; For Fasenra, approve loading dose for new starts and the maintenance dose for the remainder of the 6 months; Renewal: up to 12 months

CONTRAINDICATION AGENTS

Contraindicated as Concomitant Therapy
Agents NOT to be used Concomitantly Abrilada (adalimumab-afzb) Actemra (tocilizumab) Adalimumab Adbry (tralokinumab-ldrm) Amjevita (adalimumab-atto) Arcalyst (rilonacept) Avsola (infliximab-axxq) Benlysta (belimumab) Bimzelx (bimekizumab-bkzx) Cibinqo (abrocitinib) Cimzia (certolizumab) Cinqair (reslizumab) Cosentyx (secukinumab) Cyltezo (adalimumab-adbm) Dupixent (dupilumab)

Contraindicated as Concomitant Therapy
Enbrel (etanercept)
Entyvio (vedolizumab)
Fasenra (benralizumab)
Hadlima (adalimumab-bwwd)
Hulio (adalimumab-fkjp)
Humira (adalimumab)
Hyrimoz (adalimumab-adaz)
Idacio (adalimumab-aacf)
Ilaris (canakinumab)
Ilumya (tildrakizumab-asmn)
Inflectra (infliximab-dyyb)
Infliximab
Kevzara (sarilumab)
Kineret (anakinra)
Leqselvi (deuruxolitinib)
Litfulo (ritlecitinib)
Nemluvio (nemolizumab-ilto)
Nucala (mepolizumab)
Olumiant (baricitinib)
Omvoh (mirikizumab-mrkz)
Opzelura (ruxolitinib)
Orencia (abatacept)
Otezla (apremilast)
Pyzchiva (ustekinumab-ttwe)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rinvoq (upadacitinib)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Saphnelo (anifrolumab-fnia)
Selarsdi (ustekinumab-aekn)
Siliq (brodalumab)
Simlandi (adalimumab-ryvk)
Simponi (golimumab)
Simponi ARIA (golimumab)
Skyrizi (risankizumab-rzaa)
Sotyktu (deucravacitinib)

Contraindicated as Concomitant Therapy
Spevigo (spesolimab-sbzo) subcutaneous injection
Stelara (ustekinumab)
Taltz (ixekizumab)
Tezspire (tezepelumab-ekko)
Tofidence (tocilizumab-bavi)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tyenne (tocilizumab-aazg)
Tysabri (natalizumab)
Velsipity (etrasimod)
Wezlana (ustekinumab-auub)
Xeljanz (tofacitinib)
Xeljanz XR (tofacitinib extended release)
Xolair (omalizumab)
Yuflyma (adalimumab-aaty)
Yusimry (adalimumab-aqvh)
Zeposia (ozanimod)
Zymfentra (infliximab-dyyb)

Interleukin-13 (IL-13) Antagonist

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Adbry® (tralokinumab-ldrm) Subcutaneous injection	Treatment of moderate-to-severe atopic dermatitis (AD) in patients aged 12 years and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Adbry can be used with or without topical corticosteroids.		1
Ebglyss™ (lebrikizumab-lbkz) Subcutaneous injection	Treatment of moderate-to-severe atopic dermatitis (AD) in patients aged 12 years and older who weigh at least 40 kg whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Ebglyss can be used with or without topical corticosteroids.		3

CLINICAL RATIONALE

Atopic Dermatitis	Atopic dermatitis (AD), also known as atopic eczema, is a chronic, pruritic inflammatory dermatosis affecting up to 25% of children and 1-5% of adults. AD follows a relapsing course and is associated with elevated serum immunoglobulin (IgE) levels and a personal or family history of type I allergies, allergic rhinitis, and/or asthma. Onset is most common between 3 and 6 months of age, with approximately 60% of patients developing the eruption in the first year of life and 90% by age 5. While the majority of affected individuals have resolution of disease by adulthood, 10 to 30% do not, and a smaller percentage first develop symptoms as adults. AD has a complex pathogenesis involving genetic, immunologic, and environmental factors, which lead to a dysfunctional skin barrier and dysregulation of the immune system. Clinical findings include erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and lichenification. These clinical findings vary by patient age and chronicity of lesions. Pruritus is a hallmark of the condition that is responsible for much of the disease burden borne by patients and their families. Typical patterns include

	facial, neck and extensor involvement in infants and children; flexure involvement in any age group, with sparing of groin and axillary regions.(2) Goals of treatment are to reduce symptoms (pruritus and dermatitis), prevent exacerbations, and minimize therapeutics risks.(6) Despite its relapsing and remitting nature, the majority of patients with AD can achieve clinical improvement and disease control with topical emollient/moisturizer use and conventional topical therapies (including corticosteroids and calcineurin inhibitors).(5,6) Moisturizers reduce signs, symptoms, and inflammation in AD, and can improve severity while also increasing time between flares. Moisturizers are considered generally safe and are strongly recommended to be used as part of a treatment regimen for AD, either as monotherapy or as concurrent use with pharmacologic treatments.(4) Topical therapies remain the mainstay of treatment due to their proven track record and generally favorable safety profile. They can be utilized individually or in combination with other topical, physical, and/or systemic treatments; as different classes of treatment have different mechanisms of action, combining therapies allows for the targeting of AD via multiple disease pathways. The American Academy of Dermatology (AAD) strongly recommends the following topical agents:(4) • Topical corticosteroids (TCS) • Calcineurin inhibitors (TCIs) (e.g., tacrolimus, pimecrolimus) • Topical PDE-4 inhibitors (e.g., crisaborole) [mild to moderate AD] • Topical JAK inhibitors (e.g., ruxolitinib) [mild to moderate AD] TCS are the most commonly utilized FDA-approved therapies in AD and are commonly used as first-line treatment for mild-to severe dermatitis in all skin regions. TCS target a variety of immune cells and suppress the release of proinflammatory cytokines. High to very high (super) potency TCS can be used to control flares and treat severe disease, while medium potency TCS are utilized for longer courses and as maintenance therapy. Lower potency TCS may be used, and it is important to consider the anatomical site (i.e., using lower potency agents on the face, neck, genitals, and body folds) and severity of the disease when choosing a steroid potency. Most studies of TCS in AD management involve twice daily application, but some studies (particularly for potent TCS) suggest once daily use may be sufficient. Traditionally, TCS were stopped once AD signs and symptoms of an AD flare were controlled. Maintenance in between AD flares with once to twice weekly use of TCS is another approach.(4)

	TCIs are a safe anti-inflammatory option for mild-to-severe AD, particularly when there is concern for adverse events secondary to corticosteroid use. Both tacrolimus and pimecrolimus have been shown to be effective in treating AD, but pimecrolimus may be more appropriate for patients who have milder disease or are sensitive to local reactions.(4) Prescribing information for pimecrolimus cream and tacrolimus ointment indicate evaluation after 6 weeks if symptoms of AD do not improve for adults and pediatrics.(8,9). When AD is more severe or refractory to topical treatment, advanced treatment with phototherapy or systemic medications can be considered. Phototherapy is conditionally recommended by the AAD as a treatment for AD based on low certainty evidence. The AAD strongly recommends the following systemic therapies:(5) • Monoclonal antibodies (biologics) (e.g., dupilumab, tralokinumab) • JAK inhibitors (e.g., upadacitinib, abrocitinib, baricitinib) In a change from the 2014 AAD AD guidelines, the use of systemic antimetabolites such as methotrexate, immunosuppressants such as systemic corticosteroids, mycophenolate mofetil, azathioprine, and cyclosporine are now conditionally recommended for AD only in a small number of select patients due to low or very low certainty of evidence and need for monitoring. The most favored first-line systemic is dupilumab.(5) There is no clear consensus on how to operationalize a definition of the FDA indication for treatment of patients with "moderate to severe" AD. The severity of AD can vary substantially over time and, from a patient's perspective, can include a complex combination of intensity of itch, location, body surface area (BSA) involvement, and degree of skin impairment. Given the variability of patient phenotype and lack of familiarity among clinicians with scoring systems used in clinical trials, it is advisable to create a broad clinically relevant definition inclusive of multiple specific measures of disease intensity for example:(11) One of the following: • Affected BSA greater than or equal to 10% • Investigator Global Assessment (IGA) greater than or equal to 3 • Eczema Area and Severity Index (EASI) greater than or equal to 16 OR

	One of the following: • Affected BSA greater than or equal to 10% • Involvement of body sites that are difficult to treat with prolonged topical corticosteroid therapy (e.g., hands, feet, face, neck, scalp, genitals/groin, skin folds) • Severe itch that has been unresponsive to topical therapies
Efficacy	The efficacy of Adbry was assessed in three randomized, double-blind, placebo-controlled trials [ECZTRA 1 (NCT03131648), ECZTRA 2 (NCT03160885), and ECZTRA 3 (NCT03363854)]. Efficacy was assessed in a total of 1934 subjects 18 years of age and older with moderate-to-severe atopic dermatitis (AD) not adequately controlled by topical medication(s). Disease severity was defined by an Investigator's Global Assessment (IGA) score greater than or equal to 3 in the overall assessment of AD lesions on a severity scale of 0 to 4, an Eczema Area and Severity Index (EASI) score greater than or equal to 16 on a scale of 0 to 72, and a minimum body surface area (BSA) involvement of greater than or equal to 10%. At baseline, 58% of subjects were male, 69% of subjects were white, 50% of subjects had a baseline IGA score of 3 (moderate AD), and 50% of subjects had a baseline IGA score of 4 (severe AD). The baseline mean EASI score was 32 and the baseline weekly averaged Worst Daily Pruritus Numeric Rating Scale (NRS) was 8 on a scale of 0-10.(1) In all three trials, subjects received subcutaneous injections of Adbry 600 mg or placebo on Day 0, followed by 300 mg every other week or placebo for 16 weeks. Responders were defined as achieving an IGA 0 or 1 ("clear" or "almost clear") or EASI-75 (improvement of at least 75% in EASI score from baseline) at week 16.(1) To evaluate maintenance of response in the monotherapy trials (ECZTRA 1 and ECZTRA 2), subjects responding to initial treatment with Adbry 300 mg every other week were re-randomized to Adbry 300 mg every other week, Adbry 300 mg every 4 weeks or placebo every other week for another 36 weeks following first dose administration. Subjects randomized to placebo in the initial treatment period who achieved a clinical response at week 16 continued to receive placebo every other week for another 36 weeks. Non-responders at week 16, and subjects who lost clinical response during the maintenance period were placed on open-label treatment with Adbry 300 mg every other week and optional use of TCS.(1) The ECZTRA 3 trial studied the use of Adbry in combination with either a topical corticosteroid or topical calcineurin inhibitor. Subjects received either Adbry 300 mg every other week with TCS or placebo with TCS and as needed topical

calcineurin inhibitors (TCI) until week 16. Subjects in the Adbry 300 mg with TCS group who achieved clinical response at week 16 were re-randomized to Adbry 300 mg every other week with TCS or Adbry every 4 weeks with TCS for another 16 weeks following first dose administration. Subjects in the placebo with TCS group who achieved clinical response at week 16 continued on placebo with TCS for another 16 weeks. Subjects who did not achieve clinical response at week 16 received Adbry 300 mg every other week for another 16 weeks. A mid-potency TCS (i.e., mometasone furoate 0.1% cream) was dispensed at each dosing visit. Subjects were instructed to apply a thin film of the dispensed TCS as needed once daily to active lesions from week 0 to week 32 and were to discontinue treatment with TCS when control was achieved. An additional, lower potency TCS or TCI could be used at the investigator's discretion on areas of the body where use of the supplied TCS was not advisable, such as areas of thin skin.(1)

All three trials assessed the primary endpoints of the proportion of subjects with an IGA 0 or 1 at week 16 and the proportion of subjects with EASI-75 at week 16. Secondary endpoints included the reduction of Worst Daily Pruritus NRS (weekly average) of at least 4 points on the 11-point itch NRS from baseline to week 16.(1)

	ECZTRA 1		**ECZTRA 2**		**ECZTRA 3**	
	ADBRY 300 mg every other week	**Placebo**	**ADBRY 300 mg every other week**	**Placebo**	**ADBRY 300 mg every other week + TCS**	**Placebo + TCS**
Number of subjects randomized and dosed (FAS)[a]	601	197	577	193	243	123
IGA 0 or 1[b,c] *Difference from Placebo (95% CI)*	16% *9% (4%,13%)*	7%	21% *12% (7%,17%)*	9%	38% *11% (1%,21%)*	27%

EASI-75[c] *Difference from Placebo (95% CI)*	25% *12%* *(6%,18%)*	13%	33% *22%* *(17%,28%)*	10%	56% *20%* *(9%,30%)*	37%
Number of subjects with baseline Worst Daily Pruritus NRS (weekly average) score greater than or equal to 4	594	194	563	192	240	123
Worst Daily Pruritus NRS (greater than or equal to 4 point reduction)[c] *Difference from Placebo (95% CI)*	20% *10%* *(4%,15%)*	10%	25% *16%* *(11%,21%)*	9%	46% *11%* *(1%,22%)*	35%

a. Full Analysis Set (FAS) includes all subjects randomized and dosed
b. Responders was defined as a subject with an IGA 0 or 1 (“clear” or “almost clear”)
c. Subjects who received rescue treatment or with missing data were considered as non-responders

	Note: Difference and 95% CI are based on the CMH test stratified by region and baseline IGA score Examination of age, gender, race, body weight, and previous treatment, including immunosuppressants, did not identify differences in response to Adbry 300 mg every other week among these subgroups.(1) In ECZTRA 1, 179 Adbry 300 mg every other week responders (IGA 0/1 or EASI-75) were re-randomized (and dosed) at week 16 to Adbry 300 mg every other week (68 subjects), Adbry 300 mg every 4 weeks (76 subjects) or placebo (35 subjects). Among these subjects, 39 subjects in Adbry 300 mg every other week arm, 36 subjects in Adbry 300 mg every 4 weeks arm and 19 subjects in placebo arm were IGA 0/1 responders at week 16. Maintenance of IGA 0/1 response at week 52 was as follows: 20 subjects (51%) in the every other week arm, 14 subjects (39%) in the every 4 weeks arm and 9 subjects (47%) in the placebo arm. Among the re-randomized subjects, 47 subjects in Adbry 300 mg every other week arm, 57 subjects in Adbry 300 mg every 4 weeks arm and 30 subjects in placebo arm were EASI-75 responders at week 16. Maintenance of EASI-75 response at week 52 was as follows: 28 subjects (60%) in the every other week arm, 28 subjects (49%) in the every 4 weeks arm and 10 subjects (33%) in the placebo arm.(1) In ECZTRA 2, 218 Adbry 300 mg every other week responders (IGA 0/1 or EASI-75) were re-randomized (and dosed) at week 16 to Adbry 300 mg every other week (90 subjects), Adbry 300 mg every 4 weeks (84 subjects) or placebo (44 subjects). Among these subjects, 53 subjects in Adbry 300 mg every other week arm, 44 subjects in Adbry 300 mg every 4 weeks arm and 26 subjects in placebo arm were IGA 0/1 responders at week 16. Maintenance of IGA 0/1 response at week 52 was as follows: 32 subjects (60%) in the every other week arm, 22 subjects (50%) in the every 4 weeks arm and 6 subjects (23%) in the placebo arm. Among the re-randomized subjects, 76 subjects in Adbry 300 mg every other week arm, 69 subjects in Adbry 300 mg every 4 weeks arm and 40 subjects in placebo arm were EASI-75 responders at week 16. Maintenance of EASI-75 response at week 52 was as follows: 43 subjects (57%) in the every other week arm, 38 subjects (55%) in the every 4 weeks arm and 8 subjects (20%) in the placebo arm.(1) In ECZTRA 3, 131 Adbry 300 mg every other week + TCS responders (IGA 0/1 or EASI-75) were re-randomized (and dosed) at week 16 to Adbry 300 mg every other week + TCS (65 subjects) or Adbry 300 mg every 4 weeks + TCS (66 subjects). Among these subjects, 45 subjects in Adbry 300 mg every other week + TCS arm and 46 subjects in Adbry 300 mg every 4 weeks + TCS arm were IGA

	0/1 responders at week 16. Maintenance of IGA 0/1 response at week 32 was as follows: 40 subjects (89%) in the every other week arm and 35 subjects (76%) every 4 weeks arm. Among the re-randomized subjects, 65 subjects in Adbry 300 mg every other week arm and 62 subjects in Adbry 300 mg every 4 weeks arm were EASI-75 responders at week 16. Maintenance of EASI-75 response at week 32 was as follows: 60 subjects (92%) in the every other week arm and 56 subjects (90%) in the every 4 weeks arm.(1)
Safety	Tralokinumab is contraindicated in patients who have known hypersensitivity to tralokinumab-ldrm or any excipients in Adbry.(1) Lebrikizumab-lbkz is contraindicated in patients with prior serious hypersensitivity to lebrikizumab-lbkz or any excipients of the product.(3)

REFERENCES

Number	Reference
1	Adbry prescribing information. LEO Pharma Inc. December 2023.
2	Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of Care for the Management of Atopic Dermatitis: Section 1. Diagnosis and Assessment of Atopic Dermatitis. *J Am Acad Dermatol*. 2014 Feb;70(2):338-51.
3	Ebglyss prescribing information. Eli Lilly and Company. September 2024.
4	Sidbury R, Alikhan A, Bercovitch L, et al. Guidelines of care for the management of atopic dermatitis in adults with topical therapies. *J Am Acad Dermatol*. 2023;89(1):e1-e20.
5	Davis DM, Drucker AM, Alikhan A, et al. Guidelines of care for the management of atopic dermatitis in adults with phototherapy and systemic therapies. *Journal of the American Academy of Dermatology*. 2024;90(2):e43-e56. doi:10.1016/j.jaad.2023.08.102
6	Sidbury R, Tom WL, Bergman JN, Cooper KD, Silverman RA, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: Section 4. Prevention of disease flares and use of adjunctive therapies and approaches. *J Am Acad Dermatol*. 2014 Dec;71(6):1218-33.
7	Reference no longer used.
8	Pimecrolimus cream prescribing information. Oceanside Pharmaceuticals. September 2020.

Number	Reference
9	Tacrolimus ointment prescribing information. Glenmark Pharmaceuticals Inc., USA. August 2023.
10	Reference no longer used.
11	Institute For Clinical and Economic Review (ICER). JAK Inhibitors and Monoclonal Antibodies for the Treatment of Atopic Dermatitis: Effectiveness and Value. Final Evidence Report. August 2021. Updated February 2023.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** All target agents are eligible for continuation of therapy 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. ONE of the following: A. The patient has a diagnosis of moderate-to-severe atopic dermatitis (AD) AND ALL of the following: 1. ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient has at least 10% body surface area involvement **OR** B. The patient has involvement of body sites that are difficult to treat with prolonged topical corticosteroid therapy (e.g., hands, feet, face, neck, scalp, genitals/groin, skin folds) **OR** C. The patient has an Eczema Area and Severity Index (EASI) score greater than or equal to 16 **OR** D. The patient has an Investigator Global Assessment (IGA) score greater than or equal to 3 **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to at least a medium-potency topical corticosteroid used in the treatment of AD after at least a 4-week duration of therapy **OR** B. The patient has an intolerance or hypersensitivity to at least a medium-potency topical corticosteroid used in the treatment of AD **OR** C. The patient has an FDA labeled contraindication to ALL medium-, high-, and super-potency topical corticosteroids used in the treatment of AD **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response to a topical calcineurin inhibitor (e.g., Elidel/pimecrolimus, Protopic/tacrolimus) used in the treatment of AD after at least a 6-week duration of therapy **OR** B. The patient has an intolerance or hypersensitivity to a topical calcineurin inhibitor used in the treatment of AD **OR** C. The patient has an FDA labeled contraindication to ALL topical calcineurin inhibitors used in the treatment of AD **AND** 4. The prescriber has documented the patient's baseline (prior to therapy with the requested agent) pruritus and other symptom severity (e.g., erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and/or lichenification) **OR** B. The patient has another FDA labeled indication for the requested agent and route of administration **AND**

Module	Clinical Criteria for Approval
	2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **OR** C. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has a diagnosis of moderate-to-severe atopic dermatitis (AD), then BOTH of the following: A. The patient is currently treated with topical emollients and practicing good skin care **AND** B. The patient will continue the use of topical emollients and good skin care practices in combination with the requested agent **AND** 3. ONE of the following: A. The patient is initiating therapy with the requested agent **OR** B. The patient has been treated with the requested agent for less than 16 consecutive weeks **OR** C. The patient has been treated with the requested agent for at least 16 consecutive weeks AND ONE of the following: 1. The patient weighs less than 100 kg and ONE of the following: A. The patient has achieved clear or almost clear skin AND the patient's dose will be reduced to 300 mg every 4 weeks **OR** B. The patient has NOT achieved clear or almost clear skin **OR** C. There is support for therapy using 300 mg every 2 weeks **OR** 2. The patient weighs greater than or equal to 100 kg **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., dermatologist, allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. ONE of the following (please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (submitted copy of clinical trials, phase III studies, guidelines required) **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent

Module	Clinical Criteria for Approval
	Compendia Allowed: AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval**: 6 months Note: Initial loading dose is allowed for Adbry and may require a Quantity Limit review. The loading dose plus maintenance dose may be approved for 1 month, followed by maintenance dosing for the remainder of the length of approval. NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. ONE of the following: A. The patient has a diagnosis of moderate-to-severe atopic dermatitis AND BOTH of the following: 1. The patient has had a reduction or stabilization from baseline (prior to therapy with the requested agent) of ONE of the following: A. Affected body surface area **OR** B. Flares **OR** C. Pruritus, erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and/or lichenification **OR** D. A decrease in the Eczema Area and Severity Index (EASI) score **OR** E. A decrease in the Investigator Global Assessment (IGA) score **AND** 2. The patient will continue standard maintenance therapies (e.g., topical emollients, good skin care practices) in combination with the requested agent **OR** B. The patient has a diagnosis other than moderate-to-severe atopic dermatitis AND has had clinical benefit with the requested agent **AND** 3. ONE of the following: A. The patient is initiating therapy with the requested agent **OR** B. The patient has been treated with the requested agent for less than 16 consecutive weeks **OR** C. The patient has been treated with the requested agent for at least 16 consecutive weeks AND ONE of the following: 1. The patient weighs less than 100 kg and ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient has achieved clear or almost clear skin AND the patient's dose will be reduced to 300 mg every 4 weeks **OR** B. The patient has NOT achieved clear or almost clear skin **OR** C. There is support for therapy using 300 mg every 2 weeks **OR** 2. The patient weighs greater than or equal to 100 kg **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., dermatologist, allergist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. ONE of the following (please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (submitted copy of clinical trials, phase III studies, guidelines required) **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed**: AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval**: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months Note: If approving initial loading dose for Adbry, approve quantity for loading dose plus maintenance for 1 month followed by maintenance dose for the remainder of the length of approval. Maintenance dosing begins 2 weeks after patient receives the loading dose.

CONTRAINDICATION AGENTS

Contraindicated as Concomitant Therapy
Agents NOT to be used Concomitantly Abrilada (adalimumab-afzb) Actemra (tocilizumab) Adalimumab Adbry (tralokinumab-ldrm) Amjevita (adalimumab-atto) Arcalyst (rilonacept) Avsola (infliximab-axxq) Benlysta (belimumab) Bimzelx (bimekizumab-bkzx) Cibinqo (abrocitinib) Cimzia (certolizumab) Cinqair (reslizumab) Cosentyx (secukinumab) Cyltezo (adalimumab-adbm) Dupixent (dupilumab) Egblyss (lebrikizumab-lbkz) Enbrel (etanercept) Entyvio (vedolizumab) Fasenra (benralizumab) Hadlima (adalimumab-bwwd) Hulio (adalimumab-fkjp)

Contraindicated as Concomitant Therapy
Humira (adalimumab)
Hyrimoz (adalimumab-adaz)
Idacio (adalimumab-aacf)
Ilaris (canakinumab)
Ilumya (tildrakizumab-asmn)
Inflectra (infliximab-dyyb)
Infliximab
Kevzara (sarilumab)
Kineret (anakinra)
Leqselvi (deuruxolitinib)
Litfulo (ritlecitinib)
Nemluvio (nemolizumab-ilto)
Nucala (mepolizumab)
Olumiant (baricitinib)
Omvoh (mirikizumab-mrkz)
Opzelura (ruxolitinib)
Orencia (abatacept)
Otezla (apremilast)
Pyzchiva (ustekinumab-ttwe)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rinvoq (upadacitinib)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Saphnelo (anifrolumab-fnia)
Selarsdi (ustekinumab-aekn)
Siliq (brodalumab)
Simlandi (adalimumab-ryvk)
Simponi (golimumab)
Simponi ARIA (golimumab)
Skyrizi (risankizumab-rzaa)
Sotyktu (deucravacitinib)
Spevigo (spesolimab-sbzo) subcutaneous injection
Stelara (ustekinumab)
Taltz (ixekizumab)
Tezspire (tezepelumab-ekko)
Tofidence (tocilizumab-bavi)

Contraindicated as Concomitant Therapy
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tyenne (tocilizumab-aazg)
Tysabri (natalizumab)
Velsipity (etrasimod)
Wezlana (ustekinumab-auub)
Xeljanz (tofacitinib)
Xeljanz XR (tofacitinib extended release)
Xolair (omalizumab)
Yuflyma (adalimumab-aaty)
Yusimry (adalimumab-aqvh)
Zeposia (ozanimod)
Zymfentra (infliximab-dyyb)

Isturisa

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Isturisa® (osilodrostat) Tablet	Treatment of adult patients with Cushing's disease for whom pituitary surgery is not an option or has not been curative		1

CLINICAL RATIONALE

Cushing's Syndrome	Cushing's syndrome is pathologic hypercortisolism caused by excessive adrenocorticotropic hormone (ACTH) production, or autonomous adrenal production of cortisol. This potentially lethal disorder is associated with significant comorbidities including hypertension, diabetes, coagulopathy, cardiovascular disease, infections, and fractures. As a result, even after cure of hypercortisolism, mortality rates may be increased. Because of this it is important to make the diagnosis as early in the disease course as possible, to prevent additional morbidity and residual disease. Signs and symptoms of Cushing's syndrome are broad and often common among the general population, such as obesity, depression, diabetes, hypertension, or menstrual irregularities. Some features are more discriminatory and unique to Cushing's syndrome, such as reddish-purple striae, plethora, proximal muscle weakness, bruising with no obvious trauma, and unexplained osteoporosis.(2) Cushing's disease is a form of Cushing syndrome. Cushing's disease occurs when a benign tumor in the pituitary gland causes the pituitary gland to produce too much ACTH. Cushing's disease can also occur with diffuse growth of the pituitary gland (pituitary hyperplasia). Pituitary hyperplasia can lead to the release of too much ACTH, which then leads to over-production of cortisol by the adrenal glands.(5) Diagnosis of Cushing's syndrome is often delayed for years, partly because of lack of awareness of the insidious progressive disease process and testing complexity. Screening and diagnostic tests for Cushing's syndrome assess

	cortisol secretory status: abnormal circadian rhythm with late-night salivary cortisol (LNSC), impaired glucocorticoid feedback with overnight 1 mg dexamethasone suppression test (DST) or low-dose 2-day dexamethasone test (LDDT), and increased bioavailable cortisol with 24-hour urinary free cortisol (UFC). The sensitivity of all tests is higher than 90%; the highest sensitivity rates are obtained with DST and LNSC and the lowest with UFC. Specificity is somewhat lower than sensitivity, with LNSC being the most specific and DST and UFC the least specific. LNSC should not be used in patients with disruption of normal day and night cycle, such as night-shift workers.(6)
	
	Clinical considerations and recommendations for Cushing's syndrome diagnosis and monitoring of Cushing's disease recurrence:(6)
	
	• If Cushing's syndrome is suspected:
	  ○ Start with UFC, LNSC or both; DST could be an option if LNSC is not feasible
	  ○ Multiple LNSC might be easier for patient collection
	
	• If confirming Cushing's syndrome:
	  ○ Can use any test
	  ○ UFC (average 2 or 3 collections) above the upper limit of normal – cutoff is assay-specific reference range
	  ○ LNSC (2 or more tests) above the upper limit of normal – cutoff is assay-specific reference range
	  ○ DST useful in night-shift workers, not in women on estrogen containing contraceptives – above cutoff of 1.8 mcg/dL
	  ○ Measuring dexamethasone concentration, with cortisol concentration the morning after 1 mg dexamethasone ingestion improves interpretability
	
	• If Cushing's syndrome due to adrenal tumor is suspected
	  ○ Start with DST as LNSC has lower specificity in these patients
	
	• Monitoring for recurrence:
	  ○ Consider which tests were abnormal at initial diagnoses
	  ○ LNSC most sensitive and should be done annually – above cutoff of 0.27 mcg/dL

	○ DST and UFC usually become abnormal after LNSC (with UFC usually the last to become abnormal) ○ UFC 1.6 X upper limit of normal ○ DST above 1.8 mcg/dL Transsphenoidal surgery is recommended as first-line therapy for patients with Cushing's disease. Remission, typically defined as postoperative serum cortisol concentrations lower than 2 mcg/dL, is seen in approximately 80% of patients with microadenomas and 60% with macroadenomas if the procedure is performed by an experienced surgeon. Patients in remission require glucocorticoid replacement until HPA axis recovery. As remission could be delayed, monitoring until postoperative cortisol nadir can usually identify such cases.(6) Recurrence after successful pituitary surgery is characterized as the reappearance of clinical and biochemical features of hypercortisolism after initial remission. Published recurrence rates vary between 5% and 35% with half of recurrences appearing within the first 5 years after surgery and half after up to 10 years or more. Compared with use in the initial diagnosis of Cushing's syndrome, LNSC, DST, UFC, and desmopressin tests have a lower sensitivity for recurrence, but specificity is high. Repeat transsphenoidal surgery can be considered in patients with biochemical evidence of recurrent Cushing's disease with visible tumor on MRI.(6) Medications used for the treatment of Cushing's disease target adrenal steroidogenesis, somatostatin, and dopamine receptors in the pituitary gland, and glucocorticoid receptors.(6) • Adrenal steroidogenesis inhibitor agents ○ Ketoconazole: European Medicines Agency (EMA) approved, off-label use in USA ○ Osilodrostat: FDA approved ○ Metyrapone: EMA approved, off-label use in USA ○ Mitotane: EMA approved, off label use in USA ○ Etomidate: Off-label use only ○ Levoketoconazole: EMA indicated, FDA approved • Somatostatin receptor ligands ○ Pasireotide: Widely approved

	○ Pasireotide long-acting: Widely approved • Dopamine receptor agonists ○ Cabergoline: Off-label use only • Glucocorticoid receptor blocker ○ Mifepristone: FDA-approved for hyperglycemia associated with Cushing's syndrome. There are several factors helpful in selection of medical therapy:(6) • If there is a need for rapid normalization of cortisol adrenal steroidogenesis inhibitors are recommended. Osilodrostat and metyrapone have the fastest action and etomidate can be used in very severe cases (high quality, strong recommendation) • In mild disease, if residual tumor is present and there is a potential for tumor shrinkage, consider pasireotide or cabergoline (moderate quality, strong recommendation) • If there is a history of bipolar or impulse control disorder, consider avoiding cabergoline (moderate quality, strong recommendation) • If an expert pituitary endocrinologist is not available to monitor treatment response, use mifepristone cautiously (low quality, discretionary recommendation) • In pregnant women or those desiring pregnancy, consider cabergoline or metyrapone (low quality, strong recommendation), although no Cushing's disease medications are approved for use in pregnancy • Drug intolerance or side-effects, as well as concomitant comorbidities such as type 2 diabetes and hypertension should further guide type of medication used (moderate quality, strong recommendation) • Consider cost and estimated therapy duration, especially if definitive treatment (i.e., pituitary or adrenal surgery) is planned or while awaiting effects of radiotherapy (low quality, discretionary recommendation) Adrenal steroidogenesis inhibitors are usually used first given their reliable effectiveness. For patient with mild disease and no visible tumor on MRI, ketoconazole, osilodrostat, or metyrapone are typically preferred. For patients with mild-to-moderate disease and some residual tumor, there might be a preference for cabergoline or pasireotide because of the potential for tumor shrinkage. For patients with severe disease, rapid normalization of cortisol is the

	most important goal. With osilodrostat and metyrapone, response will typically be seen within hours, and with ketoconazole within a few days.(6) Change in treatment should be considered if cortisol levels are persistently elevated after 2-3 months on maximum tolerated doses. If cortisol does not normalize but is reduced or there is some clinical improvement, combination therapy can be considered (low quality, discretionary recommendation). Many experts consider combining ketoconazole with metyrapone or potentially ketoconazole with osilodrostat to maximize adrenal blockade when monotherapy is not effective, or to allow lower doses of both drugs (low quality, discretionary recommendation). Ketoconazole plus cabergoline or pasireotide, and pasireotide plus cabergoline could be rational combinations if there is visible tumor present (low quality, discretionary recommendation). Other combinations that can be used include triplets of cabergoline, pasireotide, plus ketoconazole, and ketoconazole, metyrapone, plus mitotane (low quality, discretionary recommendation).(6) Radiotherapy is primarily used as adjuvant therapy for patients with persistent or recurrent disease after transsphenoidal surgery or for aggressive tumor growth.(6)
Efficacy	Isturisa is a cortisol synthesis inhibitor. It inhibits 11beta-hydroxylase (CYP11B1), the enzyme responsible for the final step of cortisol biosynthesis in the adrenal gland. The safety and efficacy of Isturisa were established in a 48-week, multicenter study that consisted of four study periods.(1) 1. Period 1: Week 1 to 12, open label, dose titration period. 137 patients received a starting dose of 2 mg twice daily that could be titrated up to a max of 30 mg twice daily at no greater than 2-week intervals. Individual dose adjustments were based on mean urinary free cortisol (mUFC). 2. Period 2: Week 13 to 24, open label, maintenance treatment period. 130 of the patients from Period 1 were entered into Period 2. The daily dose, for patients that achieved a mUFC within the normal range in Period 1, was maintained during Period 2. Patients who did not require further dose increase, tolerated the drug, and had a mUFC less than or equal to the upper limit of normal (ULN) at week 24 (end of Period 2) were to be considered responders and eligible to enter the Randomization Withdrawal phase (Period 3). Patients whose mUFC became elevated during Period 2 could have their dose increased further, if tolerated, up to 30 mg twice daily. These patients were considered non-responders and did not enter Period 3 but continued open-label treatment together

	with the patients who did not achieve normal mUFC at week 12 and were followed for long-term safety and response to treatment. 3. Period 3: Week 26 to 34, double-blind, placebo-controlled, randomized withdrawal treatment period (provided data for primary endpoint). At week 26, 71 patients were considered responders and were randomized 1:1 to continue receiving Isturisa (n=36) or to switch to placebo (n=35) for 8 weeks. Patients were stratified at randomization according to dose received at week 24 (less than or equal to 5 mg twice daily vs 5 mg twice daily) and history of pituitary irradiation (yes/no). Patients were to remain on their assigned treatment and dose throughout Period 3 if mUFC were within the normal range. Blinded dose reduction or temporary discontinuation for safety or tolerability reasons were permitted. Dose increases were not permitted during Period 3. Patients with mUFC increase greater than 1.5 x ULN or who required a dose increase were considered non-responders and discontinued from Period 3 but allowed to receive open-label treatment during Period 4. 4. Period 4: Open label treatment period from weeks 26 or 34 to 48. This period included patients who were not eligible for randomization (n=47) at week 26, patients who were considered non-responders during Period 3 (n=29), and patients who were considered responders during Period 3 (n=41). Open label treatment with Isturisa continued in these patients until week 48 when patients who maintained clinical benefit on Isturisa, as judged by the Investigator, had an option to enter an extension period. The trial enrolled patients with confirmed persistent or recurrent Cushing's disease despite pituitary surgery or de novo patients for whom surgery was not indicated or who had refused surgery. Inclusion criteria included the following(4): • Patient's age 18-75 years • Confirmed Cushing's disease that is persistent or recurrent as evidenced by all of the following criteria being met (i.e., a, b and c): 1. Mean Urine Free Cortisol (mUFC) greater than 1.3 x upper limit of normal [ULN (Mean of three 24-hour urine samples collected preferably on 3 consecutive days, during screening after washout of prior medical therapy for Cushing's disease [if applicable], confirmed by the central laboratory and available before Day 1)], with greater than or equal to 2 of the individual UFC values being greater than 1.3 x ULN 2. Morning plasma ACTH above Lower Limit of Normal

3. Confirmation (based on medical history) of pituitary source of excess ACTH as defined by any one or more of the following three criteria:
   a. Histopathologic confirmation of an ACTH-staining adenoma in patients who have had prior pituitary surgery OR
   b. MRI confirmation of pituitary adenoma greater than 6 mm OR
   c. Bilateral inferior petrosal sinus sampling (BIPSS) with either CRH or DDAVP stimulation for patients with a tumor less than or equal to 6mm. The criteria for a confirmatory BIPSS test are any of the following: Pre-dose central to peripheral ACTH gradient greater than 2; Post-dose central to peripheral ACTH gradient greater than 3 after either CRH or DDAVP stimulation

The primary endpoint of the study was to compare the percentage of complete responders at the end of the 8-week randomized withdrawal period (Period 3) between patients randomized to continue Isturisa versus the patients switched to placebo. A complete responder for the primary endpoint was defined as a patient who had mUFC less than or equal to ULN based on central laboratory result at the end of Period 3 (week 34), and who neither discontinued randomized treatment or the study nor had any dose increase above their week 26 dose. The key secondary endpoint was to assess the complete responder rate at the end of Period 2 (week 24). A complete responder for the key secondary endpoint was defined as a patient with mUFC less than or equal to ULN at week 24 who did not require an increase in dose above the level established at the end of Period 1 (week 12). Patients who were missing mUFC assessment at week 24 were counted as non-responders for the key secondary endpoint.(1)

Primary Endpoint	Isturisa (n=36) n(%)	Placebo (n=34) n(%)	Complete Responder Rate Difference in %
Complete responder rate at the end of the 8-week randomized withdrawal period (Week 34) (95% CI)	31 (86) (71,95)	10 (29) (15,47)	57 (38,76) p-value<0.001

	At the end of Period 3, the percentage of complete responders for the primary endpoint was 86% and 29% in the Isturisa and placebo groups, respectively. The difference in percentage of complete responders between Isturisa and placebo groups was 57%, with 95% two-sided CI of (38, 76). The 95% CI were not presented by individual strata due to the small sample sizes of some of these strata. The key secondary endpoint, complete responder rate after 24 weeks of treatment with Isturisa was achieved by 72/137 patients (52.6%) with 95% two-sided CI of (43.9, 61.1). The lower bound of this 95% CI exceeded 30%, the prespecified threshold for statistical significance and minimum threshold for clinical benefit. At week 48, 91/137 patients (66%) had normal mUFC levels. Variable decreases from baseline for blood pressure, glucose parameters, weight and weight circumference were observed at week 48. However, because the study allowed initiation of anti-hypertensive and anti-diabetic medications and dose increases in patients already receiving such medications and the absence of a control group, the individual contribution of Isturisa or of anti-hypertensive and anti-diabetic medication adjustments cannot be clearly established.(1)
Safety	Isturisa (osilodrostat) has no known FDA labeled contraindications for use.(1)

REFERENCES

Number	Reference
1	Isturisa prescribing information. Recordati Rare Disease, Inc. November 2023.
2	Nieman, Lynnette K. Recent Updates on the Diagnosis and Management of Cushing's Syndrome. Endocrinology and Metabolism. 2018 Jun;33:139-146. doi: 10.3803/EnM.2018.33.2.139.
3	Reference no longer used
4	Novartis Pharmaceuticals. A Phase III, Multi-center, Randomized, Double-blind, 48 Week Study With an Initial 12 Week Placebo-controlled Period to Evaluate the Safety and Efficacy of Osilodrostat in Patients With Cushing's Disease. Identification No. NCT02697734. https://clinicaltrials.gov/ct2/show/NCT02697734.
5	Endocrine Society. Cushing's disease. Accessed at: https://www.hormone.org/diseases-and-conditions/cushings-disease

Number	Reference
6	Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol December 2021;9 847-75.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** All target agents are eligible for continuation of therapy 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. The patient has a diagnosis of Cushing's disease AND ALL of the following: 1. ONE of the following: A. The patient had an inadequate response to pituitary surgery **OR** B. The patient is NOT a candidate for pituitary surgery **AND** 2. The patient's disease is persistent or recurrent as evidenced by ONE of the following: A. The patient has a mean of three 24-hour urine free cortisol (UFC) greater than 1.3 times the upper limit of normal **OR** B. Morning plasma adrenocorticotropic hormone (ACTH) above the lower limit of normal **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response, to at least ONE of the following conventional agents:

Module	Clinical Criteria for Approval
	1. Mifepristone 2. Signifor/Signifor LAR (pasireotide) 3. Recorlev (levoketoconazole) 4. Cabergoline 5. Metyrapone 6. Lysodren (mitotane) **OR** B. The patient has an intolerance or hypersensitivity to mifepristone, pasireotide, or levoketoconazole **OR** C. The patient has an FDA labeled contraindication to mifepristone, pasireotide, and levoketoconazole **AND** 4. ONE of the following: A. The patient has tried and had an inadequate response to ketoconazole tablets **OR** B. The patient has an intolerance or hypersensitivity to ketoconazole tablets (medical records required) **OR** C. The patient has an FDA labeled contraindication to ketoconazole tablets (medical records required) **AND** 5. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient will NOT be using the requested agent in combination with glucocorticoid replacement therapy **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: Patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND**

Module	Clinical Criteria for Approval
	3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with glucocorticoid replacement therapy **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months

Joenja (leniolisib)

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Joenja® (leniolisib) Tablets	Treatment of activated phosphoinositide 3-kinase delta (PI3K-delta) syndrome (APDS) in adult and pediatric patients 12 years of age and older		1

CLINICAL RATIONALE

Primary Immunodeficiencies	Primary immunodeficiencies (PIDs) are a group of inborn error disorders that cause immune dysfunction and manifest with increased susceptibility to infections. Many PIDs are monogenic diseases. To date, mutations in more than 300 genes have been shown to cause various PIDs. Activated phosphoinositide 3-kinase delta syndrome (APDS) is a PID that results from pathogenic variant mutations in either the PIK3CD gene (APDS1) or the PIK3R1 gene (APDS2). Both genes are important for the growth, survival and function of lymphocytes.(2,3,4,6) Definitive diagnosis is made through genetic testing, which Pharming Healthcare Inc offers at no-charge (including counseling) for individuals who are suspected to carry a pathogenic variant in PIK3CD or PIK3R1. Patients may present in childhood or later in life with severe, persistent and recurrent bacterial and viral infections, bronchiectasis, lymphadenopathy, delayed development (e.g., speech, growth), and/or hepato- or splenomegaly. Additionally, patients may present with signs of autoimmune or inflammatory conditions, such as anemia, cytopenias, nodular lymphoid hyperplasia, enteropathy, glomerulonephritis, organ dysfunction.(5,7,8) Before Joenja, the only treatments for APDS were focused on managing symptoms, with a combination of long-term immunoglobulin replacement therapy to help support the immune system, immunosuppressive medications to help with symptoms due to autoimmunity and inflammation, and daily antibiotics to help prevent infections before they happen.(2,3,5) Joenja is targeted at the actual problem (gain-of-function mutation in the PIK3CD disrupts normal

	development of immune cells; Joenja selectively inhibits a subunit of PI3K, which specifically reverses the pathophysiology of APDS in a molecularly targeted manner.(6,9)
Efficacy	Joenja (leniolisib) is an oral selective PI3K-delta inhibitor. In cell-based assays, Joenja inhibited the signaling pathways that lead to the dysregulation of B and T cells.(1) The efficacy of Joenja was evaluated in the placebo-controlled portion of Study 2201 (NCT02435173), a 12-week blinded, randomized, placebo-controlled study in adult and pediatric patients 12 years of age and older with confirmed APDS-associated genetic PI3K-delta mutation with a documented variant in either PIK3CD or PIK3R1. Patients had nodal and/or extranodal lymphoproliferation, as measured by index nodal lesion selected by the Cheson methodology on CT or MRI and clinical findings and manifestations compatible with APDS (e.g., history of repeated oto-sino-pulmonary infections, organ dysfunction). Thirty-one patients were randomized 2:1 to receive either Joenja 70 mg (N=21) or placebo (N=10) twice a day for 12 weeks. The co-primary efficacy endpoints were improvement in lymphoproliferation as measured by a change from baseline in lymphadenopathy measured by the log10-transformed sum of product diameters and the normalization of immunophenotype as measured by the percentage of naïve B cells out of total B cells. Findings showed that leniolisib met the coprimary endpoints demonstrating a statistically significant reduction in index lymph node size (p=.006) and normalization of immunodeficiency (as evidenced by an increased proportion of naïve B cells from baseline; p=.002), compared with placebo.(1,6)
Safety	Joenja (leniolisib) has no FDA labeled contraindications for use.(1)

REFERENCES

Number	Reference
1	Joenja prescribing information. Pharming Technologies BV. March 2023.
2	Singh A, Joshi V, Jindal AK, et al. An Updated Review on Activated PI3 Kinase Delta Syndrome (APDS). Genes Dis. 2020 Mar;7(1):67-74.
3	Michalovich D, Nejentsev S. Activated PI3 Kinase Delta Syndrome: From Genetics to Therapy. Front Immunol. 2018 Feb;9:369.

Number	Reference
4	Ewertowska M, Grzesk E, Urbanczyk A, et al. Activated Phosphoinositide 3-Kinase Delta Syndrome 1 and 2 (APDS 1 and APDS 2): Similarities and Differences Based on Clinical Presentation in Two Boys. Allergy Asthma Clin Immunol. 2020 Apr;16:22.
5	Oh J. Activated Phosphoinositide 3-Kinase Delta Syndrome (APDS). National Organization of Rare Diseases (NORD). Last updated: April 2023. Available at: https://rarediseases.org/rare-diseases/activated-phosphoinositide-3-kinase-delta-syndrome-apds/
6	Rao VK, Webster S, Sediva A, et al. A Randomized, Placebo-Controlled Phase 3 Trial of the PI3K-delta Inhibitor Leniolisib for Activated PI3K-delta Syndrome. Blood. 2023 Mar;141(9):971-983.
7	International Patient Organization for Primary Immunodeficiencies (IPOPI). Primary Immunodeficiencies: APDS - Activated PI3K Delta Syndrome. 2020. Available at: http://www.immunodeficiencyuk.org/static/media/up/IPOPIADPS.pdf
8	All About APDS - Healthcare Professionals. Available at: https://allaboutapds-hcp.com/. Accessed December 2023.
9	Rao VK, Webster S, Dalm VASH, et al. Effective "Activated PI3K-Delta Syndrome"-Targeted Therapy with the PI3K-Delta Inhibitor Leniolisib. Blood. 2017 Nov;130(21):2307-2316.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** Joenja

Module	Clinical Criteria for Approval
	1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. ALL of the following: 1. The patient has a diagnosis of activated phosphoinositide 3-kinase (PI3K) delta syndrome (APDS) **AND** 2. The patient has a variant in either PIK3CD or PIK3R1 **AND** 3. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The patient's weight is 45 kg or greater **AND** 3. The prescriber has assessed the patient's baseline (prior to therapy with the requested agent) status of clinical manifestations of APDS (e.g., recurrent sinopulmonary infections, recurrent herpesvirus infections, lymphadenopathy, hepatomegaly, splenomegaly, nodular lymphoid hyperplasia, autoimmunity, cytopenias, enteropathy, bronchiectasis, organ dysfunction) **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., geneticist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation] **AND** 2. The patient has had improvements or stabilization with the requested agent (e.g., sinopulmonary infections, herpesvirus infections, lymphadenopathy, hepatomegaly,

Module	Clinical Criteria for Approval
	splenomegaly, nodular lymphoid hyperplasia, autoimmunity, cytopenias, enteropathy, bronchiectasis, organ dysfunction) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., geneticist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support of therapy with a higher dose for the requested indication **Length of Approval:** Initial up to 3 months; Renewal up to 12 months

Jynarque

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Jynarque® (tolvaptan) Tablet	To slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD)		1

CLINICAL RATIONALE

ADPKD	Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cause of kidney disease that affects approximately 12.5 million people worldwide. Mutations in two genes have been identified to be the major cause of ADPKD. Mutations in the PKD1 gene (located on chromosome 16) account for 85% of cases, while mutations in the PKD2 gene (located on chromosome 4) account for 15% of cases. ADPKD is a systemic disorder characterized by continuous cyst development and growth within the kidneys and other organs, leading to numerous clinical manifestations. End stage renal disease ensues, typically after the fourth decade of life.(2-4)
	
	Widely accepted practice guidelines do not currently exist for ADPKD diagnosis, evaluation, prevention, and treatment. Multiple guidelines offer similar diagnostic criteria.
	
	• American Academy of Family Physicians(3)
	  ○ Ultrasonography is the preferred screening method due to increased availability, lower cost, and lack of radiation exposure, although magnetic resonance imaging (MRI) and computed tomography (CT) are slightly more sensitive
	  ○ Ultrasonography (at-risk ADPKD type 1)
	  ▪ Less than 30 years of age: greater than or equal to 2 cysts in one kidney or both kidneys
	  ▪ 30-59 years of age: greater than or equal to 2 cysts in each kidney

	▪ 60 years of age and older: greater than or equal to 4 cysts in each kidney ○ Ultrasonography (at-risk and unknown genotype) ▪ 15-39 years of age: greater than or equal to 3 cysts in one or both kidneys ▪ 40-59 years of age: greater than or equal to 2 cysts in each kidney ▪ 60 years of age and older: greater than or equal to 4 cysts in each kidney ○ MRI (at-risk) ▪ Less than 30 years of age: greater than or equal to 5 cysts in each kidney ▪ 30-44 years of age: greater than or equal to 6 cysts in each kidney ▪ 45-59 years of age (females): greater than 6 cysts in each kidney ▪ 45-59 years of age (males): greater than 9 cysts in each kidney ○ Genetic testing is not standard practice, but is useful in certain scenarios, such as unknown family history with findings of enlarged kidneys with renal cysts, or at-risk patient wishing to be a kidney donor • Autosomal Dominant Polycystic Kidney Disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference(2) ○ Asymptomatic patients - screening with renal ultrasonography is usually used because it is inexpensive and widely available ▪ At-risk patients (defined as first-degree relatives of individuals diagnosed or suspected to have ADPKD) • Children: screening is not currently recommended • Ultrasonography for diagnosis of ADPKD ○ 15-39 years of age: a total of greater than or equal to 3 renal cysts (unilateral or bilateral) ○ 40-59 years of age: greater than or equal to 2 renal cysts in each kidney • Ultrasonography can also be used for exclusion of ADPKD ○ 40 years of age and older: absence of any renal cyst • MRI can be used for exclusion of ADPKD

	○ 40 years of age or younger: less than 5 renal cysts ○ Genetic testing is not required but may be considered in patients with equivocal or atypical renal finding, marked discordant disease within family, very mild PKD, sporadic PKD with no family history, reproductive counseling, and early and severe PKD or PKD with syndromic features • A panel of Canadian nephrologists developed the following updated recommendations for assessing the risk of disease progression and pharmacological management of patients with ADPKD based on evidence published since the development of the first consensus recommendation(4) ○ Identifying patient with ADPKD ▪ Patients should be referred to a nephrologist for initial assessment. Initial assessment should include kidney imaging and, in some cases, genetic testing to determine the patient's risk of rapid progression and to determine what treatment should be initiated. ○ Renal imaging for diagnosis, prognosis, and disease progression ▪ The preferred method for confirming the presence of ADPKD in patients with a family history is ultrasounds imaging and the use of the Unified Criteria to establish diagnosis and determine if typical or atypical. ▪ In select circumstances, such as in patients without a family history of ADPKD, other imaging modalities, including CT or MRI, may be considered to diagnose ADPKD, particularly to detect cysts in younger patients. ▪ A baseline assessment of renal size should be undertaken in patients with ADPKD. The objective of these measurements is to determine which patients are suitable candidates to be considered for therapeutic intervention based on their risk of progression. ▪ In patients with typical morphology, use US to measure kidney length (KL), or MRI or CT to measure total kidney volume (TKV) (and to calculate height adjusted TKV [htTKV] where appropriate) if a more precise measurement is required for therapeutic decisions. In cases where historical images are available, those images should be consulted before requesting new imaging.

	▪ After a baseline assessment of renal size, not all patients require routine reassessment of renal size. If renal size reassessment is done, it should not exceed a frequency of once yearly. ○ Assessing disease progression ▪ In current clinical practice, patients with a htTKV measurement are categorized in terms of their risk of progression as per the Mayo Clinic classification or other validated clinical tools (e.g., PROPKD scoring, genetic scoring). ▪ Currently available TKV-based prognostication tools should be applied only to class 1 (typical morphology) patients, as these patients are likely to be rapid progressors. Certain patients may require further clinical evaluation. ▪ Patients should be considered at risk of rapid progression of ADPKD renal disease if they meet either of the following criteria: 1) classified as Mayo class 1C, 1D, or 1E, or 2) have an US KL of greater than 16.5 cm bilaterally. ▪ Suggest the following be used as markers of rapid progression: 1) a sequential increase of greater than 5% annually in htTKV on imaging, or 2) documented disease progression (e.g., rapid decline in eGFR, defined as decline in eGFR greater than 2.5 mL/min/1.73 m^2 annually; patients in the placebo group of the TEMPO 3:4 study showed an annual decline in eGFR of 3.5 mL/min/1.73 m^2 over the three years of observation). ○ ADPKD-specific treatment options ▪ Treatment with tolvaptan for patients who fulfill the enrollment criteria of the TEMPO 3:4 study: • 18 to 50 years of age with TKV greater than 750 mL and eGFR greater than 45 mL/min/1.73 m^2 ▪ Treatment with tolvaptan for patients who fulfill the enrollment criteria of the REPRISE study: • 18 to 55 years of age with eGFR of 25 to 65 mL/min/1.73 m^2 • 56 to 65 years of age with eGFR of 25 to 44 mL/min/1.73 m^2 with historical evidence of a decline in eGFR >2.0 mL/min/1.73 m^2 /year

	• We believe that, although there were no inclusion criteria for kidney size, based on the abundance of evidence that increased size of kidneys is relevant, these REPRISE criteria relate to those patients with ADPKD who have enlarged kidneys. In those patients with advanced or rapidly progressive CKD without enlarged kidneys, an alternate diagnosis for CKD should be investigated. ▪ Suggest treatment with tolvaptan for patients who, according to the Mayo Classification, are classified as 1D or 1E with eGFR in CKD stages 1-4 (eGFR greater than 25 mL/min). Treatment with tolvaptan may be considered for patients who are classified as 1C and are younger than 50 years old or have other risk factors for rapid progression (such as an annual decrease in eGFR of >2.5 mL/min/1.73 m^2 and/or increase in TKV of >5% per year).
Efficacy	Tolvaptan was shown to slow the rate of decline in renal function in patients at risk of rapidly progressing ADPKD in two trials; TEMPO 3:4 in patients at earlier stages of disease and REPRISE in patients at later stages.(1) TEMPO 3:4 was a phase 3, double-blind, placebo-controlled, randomized trial which included 1445 adult patients (age greater than 18 years) with early (estimated creatinine clearance [eCrCl] greater than or equal to 60 mL/min), rapidly progressing (TKV greater than or equal to 750 mL and age less than 51 years) ADPKD (diagnosed by modified Ravine criteria). The trial met its prespecified primary endpoint of 3-year change in TKV (p less than 0.0001). Over the 3-year period, TKV increased by 2.8% per year (95% confidence interval [CI], 2.5 to 3.1) with tolvaptan versus 5.5% per year (95% CI, 5.1 to 6.0) with placebo. The relative rate of ADPKD-related events was decreased by 13.5% in tolvaptan-treated patients, (44 vs. 50 events per 100 person-years; hazard ratio, 0.87; 95% CI, 0.78 to 0.97; p=0.0095).(1) REPRISE was a double-blind, placebo-controlled randomized withdrawal trial in adult patients (age 18-65) with chronic kidney disease (CKD) with an eGFR between 25 and 65 mL/min/1.73 m^2 if younger than age 56; or eGFR between 25 and 44 mL/min/1.73 m^2, plus eGFR decline greater than 2.0 mL/min/1.73 m^2/year if between age 56-65. Subjects were to be treated for 12 months; after completion of treatment, patients entered a 3-week follow-up period to assess

	renal function. The change of eGFR from pretreatment baseline to post-treatment follow-up was –2.3 mL/min/1.73 m^2/year with tolvaptan as compared with – 3.6 mL/min/1.73 m^2/year with placebo, corresponding to a treatment effect of 1.3 mL/min/1.73 m^2/year (p less than 0.0001). The key secondary endpoint (eGFR slope in ml/min/1.73 m^2/year assessed using a linear mixed effect model of annualized eGFR (CKD-EPI)) showed a difference between treatment groups of 1.0 ml/min/m^2/year that was also statistically significant (p less than 0.0001).(1)
Safety	Jynarque has the following boxed warnings:(1) • Jynarque can cause serious and potentially fatal liver injury. Acute liver failure requiring liver transplantation has been reported • Measure ALT, AST, and bilirubin before initiating treatment, at 2 weeks and 4 weeks after initiation, then continuing monthly for the first 18 months and every 3 months thereafter. Prompt action in response to laboratory abnormalities, signs, or symptoms indicative of hepatic injury can mitigate, but not eliminate, the risk of serious hepatotoxicity. • Jynarque is available only through a restricted distribution program called the Jynarque REMS Program Jynarque has the following contraindications:(1) • History of signs or symptoms of significant liver impairment or injury, does not include uncomplicated polycystic liver disease • Concomitant use with strong CYP 3A inhibitors • Uncorrected abnormal blood sodium concentrations • Unable to sense or respond to thirst • Hypovolemia • Hypersensitivity to tolvaptan or component of the product • Uncorrected urinary outflow obstruction • Anuria

REFERENCES

Number	Reference
1	Jynarque prescribing information. Otsuka America Pharmaceuticals, Inc. October 2020.
2	Chapman, A.B., Devuyst, O., Eckardt, K.-U., Gansevoort, R. T., Harris, T., Horie, S., Kasiske, B. L., Odland, D., Pei, Y., Perrone, R. D., Pirson, Y., Schrier, R. W., Torra, R., Torres, V. E., Watnick, T., & Wheeler, D. C.

Number	Reference
	(2015). Autosomal-dominant polycystic kidney disease (ADPKD): Executive summary from a kidney disease: Improving global outcomes (KDIGO) controversies conference. *Kidney International*, *88*(1), 17–27. https://doi.org/10.1038/ki.2015.59
3	Srivastava, A., Patel, N., Autosomal dominant polycystic kidney disease. *American Academy of Family Physician*. 2014;90(5):303-307.
4	Soroka, S., Alam, A., Bevilacqua, M., Girard, L.-P., Komenda, P., Loertscher, R., McFarlane, P., Pandeya, S., Tam, P., & Bichet, D. G. (2018). Updated Canadian expert consensus on assessing risk of disease progression and pharmacological management of autosomal dominant polycystic kidney disease. *Canadian Journal of Kidney Health and Disease*, *5*, 205435811880158. https://doi.org/10.1177/2054358118801589

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of autosomal dominant polycystic kidney disease (ADPKD) and BOTH of the following: A. The patient does not have stage 5 chronic kidney disease (CKD) **AND** B. The patient is not on dialysis **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The patient will NOT be using the requested agent in combination with another tolvaptan agent **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., nephrologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent

Module	Clinical Criteria for Approval
	Length of Approval: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The patient will NOT be using the requested agent in combination with another tolvaptan agent **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., nephrologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity limit for Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months

Kerendia

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Kerendia® (finerenone) Tablets	To reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D)		1

CLINICAL RATIONALE

Chronic Kidney Disease (CKD) and Diabetes	Chronic kidney disease (CKD) is diagnosed by blood and urine laboratory tests, which include screening for albuminuria and a low estimated glomerular filtration rate (eGFR). These tests are often paired with biopsies and imaging to determine the underlying cause of renal dysfunction. It is crucial to emphasize that CKD, commonly known as diabetic kidney disease when linked to diabetes, affects 20-40% of adults with diabetes. This association underscores the critical need for regular monitoring and early intervention in diabetic patients, as it can significantly reduce the risk of complications. Diabetic kidney disease is associated with increased morbidity and mortality, primarily due to poor cardiovascular outcomes and a progression to end-stage kidney disease.(2) The American Diabetes Association's (ADA) Standards of Medical Care in Diabetes-2024 recommends routine annual urinary albumin and eGFR screening for individuals with type 2 diabetes. More frequent screening is recommended for people with diabetic kidney disease, depending on the stage of kidney disease. Treatment of diabetic kidney disease focuses on the optimization of glucose control to prevent the progression of CKD. Additionally, an emphasis is placed on adequate blood pressure control to reduce adverse cardiovascular outcomes and slow the progression of CKD.(2,3) The International Society of Nephrology Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend that people who have both CKD and diabetes should utilize a broad-based treatment strategy that emphasizes improving cardiovascular and kidney outcomes.(4)

	Guidelines for the management of CKD in patients with type 2 diabetes recommend control of hypertension and hyperglycemia, as well as the use of a renin–angiotensin system (RAS) blocker (an angiotensin-converting–enzyme [ACE] inhibitor or angiotensin-receptor blocker [ARB]) and, more recently, a sodium–glucose cotransporter 2 (SGLT2) inhibitor.(2) Both the ADA and KDIGO guidelines recommend ACEIs or ARBs for slowing the progression of CKD in patients with diabetes, with the dose titrated to the highest approved dose that is tolerated.(2,3,4) Additionally, the KDIGO guidelines also state that glycemic management for patients with type 2 diabetes and CKD should include first-line treatment with metformin and a sodium-glucose cotransporter-2 (SGLT2) inhibitor, with further drug therapy as needed for glycemic control, (unless pretreatment eGFR less than 20 ml/min). SGLT2 inhibitors have a significant effect on reducing CKD progression that appears to be independent of eGFR. Even when glycemic targets are achieved on metformin, an SGLT2 inhibitor should be added for their beneficial effects. The KDIGO guidelines recommend that selecting an SGLT2 inhibitor should prioritize agents with documented kidney or cardiovascular benefits and consider eGFR.(4) Of these, canagliflozin, dapagliflozin, and empagliflozin have obtained FDA approval for reducing the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with CKD at risk of progression.(2,3) Nonetheless, despite recommended treatment, a risk of CKD progression remains. Evidence supports a pathophysiological role for the overactivation of the mineralocorticoid receptor in cardiorenal diseases, including CKD and diabetes, through inflammation and fibrosis that leads to progressive kidney and cardiovascular dysfunction.(2,4) In the 2024 edition of the American Diabetes Association's Standards of Medical Care in Diabetes, a recommendation was made for patients with type 2 diabetes and chronic kidney disease who are at increased risk for cardiovascular events or chronic kidney disease progression. In these patients, consideration should be given for the use of SGLT2 inhibitors; a glucagon-like peptide 1 agonist (GLP1) or a nonsteroidal mineralocorticoid receptor antagonist (finerenone) is recommended to reduce chronic kidney disease progression and cardiovascular events.(2,3) The (KDIGO) guidelines recommend a nonsteroidal mineralocorticoid receptor antagonist (finerenone) with proven kidney or cardiovascular benefit for patients with type 2 diabetes, an eGFR greater than or equal to 25 ml/min per 1.73 m^2, normal serum potassium concentration, and albuminuria (greater than or equal to 30 mg/g [greater than or equal to 3 mg/mmol]) despite maximum tolerated dose of a renin–angiotensin system (RAS) blocker.(4) These recommended treatments offer hope and optimism for the management of CKD in diabetic patients, potentially improving their quality of

	life and reducing the risk of complications. Finerenone is a nonsteroidal, selective antagonist of the mineralocorticoid receptor (MR), which is activated by aldosterone and cortisol and regulates gene transcription. Finerenone blocks MR-mediated sodium reabsorption and MR overactivation in both epithelial (e.g., kidney) and nonepithelial (e.g., heart and blood vessels) tissues. MR overactivation is thought to contribute to fibrosis and inflammation.(1)
Efficacy	The FIDELIO-DKD and FIGARO-DKD studies were randomized, double-blind, placebo-controlled, multicenter studies in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes. Both trials excluded patients with known significant non-diabetic kidney disease. All patients were to have a serum potassium less than or equal to 4.8 mEq/L at screening and be receiving standard of care background therapy, including a maximum tolerated labeled dose of an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. Patients with a clinical diagnosis of chronic heart failure with reduced ejection fraction and persistent symptoms (New York Heart Association class II to IV) were excluded. The starting dose of Kerendia was based on screening eGFR. The dose of Kerendia could be titrated during the study, with a target dose of 20 mg daily. The FIDELIO-DKD patients were followed for 2.6 years and the FIGARO-DKD patients were followed for 3.4 years.(1) At baseline, 99.8% of patients were treated with an ACEi or ARB. Approximately 97% were on an antidiabetic agent (insulin [64.1%], biguanides [44%], glucagon-like peptide-1 [GLP-1] receptor agonists [7%], sodium-glucose cotransporter 2 [SGLT2] inhibitors [5%]), 74% were on a statin, and 57% were on an antiplatelet agent. In the FIGARO-DKD study, background therapies were similar to the FIDELIO-DKD study.(1) In the FIDELO-DKD trial, Kerendia reduced the incidence of the primary composite endpoint of a sustained decline in eGFR of greater than or equal to 40%, kidney failure, or renal death (HR 0.82, 95% CI 0.73-0.93, p=0.001). The treatment effect reflected a reduction in a sustained decline in eGFR of greater than or equal to 40% and progression to kidney failure. Kerendia also reduced the incidence of the composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (MI), and non-fatal stroke or hospitalization for heart failure (HR 0.86, 95% CI 0.75-0.99, p=0.034). The treatment effect reflected a reduction in CV death, non-fatal MI, and hospitalization for heart failure. In the FIGARO-DKD study, Kerendia reduced the incidence of the primary composite endpoint of CV death, non-fatal MI, non- fatal stroke or hospitalization for heart failure (HR 0.87, 95% CI 0.76-0.98, p = 0.026). The treatment effect was mainly

	driven by an effect on hospitalization for heart failure, though CV death also contributed to the treatment effect.(1)
Safety	Kerendia is contraindicated in patients concomitantly using strong CYP3A4 inhibitors and in patients with adrenal insufficiency. Treatment with Kerendia should not be initiated if serum potassium is greater than 5 mEq/L. Initiation of treatment with Kerendia is not recommended if estimated glomerular filtration rate (eGFR) is less than 25 mL/min/1.73m^2.(1)

REFERENCES

Number	Reference
1	Kerendia prescribing information. Bayer HealthCare Pharmaceuticals Inc. September 2022.
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3	ElSayed NA, Grazia Aleppo, Bannuru RR, et al. 10. Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2024*. *Diabetes Care*. 2023;47(Supplement_1):S179-S218. doi:https://doi.org/10.2337/dc24-s010
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QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds than the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Ketorolac

Quantity Limit

ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
66100037100320		Ketorolac Tromethamine Tab 10 MG	10 MG	The quantity limit will allow for 20 tablets or 5 bottles of nasal spray per prescription to follow product labeling recommendations for no more than 5 days of therapy with no more than 4 doses/day"			
66100037102090	Sprix	Ketorolac Tromethamine Nasal Spray 15.75 MG/SPRAY	15.75 MG/SPRAY	The quantity limit will allow for 20 tablets or 5 bottles of nasal spray per prescription to follow product labeling recommendations for no more than 5 days of therapy with no more than 4 doses/day"			

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **Length of Approval**: up to 12 months

Korlym (mifepristone)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Korlym® (mifepristone)* Tablet	To control hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing's syndrome who have type 2 diabetes mellitus or glucose intolerance and have failed surgery or are not candidates for surgery Limitations of Use: Do not use for the treatment of type 2 diabetes mellitus unrelated to endogenous Cushing's syndrome.	*generic available	1

CLINICAL RATIONALE

Cushing's Syndrome	Cushing's syndrome is pathologic hypercortisolism caused by excessive adrenocorticotropic hormone (ACTH) production or autonomous adrenal production of cortisol. This potentially lethal disorder is associated with significant comorbidities including hypertension, diabetes, coagulopathy, cardiovascular disease, infections, and fractures. As a result, even after cure of hypercortisolism, mortality rates may be increased. Because of this it is important to make the diagnosis as early in the disease course as possible to prevent additional morbidity and residual disease. Signs and symptoms of Cushing's syndrome are broad and often common among the general population such as obesity, depression, diabetes, hypertension, or menstrual irregularities. Some features are more discriminatory and unique to Cushing's syndrome such as reddish-purple striae, plethora, proximal muscle weakness, bruising with no obvious trauma, and unexplained osteoporosis.(3) Guidelines recommend a multidisciplinary team, including an endocrinologist, providing education and treatment options to the patient. Goals of treatment in Cushing's syndrome include reversing the patient's clinical features, normalizing biochemical changes with minimal morbidity, and sustained control without recurrence. Surgical resection of the causal lesion(s) is the first-line approach. When surgery is delayed, contraindicated, or unsuccessful, second-line treatments, including medical therapy, bilateral adrenalectomy, and radiation

	therapy, must be considered. Glucocorticoid antagonists, such as mifepristone, are suggested in patients with diabetes or glucose intolerance who are not surgical candidates or who have persistent disease after surgery.(2) The American Diabetes Association defines impaired glucose tolerance (glucose intolerance) in prediabetes as plasma glucose of 140 mg/dL to 199 mg/dL (7.8 mmol/L to less than 11.1 mmol/L), and in diabetes as plasma glucose of greater than or equal to 200 mg/dL (11.1 mmol), after the oral glucose tolerance test (OGTT). The OGTT is a two-hour test that checks plasma glucose levels before and 2 hours after drinking a glucose-containing drink.(4)
Efficacy	The safety and efficacy of Korlym in the treatment of endogenous Cushing's syndrome was evaluated in an uncontrolled, open-label, 24-week, multicenter clinical study. The study enrolled 50 subjects with clinical and biochemical evidence of hypercortisolemia despite prior surgical treatment and radiotherapy. The reasons for medical treatment were failed surgery, recurrence of disease, and poor medical candidate for surgery. Patients belonged to one of two cohorts: a diabetes cohort or a hypertension cohort. While results in the hypertension cohort showed no changes in mean systolic and diastolic blood pressures at the end of the trial, the diabetes cohort showed improvements in glucose response [defined as a greater than or equal to 25% reduction from baseline in glucose area under the curve (AUC) in standard oral glucose tolerance test] in 60% of patients, and reduction in glycated hemoglobin (HbA1c) in all patients.(1)
Safety	Mifepristone has a boxed warning for pregnancy termination. Mifepristone has potent antiprogestational effects and will result in the termination of pregnancy. Pregnancy must therefore be excluded before the initiation of treatment with mifepristone, or if the treatment is interrupted for more than 14 days in females of reproductive potential.(1) Mifepristone is contraindicated in:(1) • Pregnancy • Patients taking drugs metabolized by CYP3A such as simvastatin, lovastatin, and CYP3A4 substrates with narrow therapeutic ranges, such as cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus • Patients receiving systemic corticosteroids for lifesaving purposes (e.g., immunosuppression after organ transplantation) • Women with a history of unexplained vaginal bleeding or with endometrial hyperplasia with atypia or endometrial carcinoma

	• Patients with known hypersensitivity to mifepristone or to any of the product components

REFERENCES

Number	Reference
1	Korlym prescribing information. Corcept Therapeutics Inc. April 2024.
2	Nieman L, Biller B, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015;100:2807–2831.
3	Nieman, Lynnette K. Recent Updates on the Diagnosis and Management of Cushing's Syndrome. Endocrinology and Metabolism. 2018 Jun;33:139-146. doi: 10.3803/EnM.2018.33.2.139.
4	American Diabetes Association Professional Practice Committee, ElSayed, N. A., Aleppo, G., Bannuru, R. R., Bruemmer, D., Collins, B. S., Ekhlaspour, L., Gaglia, J. L., Hilliard, M. E., Johnson, E. L., Khunti, K., Lingvay, I., Matfin, G., McCoy, R. G., Perry, M. L., Pilla, S. J., Polsky, S., Prahalad, P., Pratley, R. E., … Gabbay, R. A. (2023, December 11). 2. diagnosis and classification of diabetes: Standards of care in diabetes-2024. American Diabetes Association. https://diabetesjournals.org/care/article/47/Supplement_1/S20/153954/2-Diagnosis-and-Classification-of-Diabetes.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Module	Clinical Criteria for Approval

Agents Eligible for Continuation of Therapy
All target agents are eligible for continuation of therapy

1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR**
2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR**

B. The patient has a diagnosis of Cushing's syndrome **AND**

1. If the patient has an FDA labeled indication, then ONE of the following:
   A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**
   B. There is support for using the requested agent for the patient's age for the requested indication **AND**
2. ONE of the following:
   A. The patient has type 2 diabetes mellitus **OR**
   B. The patient has glucose intolerance as defined by a 2-hr glucose tolerance test plasma glucose value of 140-199 mg/dL **AND**
3. ONE of the following:
   A. The patient has had an inadequate response to surgical resection **OR**
   B. The patient is NOT a candidate for surgical resection **AND**

2. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:

Brand	Generic Equivalent
Korlym	mifepristone

A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent **OR**
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent **OR**
C. There is support for the use of the requested brand agent over the generic equivalent **AND**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent AND
5. The requested dose does NOT exceed 20 mg/kg/day

Length of Approval: 6 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: Patients not previously approved for the requested agent will require initial evaluation review] AND
2. The patient has had clinical benefit with the requested agent AND
3. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:

<table>
<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Korlym</td><td>mifepristone</td></tr>
</table>

1. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
2. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
3. There is support for the use of the requested brand agent over the generic equivalent AND
4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND
5. The patient does NOT have any FDA labeled contraindications to the requested agent AND
6. The requested dose does NOT exceed 20 mg/kg/day

Length of Approval: 12 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
</td></tr>
</table>

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months

Low Molecular Weight Heparins (LMWH) and Arixtra

Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Arixtra® (fondaparinux)* Subcutaneous injection	• Treatment of acute symptomatic PE +/- DVT • Outpatient treatment of acute DVT without PE • Prophylaxis of DVT, which may lead to PE, in patients undergoing abdominal surgery who are at risk of thromboembolic complications • Prophylaxis of DVT, which may lead to PE, in patients undergoing hip fracture surgery • Prophylaxis of DVT, which may lead to PE, in patients undergoing hip replacement • Prophylaxis of DVT, which may lead to PE, in patients undergoing knee replacement	*generic available PE = pulmonary embolism; DVT = deep vein thrombosis	1
Fragmin® (dalteparin) Injection	• Prophylaxis of DVT, which may lead to PE in patients undergoing abdominal surgery who are at risk of thromboembolic complications • Prophylaxis of DVT, which may lead to PE in patients undergoing hip replacement • Prophylaxis of DVT, which may lead to PE in patients at risk of thromboembolism due to severely restricted mobility during acute illness • Prophylaxis of ischemic complications of unstable angina and non-Q-wave MI • Extended treatment of symptomatic VTE (proximal DVT and/or PE), to reduce the recurrence of VTE in patients with cancer • Treatment of symptomatic VTE, to reduce the recurrence of VTE in pediatric patients 1 month of age and older	DVT = deep vein thrombosis; MI = myocardial infarction; PE = pulmonary embolism; VTE = venous thromboembolism	2

Agent(s)	FDA Indication(s)	Notes	Ref#
Lovenox® (enoxaparin)* Injection	• Inpatient treatment of acute symptomatic DVT` • Outpatient treatment of acute DVT without PE • Prophylaxis of DVT, which may lead to PE in:Patients undergoing abdominal surgery who are at risk of thromboembolic complications • Patients undergoing hip replacement • Patients undergoing knee replacement • Patients at risk of thromboembolism due to severely restricted mobility during acute illness • Prophylaxis of ischemic complications of unstable angina and non-Q-wave MI • Treatment of acute ST-segment elevation MI (STEMI)	*generic available DVT = deep vein thrombosis; MI = myocardial infarction; PE = pulmonary embolism	3

CLINICAL RATIONALE

Deep vein thrombosis and pulmonary embolism	The most common presentations of venous thrombosis are deep vein thrombosis (DVT) of the lower extremity and pulmonary embolism (PE). The causes of venous thrombosis can be divided into two groups: hereditary and acquired, and are often multiple in a given patient.(4) The quantity limit is per 90 days to allow a single course of therapy. Quantities above this quantity limit will be approved for primary or secondary prophylaxis of thromboembolism during pregnancy, or for patients that have cancer and require extended prophylaxis and/or treatment of symptomatic venous thromboembolism (VTE).
Thromboembolism in pregnancy	Pregnancy and puerperium are well-established risk factors for DVT and PE, collectively known as VTE. VTE can occur at any stage of pregnancy, but the time of highest risk is in the puerperium (the period of about six weeks after childbirth) with estimates of relative risk of approximately 20-fold.(6) The 2012 American College of Chest Physicians (ACCP) CHEST guidelines suggest up to 6 weeks of puerperium thromboprophylaxis to postpartum women considered at high risk for VTE.(7) The need for thromboprophylaxis should be assessed antepartum, postpartum, and at any time the patient transitions from the outpatient to the inpatient setting.(6)

	Prevention of VTE can be defined as primary or secondary. Primary thromboprophylaxis is the preferred method of VTE prevention because efficacy is well established, and it is more cost effective than treatment of complications. Primary prophylaxis is carried out using either drugs or mechanical methods (e.g., intermittent pneumatic compression boots). Secondary thromboprophylaxis involves the early detection and treatment of subclinical VTE by screening medical patients with objective tests that are sensitive for the presence of DVT (e.g., contrast venography, venous ultrasound, MRI venography). Secondary thromboprophylaxis is also used during pregnancy in women with a high clinical suspicion for DVT but negative testing results.(8) The ACCP recommends low-molecular-weight heparins or fondaparinux for the prevention and treatment of VTE in pregnant women instead of unfractionated heparin.(7,8)
Venous thromboembolism in cancer patients	VTE is a common and life-threatening condition in cancer patients. Results from a retrospective study of hospitalized adult cancer patients with neutropenia showed that approximately 3% to 12% of these patients, depending on the type of malignancy, experienced VTE during their first hospitalization.(5) Although only dalteparin (Fragmin) carries FDA approval for the specific indication of VTE in cancer patients, guidelines recommend both dalteparin and enoxaparin (Lovenox) as options to treat VTE in cancer patients. For patients with heparin-induced thrombocytopenia (HIT) or a history of HIT, fondaparinux (Arixtra) represents a safer alternative.(5,9,10) Anticoagulant therapy is indicated for all patients with proximal DVT (e.g., popliteal, femoral, or iliac vein) because the risk of complications is higher, especially embolization and death. Patients with distal DVT (e.g., peroneal, anterior or posterior tibial, or muscular veins of the calf) are at approximately half the risk of embolization as those with proximal DVT. Because of this, treatment of isolated distal DVT varies among centers and clinicians, with some experts choosing not to treat select patients considered low risk of embolization.(9) However, there are several indications for anticoagulation in any patient with distal DVT with one of the indications being patients with active cancer.(5,9)

REFERENCES

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2	Fragmin prescribing information. Pfizer Inc. October 2022.

Number	Reference
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ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
83103030102020	Arixtra	Fondaparinux Sodium Subcutaneous Inj 2.5 MG/0.5ML	2.5 MG/0.5ML	a single course of therapy			

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The patient requires extended treatment for primary or secondary prophylaxis of thromboembolism during pregnancy and/or puerperium **OR** 3. The patient requires extended prophylaxis and/or treatment of symptomatic VTE (DVT and/or PE) **AND** the patient has cancer **OR** 4. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does not have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Long Acting Insulin

Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Basaglar® (insulin glargine) Injection	To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus. Limitations of Use: Not recommended for treating diabetic ketoacidosis.		1
Lantus® (insulin glargine) Injection	To improve glycemic control in adult and pediatric patients with diabetes mellitus Limitations of Use: Not recommended for the treatment of diabetic ketoacidosis		2
Levemir® (insulin detemir) Injection	To improve glycemic control in adult and pediatric patients with diabetes mellitus. Limitations of Use: Not recommended for the treatment of diabetic ketoacidosis.		3
Rezvoglar™ (insulin glargine-aglr) Injection	To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus Limitation of use: Not recommended for treating diabetic ketoacidosis		9
Semglee®, Glargin-yfgn Injection	To improve glycemic control in adults and pediatric patients with type 1 diabetes mellitus and in adults with type 2 diabetes mellitus Limitation of use: Not recommended for treating diabetic ketoacidosis		4
Toujeo®, Toujeo® Max	To improve glycemic control in adults and pediatric patients 6 years and older with diabetes mellitus		5

Agent(s)	FDA Indication(s)	Notes	Ref#
(insulin glargine) Injection	Limitation of use: Not recommended for treating diabetic ketoacidosis		
Tresiba®, Insulin degludec Injection	To improve glycemic control in patients 1 year of age and older with diabetes mellitus Limitation of use: Not recommended for treating diabetic ketoacidosis		6

CLINICAL RATIONALE

Overview	The American Diabetes Association Standards of Medical Care in Diabetes recommend the following therapy for type 1 diabetes mellitus:(7) • Most individuals with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or subcutaneous insulin infusion. • Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. • Individuals with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake, fat and protein content, and anticipated physical activity. • For type 2 diabetes mellitus, the American Diabetes Association recommends the following:(7) • Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. • In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. • Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy.

	• Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals. • Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. • Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. • The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (greater than or equal to 300 mg/dL [16.7 mmol/L]) are very high. • A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. • Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. • In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. • If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. • Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment. • Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose more than ~0.5 units/kg/day, high bedtime–morning or postpreprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of overbasalization should prompt reevaluation to further individualize therapy.

	The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) 2023 algorithm for type 2 diabetics (T2D) recommends the overall goal of insulin therapy is to achieve glycemic control after failure of noninsulin antihyperglycemic agents. Glycemic targets should be individualized, although an A1C of 6.5% to 7% for persons on insulin is recommended for most patients. Although A1C is a key measure, insulin titration requires use of multiple glycemic parameters including fasting blood glucose (FBG), premeal or 2-hour postprandial blood glucose, and data from continuous glucose monitoring (CGM), when available. In general, targets for fasting and premeal glucose are <110 mg/dL without hypoglycemia and can be individualized based on a person's comorbidities and clinical status. The use of CGM is recommended for persons treated with insulin to optimize glycemic control while minimizing hypoglycemia.(8) Given that T2D is a progressive disease, many individuals will require >1 antihyperglycemic medication to achieve their individualized A1C target over the course of the disease. Clinicians should consider multiple factors when selecting the second agent, including presence of overweight or obesity, hypoglycemia risk, access/cost, and presence of severe hyperglycemia. Patients often present with >1 of these factors, so using a patient-centered, shared decision-making approach is important. The order that medications are listed in the algorithm denotes the suggested preference hierarchy for selection. In those patients with overweight or obesity and the additional goal of weight loss, dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist (GIP/GLP-1 RA), GLP-1 RA, or sodium glucose cotransporter 2 inhibitor (SGLT2i) class are preferred options. Persons with a history of hypoglycemia, at high risk of hypoglycemia, and/or at risk for severe complications from hypoglycemia should preferentially be initiated with an agent associated with low risk for hypoglycemia, including GLP-1 RA, SGLT2i, dual GIP/GLP-1 RA, thiazolidinedione (TZD), or dipeptidyl peptidase-4 inhibitor (DPP-4i).(8) Patients with symptomatic hyperglycemia and/or an A1C >10% suggestive of marked insulin deficiency should start basal insulin to improve glycemia as quickly as possible. Basal insulin can be initiated with or without initiation and titration of a GLP-1 RA if the patient is not already on this class of agents. Some patients with severe hyperglycemia may need simultaneous initiation of bolus insulin. Clinicians should be cognizant that combination of incretin-based therapies is not recommended (i.e., DPP-4i with GLP-1 RA or dual GIP/GLP-1 RA). Antihyperglycemic medications should be titrated to the maximally tolerated dose to achieve the individualized A1C goal, and additional antihyperglycemic agents should be considered in a timely fashion to avoid

	therapeutic inertia. If the A1C is >9% or >1.5% above goal, greater than 2 antihyperglycemic agents may need to be initiated at once.(8) Basal with or without prandial insulin treatment may be needed as initial therapy if the A1C is >10% and/or glucose values are >300 mg/dL, combined with catabolic symptoms, such as weight loss. If symptomatic hyperglycemia is present, a GLP-1 RA alone is not recommended as it requires titration and may delay glucose control. The goal of initial intensive insulin therapy for symptomatic hyperglycemia is to reduce glucose levels safely and promptly. After improved glycemic control is achieved with short-term insulin therapy, especially with a new diagnosis of DM, a role for noninsulin antihyperglycemic agents could be considered. For most persons who need intensification of glycemic control and who are already undergoing 3 to 4 oral therapies, a GLP-1 RA or GIP/GLP-1 RA should be the initial choice, if not already in use. If glycemic targets are not achieved with these therapies, basal insulin should be added alone or as a basal insulin/GLP-1 RA combination injection. Stepwise addition of prandial insulin at 1 to 3 meals is recommended if additional glycemic control is required. The dose of basal insulin can be based on A1C levels at the time of initiation. For an A1C <8%, basal insulin can be started at 0.1 to 0.2 U/kg/day and for an A1C >8%, 0.2 to 0.3 U/kg/day can be considered. Analog insulins, including detemir, glargine, or degludec are preferred over human insulins such as neutral protamine Hagedorn (NPH) to reduce hypoglycemia.(8)
Safety	Basaglar, Lantus, Rezvoglar, Semglee, and Toujeo products have the following contraindications:(1,2,4,5,9) • During episodes of hypoglycemia. • Hypersensitivity to insulin glargine products or any excipients. Levemir has the following contraindications:(3) • During episodes of hypoglycemia. • Hypersensitivity to insulin detemir products or any excipients. Tresiba has the following contraindications:(6) • During episodes of hypoglycemia. • Hypersensitivity to insulin degludec or any excipients.

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2	Lantus prescribing information. Sanofi-Aventis US, LLC. June 2023.
3	Levemir prescribing information. Novo Nordisk, Inc. December 2022.
4	Semglee prescribing information. Mylan Specialty L.P. July 2023.
5	Toujeo, Toujeo Max prescribing information. Sanofi-Aventis U.S. LLC. March 2023.
6	Tresiba prescribing information. Novo Nordisk Inc. July 2022.
7	American Diabetes Association, 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023. Diabetes Care 1 January 2023; 46 (Supplement_1): S140–S157. https://doi.org/10.2337/dc23-S009.
8	Samson, S. L., Vellanki, P., Blonde, L., et. al. (2023). American association of clinical endocrinology consensus statement: Comprehensive type 2 diabetes management algorithm – 2023 update. Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, 29(5), 305–340. https://doi.org/10.1016/j.eprac.2023.02.001
9	Rezvoglar prescribing information. Sanofi-Aventis US, LLC. November 2022.

ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
27104003	Basaglar kwikpen ; Basaglar tempo pen ; Rezvoglar kwikpen ; Semglee ; Toujeo max solostar ; Toujeo solostar	Insulin Glargine Inj ; insulin glargine inj ; insulin glargine pen-inj with transmitter port ; insulin glargine soln pen-injector ; insulin glargine-aglr soln pen-injector ; insulin glargine-yfgn inj ; insulin glargine-yfgn soln pen-injector	100 UNIT/ML ; 300 UNIT/ML	Quantity limit is cumulative at GPI 8 for injectable formulations.			
27104006	Levemir ; Levemir flexpen ; Levemir flextouch	insulin detemir inj ; insulin detemir soln pen-injector	100 UNIT/ML	Quantity limit is cumulative at GPI 8 for injectable formulations.			
27104007	Tresiba ; Tresiba flextouch	insulin degludec inj ; insulin degludec soln pen-injector	100 UNIT/ML ; 200 UNIT/ML	Quantity limit is cumulative at GPI 8 for injectable formulations.			

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL Standalone	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR**

Module	Clinical Criteria for Approval
	2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Lupus

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Benlysta® (belimumab) Subcutaneous injection	Treatment of patients 5 years of age and older with active systemic lupus erythematosus (SLE) who are receiving standard therapy Treatment of patients 5 years of age and older with active lupus nephritis (LN) who are receiving standard therapy Limitations of use: • Efficacy has not been evaluated in patients with severe active central nervous system lupus. Use of Benlysta is not recommended in this situation		1
Lupkynis® (voclosporin) Capsule	In combination with a background immunosuppressive therapy regimen for the treatment of adult patients with active lupus nephritis Limitations of use: • Safety and efficacy of Lupkynis have not been established in combination with cyclophosphamide. Use is not recommended in this situation.		9

CLINICAL RATIONALE

Systemic Lupus Erythematosus (SLE)	Systemic Lupus Erythematosus (SLE) is a chronic inflammatory autoimmune disease of unknown cause. It has a broad range of clinical and serological manifestations and can affect many organs. Clinical symptoms of SLE include fatigue, fever, arthralgia, myalgia, changes in weight, skin and mucus membrane lesions and ulcers, and vascular disease. SLE can also include cardiac, renal,

	pulmonary, and neurologic involvement. Due to its multisystem involvement and likelihood of changes in presentation, the diagnosis of SLE may be difficult.(2) The American College of Rheumatology (ACR) recommends referral to a rheumatologist and/or another appropriate specialist to establish the diagnosis of SLE; assess activity and severity level; and management of the disease.(3) The 2023 update of the EULAR recommendations for the management of SLE recommend the following:(5) • Hydroxychloroquine is recommended for all patients with SLE, unless contraindicated, at a target dose of 5 mg/kg real body weight/day. Dose to be individualized based on risk for flare and retinal toxicity. • Glucocorticoids, if needed, are dosed based on the type and severity of organ involvement, and should be reduced to maintenance dose of less than or equal to 5mg/day (prednisone equivalent) and, when possible, withdrawn; in patients with moderate-to-severe disease, pulses of intravenous methylprednisolone (125–1000mg/day, for 1–3 days) can be considered. • In patients not responding to hydroxychloroquine (alone or in combination with glucocorticoids) or patients unable to reduce glucocorticoids below doses acceptable for chronic use, addition of immunomodulating/immunosuppressive agents (e.g., methotrexate, azathioprine, or mycophenolate) and/or biological agents (e.g., belimumab or anifrolumab) should be considered. • In patients with organ-threatening or life-threatening disease, intravenous cyclophosphamide should be considered; in refractory cases, rituximab may be considered. • Treatment of active skin disease should include topical agents (glucocorticoids, calcineurin inhibitors), antimalarials (hydroxychloroquine, chloroquine), and/or systemic glucocorticoids as needed, with methotrexate, mycophenolate, anifrolumab, or belimumab considered as second-line therapy. HHS notes that the same management strategies apply to children and adolescents with SLE.(4)
Lupus Nephritis (LN)	Lupus nephritis (LN) is a common cause of kidney injury and failure in patients with SLE. Roughly 50% of patients with SLE will develop LN at some point in their SLE disease course and between 10% to 30% of those patients will progress to kidney failure requiring kidney transplant. Mortality in patients with LN is significantly higher than those that do not develop LN, with death occurring in 5%

	to 25% of patients with proliferative LN. LN typically develops early in SLE disease course and can often be present at initial diagnosis of SLE. LN results due to an accumulation of immune complex in the glomeruli. Intrarenal inflammation occurs leading to permanent damage to the kidney.(6)
	
	Diagnosis of LN can be challenging, especially if the patient has not been initially diagnosed with SLE. Serum creatinine levels, urine dipstick testing, and urine sediment are necessary tools for LN evaluation. Proteinuria in patients with SLE is suggestive of a diagnosis of LN.(6) The American College of Rheumatology (ACR) indicates that all patients with clinical evidence of LN should undergo a renal biopsy to determine disease classification and confirm diagnosis of LN. The ACR also indicates that treatment should be based off of the International Society of Nephrology/Renal Pathology Society (ISN/RPS) LN classification. The ISN/RPS breaks down LN into the following 6 classes:(8)
	
	• Class I: minimal mesangial lupus nephritis
	• Class II: mesangial proliferative lupus nephritis
	• Class III: focal lupus nephritis
	• Class IV: diffuse lupus nephritis
	• Class V: membranous lupus nephritis
	• Class VI: advanced sclerotic lupus nephritis
	
	Kidney Disease: Improving Global Outcomes (KDIGO) 2024 clinical practice guideline for the management of lupus nephritis recommends the following:(10)
	
	Initial therapy of active Class III/IV:
	
	• Patients with active Class III or IV LN, with or without a membranous component, should be treated initially with glucocorticoids plus any one of the following:
	  ○ Mycophenolic acid analogs (MPAA)
	  ○ Low-dose intravenous cyclophosphamide or oral cyclophosphamide
	  ○ Belimumab and either MPAA or low-dose intravenous cyclophosphamide
	  ▪ Belimumab duration up to 2.5 years
	  ○ MPAA and a calcineurin inhibitor (CNI) when kidney function is not severely impaired (i.e., estimated glomerular filtration rate [eGFR] less than or equal to 45 mL/min per 1.73 m^2)
	  ▪ CNI duration up to 3 years
	• Initial therapy with an immunosuppressive regimen that includes a CNI (voclosporin, tacrolimus, or cyclosporine) may be preferred in patients

	with relatively preserved kidney function and nephrotic-range proteinuria likely due to extensive podocyte injury, as well as patients who cannot tolerate standard-dose MPAA or are unfit for or will not use cyclophosphamide-based regimens.
	• A triple immunosuppressive regimen of belimumab with glucocorticoids and either MPAA or reduced-dose cyclophosphamide may be preferred in patients with repeated kidney flares or at high-risk for progression to kidney failure due to severe chronic kidney disease.
	
	Maintenance therapy for Class III/IV:
	
	• After completion of initial therapy, patients should be placed on MPAA for maintenance
	  ○ Azathioprine (AZA) is an alternative to MPAA after completion of initial therapy in patients who do not tolerate MPAA, who do not have access to MPAA, or who are considering pregnancy
	• Patients treated with triple immunosuppressive regimens that include belimumab or a CNI in addition to standard immunosuppressive therapy can continue with a triple immunosuppressive regimen as maintenance therapy
	• If MPAA and azathioprine cannot be used for maintenance, CNIs or mizoribine or leflunomide can be considered
	
	Pure Class V:
	
	• Patients with low-level proteinuria:
	  ○ Renin-angiotensin system blockade and blood pressure control
	  ○ Immunosuppressive treatment guided by extrarenal manifestations of systemic lupus erythematosus
	  ○ Hydroxychloroquine
	• Patients with nephrotic-range proteinuria:
	  ○ Renin-angiotensin system blockade and blood pressure control
	  ○ Combined immunosuppressive treatment with glucocorticoid and one other agent (e.g., mycophenolic acid analogs, cyclophosphamide, CNI, rituximab, AZA)
	  ○ Hydroxychloroquine
	
	Lupus nephritis in children:
	
	• Treat pediatric patients with LN using immunosuppression regimens similar to those used in adults, but consider issues relevant to this

	population, such as dose adjustment, growth, fertility, and psychosocial factors, when devising the therapy plan
Efficacy	**Benlysta SLE trials(1)** The safety and efficacy of belimumab was evaluated in two randomized, double-blind, placebo-controlled, phase III studies involving patients age 18 and older with SLE (BLISS-52 and BLISS-76 study). The design of these studies was based on the results of a phase II study which identified that patients who were autoantibody-positive had a better response to belimumab. As a result, BLISS-52 and BLISS-76 limited the study population to only include autoantibody-positive SLE patients. Patients were on a standard of care SLE treatment regimen comprising of at least one of the following: corticosteroids, antimalarials, nonsteroidal anti-inflammatory drugs (NSAIDS), and/or immunosuppressives (azathioprine, methotrexate, or mycophenolate). Patients with severe active lupus nephritis and severe central nervous system (CNS) lupus were excluded. Patients using other biologics including B-cell targeted therapies such as rituximab or intravenous cyclophosphamide in the previous six months were also excluded. BLISS-52 (N=865) and BLISS-76 (N=826) had similar designs with the exception of duration. BLISS-76 was 76 weeks in duration and BLISS-52 was 52 weeks in length. Eligible patients had active SLE disease which was defined as a Safety of Estrogen in Lupus Erythematosus National Assessment-SLE Disease Activity Index (SELENA-SLEDAI) score greater than or equal to 6. Patients were randomly assigned to receive belimumab 1 mg/kg, 10 mg/kg, or placebo in addition to standard of care. The study medication was administered on Days 0, 14, 28, and then every 28 days for 48 weeks in BLISS-52 and 72 weeks in BLISS-76. In both BLISS-52 and BLISS-76, the proportion of SLE patients achieving a SLE Responder Index-4 (SRI-4) response was significantly higher in the belimumab 10 mg/kg group than placebo while the effect on SRI-4 was not consistently significantly different for the belimumab 1 mg/kg group. The safety and efficacy of Benlysta in pediatric patients was evaluated in an international, randomized, double-blind, placebo-controlled, 52-week study conducted in 93 patients with a clinical diagnosis of SLE according to the ACR classification criteria. Patients had a SELENA-SLEDAI score greater than or equal to 6 and positive autoantibodies at screening. Patients were on stable SLE treatment regimen and had similar inclusion and exclusion criteria as in the adult studies. The primary endpoint was the same as the adult trials, and there was a numerically higher proportion of pediatric patients achieving a response in SRI-4

	and its components in patients receiving Benlysta plus standard therapy compared with placebo plus standard therapy (53% vs 44%, odds ratio 1.49 [CI 0.64, 3.46]). **Benlysta LN clinical trials(1,7)** The safety and efficacy of Benlysta in patients with lupus nephritis was evaluated in a 104 week, randomized, double-blind, placebo controlled trial that included 448 patients with active proliferative and/or membranous lupus nephritis. Patients had to be at least 18 years of age and ANA positive SLE that fulfilled the ACR classification criteria. Patients were required to have a urine protein to creatinine ratio of 1 or more and biopsy-proven lupus nephritis ISN/RPS class III, IV, or V. Induction therapy had to be initiated within 60 days before randomization and therapies had to include either: induction with glucocorticoids in combination with 1) mycophenolate mofetil (MMF) for induction followed by MMF for maintenance therapy, or 2) IV cyclophosphamide for induction followed by azathioprine (AZA) for maintenance therapy. The primary efficacy endpoint was Primary Efficacy Renal Response (PERR) at week 104, defined as a response at Week 100 confirmed by a repeat measurement at week 104 of the following parameters: urine protein:creatinine ratio (uPCR) less than or equal to 0.7 g/g and estimated glomerular filtration rate (eGFR) greater than or equal to 60 mL/min/1.73 m2 or no decrease in eGFR of greater than 20% from pre-flare value. The major secondary endpoints included Complete Renal Response (CRR) (defined as a response at week 100 confirmed by a repeat measurement at week 104 of the following parameters: uPCR less than 0.5 g/g and eGFR greater than or equal to 90 mL/min/1.73 m2 or no decrease in eGFR of greater than 10% from pre-flare value); PERR at week 52; and time to renal-related event or death (renal-related event defined as first event of end-stage renal disease, doubling of serum creatinine, renal worsening [defined by quantified increase in proteinuria and/or impaired renal function], or receipt of renal disease-related prohibited therapy due to inadequate lupus nephritis control or renal flare management). The proportion of patients achieving PERR at Week 104 was significantly higher in patients receiving Benlysta plus standard therapy compared with placebo plus standard therapy (43% vs 32%, p=0.031). The subgroup analysis of PERR and CRR by biopsy class indicated the odds ratios for patients with class 5 without combined class III or class IV favored placebo plus standard therapy over Benlysta plus standard therapy. The odds ratio for all other classes or combinations favored Benlysta plus standard therapy. Most of the secondary

endpoint were statistically significant (CRR at week 100 p=0.017 [30% vs 20% Benlysta vs placebo], PERR at week 52 p=0.025 [47% vs 35% Benlysta vs placebo]). The table below shows the time to renal related event or death.

End point	Placebo + standard therapy (n=223) No. (%)	Benlysta + standard therapy (n=223) No. (%)
Any Event	63 (28%)	35 (16%)
Death from any cause	2	1
Progression to ESRD	1	0
Doubling of creatinine level from baseline	1	1
Increased proteinuria, impaired kidney function, or both	39	17
Treatment failure related to kidney event	20	16

Lupkynis LN trial(9)

The safety and efficacy of Lupkynis were investigated in a 52-week, randomized, double-blind, placebo-controlled trial in patients with a diagnosis of systemic lupus erythematosus and with International Society of Nephrology/Renal Pathology Society (ISN/RPS) biopsy-proven active Class III or IV LN (alone or in combination with Class V LN) or Class V LN. A total of 357 patients with LN were randomized in a 1:1 ratio to receive either Lupkynis 23.7 mg twice daily or placebo. Patients in both arms received background treatment with MMF and corticosteroids.

The primary efficacy endpoint was the proportion of patients achieving complete renal response at week 52. In order to be considered a responder, the patient must not have received more than 10 mg prednisone for greater than or equal to 3 consecutive days or for greater than or equal to 7 days in total during weeks 44 through 52. Patients who received rescue medication or withdrew from the study were considered non-responders. A higher proportion of patients in the Lupkynis arm than the placebo arm achieved complete renal response at week 52 (Lupkynis 40.8% vs placebo 22.5%, p less than 0.001).

A higher proportion of patients in the Lupkynis arm than the placebo arm achieved complete renal response at week 24 (32.4% vs. 19.7%; odds ratio: 2.2;

	95% CI: 1.3, 3.7). Time to UPCR of less than or equal to 0.5 mg/mg was shorter in the Lupkynis arm than the placebo arm (median time of 169 days vs. 372 days; hazard ratio: 2.0; 95% CI: 1.5, 2.7).
Safety	Benlysta is contraindicated in patients that have experienced anaphylaxis with belimumab.(1) Lupkynis is contraindicated in the following:(9) • Patients concomitantly using strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin) because these medications can significantly increase exposure to Lupkynis which may increase the risk of acute and/or chronic nephrotoxicity • Patients who have a known serious or severe hypersensitivity reaction to Lupkynis or any of its excipients Lupkynis has a boxed warning due to the increased risk for developing malignancies and serious infections with Lupkynis or other immunosuppressants that may lead to hospitalization or death.(9)

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** All target agents are eligible for continuation of therapy 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR**

Module	Clinical Criteria for Approval
	B. BOTH of the following: 1. ONE of the following: A. The patient has a diagnosis of active systemic lupus erythematosus (SLE) disease WITHOUT active lupus nephritis (LN) AND BOTH of the following: 1. The requested agent is FDA labeled for SLE **AND** 2. BOTH of the following: A. ONE of the following: 1. The patient has tried and had an inadequate response to hydroxychloroquine **OR** 2. The patient has an intolerance or hypersensitivity to hydroxychloroquine **OR** 3. The patient has an FDA labeled contraindication to hydroxychloroquine **AND** B. ONE of the following: 1. The patient has tried and had an inadequate response to a corticosteroid OR an immunosuppressive (i.e., azathioprine, methotrexate, cyclophosphamide, mycophenolate) **OR** 2. The patient has an intolerance or hypersensitivity to a corticosteroid OR an immunosuppressive (i.e., azathioprine, methotrexate, cyclophosphamide, mycophenolate) **OR** 3. The patient has an FDA labeled contraindication to ALL corticosteroids AND immunosuppressives (i.e., azathioprine, methotrexate, cyclophosphamide, mycophenolate) **OR** B. The patient has a diagnosis of active lupus nephritis (LN) AND BOTH of the following: 1. The requested agent is FDA labeled for LN **AND** 2. The patient has Class III, IV, or V lupus nephritis confirmed via kidney biopsy **OR** C. The patient has another FDA labeled indication for the requested agent and route of administration **OR** D. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient's age is within FDA labeling for the requested indication for the requested agent and route of administration **OR** B. There is support for using the requested agent for the patient's age for the requested indication and route of administration **AND** 2. If the patient has a diagnosis of active systemic lupus erythematosus (SLE) disease WITHOUT active LN, then BOTH of the following: A. The patient is currently using standard SLE therapy (i.e., corticosteroids, hydroxychloroquine, azathioprine, methotrexate, cyclophosphamide, mycophenolate) **AND** B. The patient will continue standard SLE therapy (i.e., corticosteroids, hydroxychloroquine, azathioprine, methotrexate, cyclophosphamide, mycophenolate) in combination with the requested agent **AND** 3. If the patient has a diagnosis of active LN, the patient will be using the requested agent with background immunosuppressive lupus nephritis therapy (e.g., corticosteroids with mycophenolate or for Benlysta corticosteroids with mycophenolate or IV cyclophosphamide) **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., rheumatologist, nephrologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have severe active central nervous system lupus **AND** 6. If the requested agent is Benlysta, then BOTH of the following: A. The patient will NOT be using the requested agent in combination with Lupkynis **AND** B. ONE of the following (Please refer to "Agents NOT to be used Concomitantly" table): 1. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** 2. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: A. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agents **AND** B. There is support for the use of combination therapy (submitted copy of clinical trials, phase III studies, guidelines required) **AND** 7. If the requested agent is Lupkynis, the patient will NOT be using the requested agent in combination with cyclophosphamide, Benlysta, OR Saphnelo **AND** 8. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months

Module	Clinical Criteria for Approval
	***Note:** An initial loading dose is allowed for subcutaneous Benlysta and may require a Quantity Limit review. The loading dose may be approved for 1 month, followed by the maintenance dose for the remainder of the length of approval. NOTE: If Quantity Limit applies, please refer to Quantity Limit criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. ONE of the following: A. The patient has a diagnosis of active systemic lupus erythematosus (SLE) disease WITHOUT active lupus nephritis (LN) AND ALL of the following: 1. The requested agent is FDA labeled for SLE **AND** 2. The patient is currently using standard SLE therapy (i.e., corticosteroids, hydroxychloroquine, azathioprine, methotrexate, cyclophosphamide, mycophenolate) **AND** 3. The patient will continue standard SLE therapy (i.e., corticosteroids, hydroxychloroquine, azathioprine, methotrexate, cyclophosphamide, mycophenolate) **OR** B. The patient has a diagnosis of active lupus nephritis (LN) AND ALL of the following: 1. The requested agent is FDA labeled for LN **AND** 2. The patient is currently using background lupus nephritis therapy (e.g., corticosteroids with mycophenolate or for Benlysta corticosteroids with mycophenolate or IV cyclophosphamide) **AND** 3. The patient will continue background lupus nephritis therapy (e.g., corticosteroids with mycophenolate or for Benlysta corticosteroids with mycophenolate or IV cyclophosphamide) **OR** C. The patient has a diagnosis other than active SLE OR active LN **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., rheumatologist, nephrologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have severe active central nervous system lupus **AND** 6. If the requested agent is Benlysta, then BOTH of the following:

Module	Clinical Criteria for Approval
	A. The patient will NOT be using the requested agent in combination with Lupkynis **AND** B. ONE of the following (Please refer to "Agents NOT to be used Concomitantly" table): 1. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** 2. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: A. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agents **AND** B. There is support for the use of combination therapy (submitted copy of clinical trials, phase III studies, guidelines required) **AND** 7. If the requested agent is Lupkynis, the patient will NOT be using the requested agent in combination with cyclophosphamide, Benlysta, OR Saphnelo **AND** 8. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval**: up to 12 months **Note:** If approving initial loading dose for subcutaneous Benlysta, approve the loading dose for 1 month, followed by maintenance dosing for the remainder of the length of approval.

CONTRAINDICATION AGENTS

Contraindicated as Concomitant Therapy
Agents NOT to be used Concomitantly Abrilada (adalimumab-afzb) Actemra (tocilizumab) Adalimumab Adbry (tralokinumab-ldrm) Amjevita (adalimumab-atto) Arcalyst (rilonacept) Avsola (infliximab-axxq) Benlysta (belimumab) Bimzelx (bimekizumab-bkzx) Cibinqo (abrocitinib) Cimzia (certolizumab) Cinqair (reslizumab) Cosentyx (secukinumab) Cyltezo (adalimumab-adbm) Dupixent (dupilumab) Enbrel (etanercept) Entyvio (vedolizumab) Fasenra (benralizumab) Hadlima (adalimumab-bwwd) Hulio (adalimumab-fkjp) Humira (adalimumab) Hyrimoz (adalimumab-adaz) Idacio (adalimumab-aacf) Ilaris (canakinumab)

Contraindicated as Concomitant Therapy
Ilumya (tildrakizumab-asmn)
Inflectra (infliximab-dyyb)
Infliximab
Kevzara (sarilumab)
Kineret (anakinra)
Leqselvi (deuruxolitinib)
Litfulo (ritlecitinib)
Nemluvio (nemolizumab-ilto)
Nucala (mepolizumab)
Olumiant (baricitinib)
Omvoh (mirikizumab-mrkz)
Opzelura (ruxolitinib)
Orencia (abatacept)
Otezla (apremilast)
Pyzchiva (ustekinumab-ttwe)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rinvoq (upadacitinib)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Saphnelo (anifrolumab-fnia)
Selarsdi (ustekinumab-aekn)
Siliq (brodalumab)
Simlandi (adalimumab-ryvk)
Simponi (golimumab)
Simponi ARIA (golimumab)
Skyrizi (risankizumab-rzaa)
Sotyktu (deucravacitinib)
Spevigo (spesolimab-sbzo) subcutaneous injection
Stelara (ustekinumab)
Taltz (ixekizumab)
Tezspire (tezepelumab-ekko)
Tofidence (tocilizumab-bavi)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tyenne (tocilizumab-aazg)
Tysabri (natalizumab)

Contraindicated as Concomitant Therapy
Velsipity (etrasimod)
Wezlana (ustekinumab-auub)
Xeljanz (tofacitinib)
Xeljanz XR (tofacitinib extended release)
Xolair (omalizumab)
Yuflyma (adalimumab-aaty)
Yusimry (adalimumab-aqvh)
Zeposia (ozanimod)
Zymfentra (infliximab-dyyb)

Lyrica and Savella

Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
LYRICA® (pregabalin)* Capsule Oral solution	Neuropathic pain associated with diabetic peripheral neuropathy (DPN) Postherpetic neuralgia (PHN) Adjunctive therapy for the treatment of partial-onset seizures in patients 1 month of age and older Fibromyalgia Neuropathic pain associated with spinal cord injury	*generic available	1
LYRICA® CR (pregabalin ER)* Tablet	The management of: • neuropathic pain associated with diabetic peripheral neuropathy (DPN) • postherpetic neuralgia (PHN) Efficacy of LYRICA CR has not been established for the management of fibromyalgia or as adjunctive therapy for adult patients with partial onset seizures.	*generic available	9
Savella® (milnacipran) Tablet Titration pack	Management of fibromyalgia Savella is not approved for use in pediatric patients.		2

CLINICAL RATIONALE

Fibromyalgia	Fibromyalgia is a chronic condition with unknown etiology. It is characterized by generalized body pain, fatigue, sleep disturbance, impaired cognition, and anxiety. Diagnosis is often made by exclusion of other conditions such as neurological syndromes and depression. There is no clear specific pathophysiological therapeutic target. Various guidelines for treatment exist and they are not in agreement. There has been an increased focus on non-pharmacologic therapies discussed in the guidelines, however, pharmacology remains the mainstay of therapy. Pharmacologic therapy varies, including classical analgesics, antidepressants, and anticonvulsants. Commonly used agents include tricyclic antidepressants (TCAs), pregabalin, gabapentin, serotonin and norepinephrine reuptake inhibitors (SNRI), selective serotonin reuptake inhibitors (SSRI), tramadol, and cyclobenzaprine.(3)
Neuropathic Pain	**Diabetic Peripheral Neuropathy** Diabetic peripheral neuropathy (DPN) develops as a late manifestation of uncontrolled or long-standing diabetes. DPN patients may develop distal symmetric polyneuropathy (DSPN), which is characterized by burning pain, paresthesias, and numbness that follows a stocking-glove pattern and progresses proximally. Poorly controlled blood glucose levels, especially greater variation in glucose levels, contribute to the occurrence and severity of painful DPN.(5) DSPN is the most important cause of foot ulceration and a prerequisite to the development of Charcot neuroarthropathy (CN), which are both recognized as late complications of DSPN. The late complications also drive amputation risk and economic costs of diabetic neuropathy and are also predictors of mortality. DSPN is also a major contributor to falls and fractures.(4) Due to lack of treatments that target the underlying nerve damage, prevention is the key component of diabetes care. Prevention of diabetic neuropathies focuses on glucose control and lifestyle modifications, which includes dietary modifications and exercise. For patients with diabetic neuropathy, foot care is important to prevent ulceration, infection, and amputation.(4) There are several pharmacological options for DPN. The American Diabetes Association (ADA) and American Academy of Family Physicians (AAFP) recommend use of pregabalin and duloxetine as first-line therapy for painful diabetic neuropathy. The ADA recommends gabapentin as the alternative first-line agent, though AAFP considers it a first-line therapy.(4,5) Other treatment options include antidepressants (e.g., amitriptyline, nortriptyline, desipramine, imipramine, venlafaxine), anticonvulsants (e.g. lamotrigine, topiramate, valproate), and topical agents (e.g., capsaicin cream, lidocaine 5%

	patch).(4,5) Tramadol has been shown to be effective in the treatment of DPN. Although tramadol has a lower potential for abuse compared with other opioids, given the safety concern it is not recommended as first or second-line treatment.(4) **Postherpetic Neuralgia** Postherpetic neuralgia (PHN), the most common complication of herpes zoster, is defined as pain in a dermatomal distribution that is sustained for at least 90 days after the rash. It occurs in approximately 20% of patients with herpes zoster, and 80% of cases occur in patients 50 years or older. PHN is caused by nerve damage secondary to an inflammatory response induced by viral replication within a nerve.(6) Gabapentin, pregabalin, and the TCAs are considered first-line therapies, along with the topical therapies of lidocaine and capsaicin. Tramadol is considered a third-line option.(6) The European consensus guideline on the management of herpes zoster recommends tricyclic antidepressants, gabapentin, or pregabalin for pain relief.(10) **Neuropathic Pain due to Spinal Cord Injury** Spinal cord injury (SCI) is an injury to the spinal cord that leads to varying degrees of motor and/or sensory deficits and paralysis. Chronic neuropathic pain is common and contributes to reduced quality of life. First-line drugs commonly used are amitriptyline, gabapentin, and pregabalin. Alternative agents are tramadol and duloxetine.(7)
Seizure Disorders	The occurrence of a single seizure does not always require initiation of antiepileptic drugs (AEDs). In the absence of risk factors, physicians should consider delaying used of AEDs until a second seizure occurs. Treatment should begin with monotherapy.(8) LYRICA has FDA approval for adjunctive therapy for the treatment of partial-onset seizures in patients 1 month of age and older.(1)
Safety	LYRICA and LYRICA CR are contraindicated in patients with a known hypersensitivity to pregabalin or any of its components.(1,9) Savella has the following contraindications:(2) • Do not use MAOIs intended to treat psychiatric disorders with Savella or within 5 days of stopping treatment with Savella • Do not use Savella within 14 days of stopping an MAOI intended to treat psychiatric disorders

	• Do not start Savella in a patient who is being treated with linezolid or intravenous methylene blue Savella carries a boxed warning for suicidality and antidepressant drugs.(2) • Increased risk of suicidal ideation, thinking, and behavior in children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders • Savella is not approved for use in pediatric patients

REFERENCES

Number	Reference
1	LYRICA prescribing information. Parke-Davis Div of Pfizer. June 2020.
2	Savella prescribing information. Allergan, Inc. September 2023.
3	Kia S, Choy E. Update on Treatment Guideline in Fibromyalgia Syndrome with Focus on Pharmacology. *Biomedicines.* 2017;5(2):20. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5489806/
4	Pop-Busui R, Boulton AJM, Feldman EL, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care.* 2017;40(1):136-154. https://care.diabetesjournals.org/content/40/1/136.
5	Snyder MJ, Gibbs LM, Lindsay TJ. Treating Painful Diabetic Peripheral Neuropathy: An Update. *Am Fam Physician*. 2016;94(3):227-234. https://www.aafp.org/afp/2016/0801/p227.html.
6	Saguil A, Kane S, Mercado M, Lauters R. Herpes Zoster and Postherpetic Neuralgia: Prevention and Management. *Am Fam Physician* 2017;96(10):656-663. https://www.aafp.org/afp/2017/1115/p656.html.
7	Hagen EM, Rekand T. Management of Neuropathic Pain Associated with Spinal Cord Injury. *Pain Ther* 2015;4(1):51-65. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4470971/#__ffn_sectitle.
8	Liu G, Slater N, Perkins A. Epilepsy: Treatment Options. *American Family Physician.* 2017; 95(2):87-96. https://www.aafp.org/afp/2017/0715/p87.html

Number	Reference
9	LYRICA CR prescribing information. Parke-Davis Div of Pfizer. June 2020.
10	Werner RN, Nikkels AF, Marinovic B, et. al. "European consensus-based (S2k) Guideline on the Management of Herpes Zoster - guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV), Part 2: Treatment. *Journal of the European Academy of Dermatology and Venereology*. 2017,31, 20-29. doi: 10.1111/jdv.13957

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Metformin ER

Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Glumetza® (metformin ER modified release)* Tablet	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.	*- generic available	1
metformin HCL Tab ER Osmotic	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.		3

CLINICAL RATIONALE

Diabetes	The American Diabetes Association (ADA) state the following concerning metformin:(2) • First-line therapy depends on comorbidities, patient-centered treatment factors, and management needs and generally includes metformin and comprehensive lifestyle modifications. • Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits.
Safety	Metformin products have the following black box warning: • Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL.

	• Risk factors include renal impairment, concomitant use of certain drugs, age greater than or equal to 65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. • If lactic acidosis is suspected, discontinue metformin product and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. Metformin products carry the following contraindications: • Severe renal impairment: (eGFR below 30 mL/minute/1.73 m^2) • Known hypersensitivity to metformin • Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma

REFERENCES

Number	Reference
1	Glumetza prescribing information. Salix Pharmaceuticals. August 2019.
2	American Diabetes Association. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2022. Available at: https://diabetesjournals.org/care/issue/45/Supplement_1
3	Metformin ER Osmotic prescribing information. AiPing Pharmaceutical, Inc. February 2019.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	2. Information has been provided to support therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Multiple Sclerosis Agents

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Aubagio® (teriflunomide)* Tablet	Treatment of patients with relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	*generic equivalent available	1
Avonex® (interferon β-1a) Injection for intramuscular use	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults		2
Bafiertam® (monomethyl fumarate) Delayed-release capsule	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults		3
Betaseron® (interferon β-1b) Injection for subcutaneous use	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults		4
Copaxone® (glatiramer acetate)* Injection for subcutaneous use	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	*generic equivalent available	5
Extavia® (interferon β-1b)	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults		6

Agent(s)	FDA Indication(s)	Notes	Ref#
Injection for subcutaneous use			
Gilenya® (fingolimod)* Capsule	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in patients 10 years of age and older	*generic equivalent available	7
Glatopa® (glatiramer acetate) Injection for subcutaneous use	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults		8
Kesimpta® (ofatumumab) Injection for subcutaneous use	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults		9
Mavenclad® (cladribine) Tablet	Treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease in adults Because of its safety profile, use of Mavenclad is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternative drug indicated for the treatment of MS Limitation of Use: Mavenclad is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile		10
Mayzent® (siponimod) Tablet	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults		11

Agent(s)	FDA Indication(s)	Notes	Ref#
Plegridy® (peginterferon β-1a) Injection for subcutaneous use or intramuscular use	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults		12
Ponvory® (ponesimod) Tablet	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults		27
Rebif® (interferon β-1b) Injection for subcutaneous use	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults		13
Tascenso® (fingolimod) Oral disintegrating tablet	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in patients 10 years of age and older		29
Tecfidera® (dimethyl fumarate)* Capsule	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults	*generic equivalent available	14
Vumerity® (diroximel fumarate) Delayed-release capsule	Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults		15

CLINICAL RATIONALE

Multiple sclerosis	Multiple sclerosis (MS) is a disorder of the central nervous system (CNS) characterized by demyelization, inflammation, and degenerative changes. Most people with MS experience relapses and remissions of neurological symptoms, particularly early in the disease, and clinical events are usually associated with areas of CNS inflammation. Gradual worsening or progression, with or without subsequent acute attacks of inflammation or radiological activity, may take place early, but usually becomes more prominent over time. While traditionally viewed as a disease solely of CNS white matter, more advanced imaging techniques have demonstrated significant early and ongoing CNS gray matter damage as well.(16) Those diagnosed with MS may have many fluctuating and disabling symptoms (including, but not limited to, fatigue, pain, bladder and bowel issues, sexual dysfunction, movement and coordination problems, visual disturbances, and cognition and emotional changes.(30) There are currently four major types of MS: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS).(23)
Relapsing remitting multiple sclerosis (RRMS)	RRMS is characterized by clearly defined attacks (relapses) of new or increasing neurologic symptoms. These relapses are followed by periods of partial or complete recovery. There is no or minimal disease progression during the periods between disease relapses, though individual relapses may result in severe residual disability. The course of MS varies, however, about 85-90% of individuals with MS demonstrate a relapsing pattern at onset, which transitions over time in the majority of untreated patients to a pattern of progressive worsening with few or no relapses or MRI activity.(23)
Secondary progressive multiple sclerosis (SPMS)	SPMS begins as RRMS, but over time the disease enters a stage of steady deterioration in function, unrelated to acute attacks. Most people with RRMS will transition to SPMS. In SPMS there is no progressive worsening of symptoms over time with no definite periods of remission.(23)
2017 McDonald Criteria for the diagnosis of Multiple Sclerosis:	Diagnostic criteria for multiple sclerosis combining clinical, imaging, and laboratory evidence have evolved over time. The increasing incorporation of paraclinical assessments, especially imaging, to supplement clinical findings has allowed earlier, more sensitive, and more specific diagnosis.(21,22) The diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in the CNS in space and time.(21) Misdiagnosis of multiple sclerosis remains an issue in clinical practice, and several factors that potentially increase this risk have been identified. Multiple sclerosis has heterogeneous clinical and imaging manifestations, which differ

between patients over time. There is no single pathognomonic clinical feature or diagnostic test; diagnosis of multiple sclerosis relies on the integration of clinical, imaging, and laboratory findings. MRI abnormalities associated with other diseases and non-specific MRI findings, which are common in the general population, can be mistaken for multiple sclerosis. The increasingly strong focus on timely diagnosis to alleviate uncertainty for patients and allow initiation of disease-modifying therapies might also increase the risk of misdiagnosis.(21)

With increasing availability and use of MRI, incidental T2 hyperintensities on brain imaging are common, the subset of individuals with MRI findings that are strongly suggestive of multiple sclerosis lesions but with no neurological manifestations or other clear-cut explanation are said to have radiologically isolated syndrome. There is no consensus on whether patients with radiologically isolated syndrome will develop MS. Some practitioners argue that these patients have a high likelihood of developing MS while others argue that up to two-thirds of these patients will not receive a diagnosis of MS in 5 years. A consensus panel decided to require clinical manifestations to make the diagnosis of MS (2017 McDonald Criteria for the diagnosis of Multiple Sclerosis).(21)

The 2017 McDonald criteria to diagnose MS is shown in the chart below.(21,22)

Clinical Presentation	**Additional Data needed to make MS diagnosis**
In a person with a typical attack/CIS at onset	
Greater than or equal to 2 attacks and objective clinical evidence of greater than or equal to 2 lesions OR Greater than or equal to 2 attacks and objective clinical evidence of 1 lesion with historical evidence of prior attack involving lesion in different location	None. Dissemination in space* and dissemination in time** have been met
Greater than or equal to 2 attacks and objective clinical evidence of 1 lesion	**ONE** of these criteria: Additional clinical attack implicating different CNS site OR

		Greater than or equal to 1 symptomatic or asymptomatic MS-typical T2 lesions in greater than or equal to 2 areas of CNS: periventricular, juxtacortical/cortical, infratentorial, or spinal cord
	1 attack and objective clinical evidence of greater than or equal to 2 lesions	**ONE** of these criteria: Additional clinical attack OR Simultaneous presence of both enhancing and non-enhancing symptomatic or asymptomatic MS-typical MRI lesions OR New T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) OR CSF specific (i.e., not in serum) oligoclonal bands
	1 attack and objective clinical evidence of 1 lesion	**ONE** of these criteria: Additional attack implicating different CNS site OR Greater than or equal to 1 MS-Typical symptomatic or asymptomatic T2 lesions in greater than or equal to 2 areas of CNS: periventricular, juxtacortical/cortical, infratentorial, or spinal cord **AND** **ONE** of these criteria: Additional clinical attack OR Simultaneous presence of both enhancing and non-enhancing symptomatic or asymptomatic MS-typical MRI lesions OR

	New T2 enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) OR CSF-specific (i.e., not in serum) oligoclonal bands *Dissemination in space is defined as one or more T2-hyperintense lesions that are characteristic of multiple sclerosis in 2 or more of four areas of the CNS (periventricular, cortical or juxtacortical, and infratentorial brain regions, and the spinal cord) demonstrated by an additional clinical attack implicating a different CNS site or by MRI.(21) **Dissemination in time is defined as simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI. The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.(21)
Treatment of MS	Both the Multiple Sclerosis Coalition and the American Academy of Neurology recommend initiating treatment with a DMA FDA approved for the patient's phenotype as soon as possible following the diagnosis of multiple sclerosis. There are several DMAs with at least 10 mechanisms of action available to people with MS. The factors affecting choice of therapy at any point in the disease course are complex and most appropriately analyzed and addressed through a shared decision-making process between the individual and the treating clinician.(16,19) The Multiple Sclerosis Coalition recommends that clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, natalizumab or ocrelizumab for newly diagnosed individuals with highly active MS. Clinicians should also consider prescribing a high efficacy medication for individuals who have breakthrough activity on another DMA regardless of the number of previously used agents.(16) The American Academy of Neurology has recommended alemtuzumab, fingolimod, and natalizumab as options for patients with MS with highly active MS. There lacks a consensus for what constitutes as highly active MS, however.(19) The National Institute for Health and Care Excellence (NICE) defines rapidly evolving severe RRMS as two or more disabling relapses in 1 year, and one or more gadolinium-enhancing

	lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.(31) Lack of response to DMAs is hard to define, as most patients with MS are not free of all disease activity. Relapses or new MRI detected lesions may develop after initiation of a DMA and before the treatment becomes effective for patients. When determining efficacy, sufficient time for the DMA therapy to take full effect and patient adherence are important considerations. Evidence of one or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination while being treated with a DMA for a 1 year period suggests a sub-optimal response, an alternative regimen (e.g., different mechanism of action) should be considered to optimize therapeutic benefit.(18) A National MS Society consensus statement recommends changing from one disease modifying therapy to another only for medically appropriate reasons (e.g., lack of efficacy, adverse effects, or if better treatments options become available).(16) Existing MS therapies are partly effective in halting ongoing inflammatory tissue damage and clinical progression. MS pathogenesis is complex and probably heterogeneous among patient, suggesting that combination therapy strategies that target a range of disease mechanisms might be more effective than medications used as monotherapy. Although preliminary studies have provided favorable results, however, several subsequent large, randomized, controlled trials have had negative of conflicting results. There also may be more adverse reactions associated with combination therapies due to the additive effect.(24) In 2020 a Canadian MS working group published recommendations on optimal therapy in relapsing forms of MS. This group notes that there are few studies that have directly compared injectable and oral DMTs. A recent network meta-analysis suggested that pegylated interferon-β-1a and dimethyl fumarate have superior efficacy to other base therapies, there are insufficient data to demonstrate that one base injectable or oral DMT is superior to another. As a result, the choice of initial treatment will need to be individualized according to disease activity, severity, and comorbidities.(25) In addition to base therapies, the working group considers 5 DMTs to be of higher efficacy which although can be used as initial therapy, they are generally reserved for patients with a poor response or tolerability with a base therapy. Patients presenting with high disease activity or aggressive/rapidly evolving MS at onset could be considered to initiate therapy with one of these more effective therapies, but the most common treatment initiation is to start on a base therapy

with the view of switching within 6-12 months. The 5 agents considered to be of higher efficacy are:(25)

- Oral agents
  - Fingolimod
  - Cladribine
- Monoclonal antibodies
  - Natalizumab
  - Ocrelizumab
  - Alemtuzumab

The MS working group discussed the criteria for switching therapies in RRMS and recommends a change in DMT is indicated for patients who meet any of the Major criteria below:(25)

	Minor	**Major**
Relapse rate	• One relapse in first 2 years of treatment	• Greater than or equal to 2 relapses in first year of treatment
Severity	• Mild • No functional impairment (school, work, daily activities, etc.) • No motor/cerebellar/brain stem /sphincter involvement	• Moderate to severe • Functional impairment • Motor/cerebellar/brain stem/sphincter involvement
Recovery	• Full recovery at 6 months • No functional impairment • EDSS change from baseline less than or equal to 1 point at 6 months unless	• Incomplete recovery • Functional impairment • If EDSS at baseline was 0 then greater than a 1.5 point change from baseline • If EDSS greater than 0 but less than or equal to 5.5 at baseline then

	baseline EDSS greater than 5.5	greater than 1 point change at 6 months • If EDSS greater than 5.5 any change would be a major concern
MRI	• One new lesion	• Greater than or equal to 3 new lesions during treatment excluding spinal cord lesions • Greater than 1 spinal cord lesion

The workgroup does note that on-treatment relapses should only be performed once the drug has achieved a full clinical effect (typically 2-6 months after drug initiation). Relapses that occur before the maximal efficacy of the drug has been reached should be given less weight, but major criteria should take precedence regardless of timing.(25)

For patients with SPMS the workgroup states that is generally advised to continue with the current DMT after onset of SPMS since many patients will have ongoing inflammatory disease and subclinical disease activity may worsen if treatment is withdrawn. A change in treatment may be warranted in patients with active SPMS who continue to have relapses or new MRI lesions, with the caveat that there is insufficient evidence to identify criteria for a suboptimal response in patients with SPMS.(25)

For patients with primary progressive MS clinicians should offer ocrelizumab to patients with active disease provided the benefits outweigh the risks. Caution is recommended when considering treatment for PPMS subgroups that are less likely to benefit from treatment, such as older patients, those with long-standing stable disease, and/or significant neurological deficits, since the limited benefits may not justify the risk associated with treatment. Rituximab may be considered as an alternative therapy for PPMS in regions that permit off-label use in MS due to cost or other considerations.(25)

The Institute for Clinical and Economic Review (ICER) evaluated a new IV treatment, ublituximab against current FDA and accepted use DMT for adults

with RRMS. Only in the case of ublituximab vs placebo/no DMT is ublituximab superior rated. The ratings are noted below.(17)

Adults with RRMS

Treatment	Comparator	Evidence Rating
Ublituximab	Natalizumab	I: Insufficient
	Ofatumumab	I: Insufficient
	Ocrelizumab	I: Insufficient
	Rituximab	I: Insufficient
	Fumarate class (dimethyl, diroximel, monomethyl)	C++: comparable or better
	Fingolimod	C++: comparable or better
	Ozanimod	C++: comparable or better
	Ponesimod	C++: comparable or better
	Siponimod	I: Insufficient
	Teriflunomide	B: Incremental
	Placebo/no DMT	A: Superior

A: Superior - High certainty of a substantial (moderate-large) net health benefit
B: Incremental - High certainty of a small net health benefit
C++: Comparable or better - Moderate certainty of a comparable, small, or substantial net health benefit, with which certainty of at least a comparable net health benefit
I: Insufficient - Any situation where the level of certainty in the evidence is low

	ICER does note that payors should consider the following:(17) • Payors should remove barriers to access to rituximab for RMS patients who are appropriate candidates for this therapy. This includes coverage of biosimilar rituximab with little or no prior authorization given the lack of concern regarding use in appropriate patients and how inexpensive it is compared with other monoclonal antibodies of equal effectiveness • Payors should not unilaterally implement policies to switch RMS patients who are stable on their chosen DMT over to lower-cost biosimilar rituximab

Safety	• **Aubagio** (teriflunomide) has a boxed warning with the following:(1)
	  ○ Hepatotoxicity: clinically significant and potentially life-threatening liver injury, including acute liver failure requiring transplant, has been reported in patients treated with Aubagio in the post marketing setting. Concomitant use of Aubagio with other hepatotoxic drugs may increase the risk of severe liver injury. Obtain transaminase and bilirubin levels within 6 months before initiation of Aubagio and monitor ALT levels at least monthly for six months. If drug induced liver injury is suspected, discontinue Aubagio and start accelerated elimination procedure
	  ○ Embryofetal toxicity: teratogenicity and embryolethality occurred in animals administered teriflunomide. Exclude pregnancy prior to initiating Aubagio therapy. Advise use of effective contraception in females of reproductive potential during treatment and during an accelerated drug elimination procedure. Stop Aubagio and use an accelerated drug elimination procedure if the patient becomes pregnant
	• **Aubagio** (teriflunomide) is contraindicated in:(1)
	  ○ Severe hepatic impairment
	  ○ Pregnant women and females of reproductive potential not using effective contraception. Aubagio may cause fetal harm
	  ○ Hypersensitivity reaction to teriflunomide, leflunomide, or any of the inactive ingredients in Aubagio
	  ○ Coadministration with leflunomide
	• **Avonex** (interferon β-1a) is contraindicated in:(2)
	  ○ History of hypersensitivity to natural or recombinant interferon beta, albumin or any other component of the formulation
	• **Bafiertam** (monomethyl fumarate) is contraindicated in:(3)

	○ Known hypersensitivity to monomethyl fumarate, dimethyl fumarate, diroximel fumarate, or any of the excipients of Bafiertam ○ Co-administration with dimethyl fumarate or diroximel fumarate • **Betaseron** (interferon β-1b) is contraindicated in:(4) ○ History of hypersensitivity to natural or recombinant interferon beta, albumin or mannitol • **Copaxone** (glatiramer) is contraindicated in:(5) ○ Known hypersensitivity to glatiramer acetate or mannitol • **Extavia** (interferon β-1b) is contraindicated in:(6) ○ History of hypersensitivity to natural or recombinant interferon beta, albumin (human), or mannitol • **Gilenya** (fingolimod) is contraindicated in:(7) ○ Recent myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure with hospitalization, or Class III/IV heart failure ○ History of Mobitz Type II 2nd degree or 3rd degree AV block or sick sinus syndrome, unless patient has a pacemaker ○ Baseline QTc interval greater than or equal to 500 msec ○ Treatment with Class Ia or Class III anti-arrhythmic drugs ○ Hypersensitivity to fingolimod or its excipients • **Glatopa** (glatiramer) is contraindicated in:(8) ○ Known hypersensitivity to glatiramer acetate or mannitol • **Kesimpta** (ofatumumab) is contraindicated in:(9) ○ Active HBV infection • **Mavenclad** (cladribine) contains a boxed warning with the following:(10) ○ Malignancies: Mavenclad may increase the risk of malignancy. Mavenclad is contraindicated in patients with current malignancy; evaluate the benefits and risks on an individual basis for patients with prior or increased risk of malignancy ○ Risk of teratogenicity: Mavenclad is contraindicated for use in pregnant women and in women and men of reproductive potential who do not plan to use effective contraception because of the risk of fetal harm • **Mavenclad** (cladribine) is contraindicated in:(10) ○ Patients with current malignancy ○ Pregnant women, and women and men of reproductive potential who do not plan to use effective contraception during Mavenclad dosing and for 6 months after the last dose in each treatment course ○ HIV infection

	○ Active chronic infections (e.g., hepatitis or tuberculosis) ○ History of hypersensitivity to cladribine ○ Women intending to breastfeed on a Mavenclad treatment day and for 10 days after the last dose • **Mayzent** (siponimod) is contraindicated in:(11) ○ Patients with a CYP2C9 *3/*3 genotype ○ Patients who in the last 6 months have experienced: myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization, or Class III/IV heart failure ○ Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker • **Plegridy** (peginterferon β-1a) is contraindicated in:(12) ○ History of hypersensitivity to natural or recombinant interferon beta or peginterferon, or any other component of Plegridy • **Ponvory** (ponesimod) is contraindicated in:(27) ○ Patients who in the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure ○ Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker • **Rebif** (interferon β-1a) is contraindicated in:(13) ○ History of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation • **Tascenso ODT** (fingolimod) is contraindicated in:(29) ○ Recent myocardial infarction, unstable angina, stroke, TIA, decompensated heart failure requiring hospitalization or Class III/IV heart failure ○ History or presence of Mobitz Type II second-degree or third-degree AV block or sick sinus syndrome, unless patient has a functioning pacemaker ○ Baseline QTc interval greater than or equal to 500 msec ○ Cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti-arrhythmic drugs ○ Hypersensitivity reaction to fingolimod or any of the excipients in Tascenso ODT. Observed reactions include rash, urticaria, and angioedema ○ Concomitant use with other products containing fingolimod • **Tecfidera** (dimethyl fumarate) is contraindicated in:(14)

	○ Known hypersensitivity to dimethyl fumarate or any of the excipients of Tecfidera • **Vumerity** (diroximel fumarate) is contraindicated in:(15) ○ Known hypersensitivity to diroximel fumarate, dimethyl fumarate, or to any of the excipients of Vumerity ○ Co-administration with dimethyl fumarate

REFERENCES

Number	Reference
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2	Avonex prescribing information. Biogen, Inc. July 2023.
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4	Betaseron prescribing information. Bayer HealthCare Pharmaceuticals, Inc. July 2023.
5	Copaxone prescribing information. Teva Neuroscience, Inc. February 2023.
6	Extavia prescribing information. Novartis Pharmaceuticals Corporation. July 2023.
7	Gilenya prescribing information. Novartis Pharmaceuticals Corporation. August 2023.
8	Glatopa prescribing information. Sandoz Inc. March 2023.
9	Kesimpta prescribing information. Novartis Pharmaceuticals Corporation. September 2022.
10	Mavenclad prescribing information. EMD Serono, Inc. September 2022.
11	Mayzent prescribing information. Novartis Pharmaceuticals Corporation. August 2023.
12	Plegridy prescribing information. Biogen, Inc. July 2023.
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Number	Reference
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Number	Reference
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29	Tascenso prescribing information. Handa Neuroscience, LLC. December 2022.
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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td>Mavenclad</td><td>Initial Evaluation
<table>
<tr><th>FDA Labeled Indication</th><th>FDA Approved Agent(s)</th></tr>
<tr><td>Clinically Isolated Syndrome (CIS)</td><td>Aubagio, Avonex, Bafiertam, Betaseron, Copaxone, Extavia, Gilenya, Glatopa, Kesimpta, Mayzent, Plegridy, Ponvory, Rebif, Tascenso ODT, Tecfidera, Vumerity</td></tr>
<tr><td>Relapsing Remitting Multiple Sclerosis (RRMS)</td><td>Aubagio, Avonex, Bafiertam, Betaseron, Copaxone, Extavia, Gilenya, Glatopa, Kesimpta, Mavenclad, Mayzent, Plegridy, Ponvory, Rebif, Tascenso ODT, Tecfidera, Vumerity</td></tr>
<tr><td>Active Secondary Progressive Multiple Sclerosis (SPMS)</td><td>Aubagio, Avonex, Bafiertam, Betaseron, Copaxone, Extavia, Gilenya, Glatopa, Kesimpta, Mavenclad, Mayzent, Plegridy,</td></tr>
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Module	Clinical Criteria for Approval

	Ponvory, Rebif, Tascenso ODT, Tecfidera, Vumerity

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Agents Eligible for Continuation of Therapy
Mavenclad (cladribine)

      1. The patient has been treated with the requested agent within the past 90 days **OR**
      2. The prescriber states the patient has been treated with the requested agent within the past 90 days AND the patient is at risk if therapy is changed **OR**

   B. BOTH of the following:
      1. The patient has ONE of the following relapsing forms of multiple sclerosis (MS):
         A. Relapsing-remitting disease (RRMS) **OR**
         B. Active secondary progressive disease (SPMS) **AND**
      2. If the patient has an FDA labeled indication, then ONE of the following:
         A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**
         B. There is support for using the requested agent for the patient's age for the requested indication **AND**
2. If the patient has been previously treated with the requested agent, BOTH of the following:
   A. The prescriber has provided the number of courses the patient has completed (one course consists of 2 cycles of 4-5 days each) **AND**
   B. The patient has NOT completed 2 courses of the requested agent (one course consists of 2 cycles of 4-5 days each) **AND**
3. A complete CBC with differential including lymphocyte count has been performed **AND**
4. The lymphocyte count is within normal limits **AND**
5. The prescriber is a specialist in the area of the patient's diagnosis (i.e., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**

Module	Clinical Criteria for Approval
	6. ONE of the following: A. The patient will NOT be using the requested agent with an additional disease modifying agent (DMA) for the requested indication **OR** B. BOTH of the following: 1. The patient is currently using the requested agent **AND** 2. There is support for the use of the additional DMA (e.g., relapse between cycles) **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 8. The requested quantity (dose) does NOT exceed the FDA labeled maximum dose based on the patient's weight **Length of Approval:** 36 weeks for new starts OR if patient is currently taking the requested agent, approve for remainder of the annual course (1 course consists of 2 cycles of 4-5 days) NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. A complete CBC with differential including lymphocyte count has been performed **AND** 4. The patient has a lymphocyte count of at least 800 cells/microliter **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (i.e., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. ONE of the following: A. The patient will NOT be using the requested agent in combination with an additional disease modifying agent (DMA) for the requested indication **OR** B. There is support for the use of the additional DMA (e.g., relapse between cycles) **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 8. It has been at least 35 weeks but not more than 67 weeks since the last dose of the requested agent **AND**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>9. BOTH of the following:
A. The prescriber has provided the number of courses the patient has completed (one course consists of 2 cycles of 4-5 days each) AND
B. The patient has NOT completed 2 courses with the requested agent (one course consists of 2 cycles of 4-5 days each) AND
10. The requested dose does NOT exceed the maximum FDA labeled dose for the patient's weight

Length of Approval: 3 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.</td></tr>
<tr><td>MS Agents other than Mavenclad</td><td>
<table>
<tr><th>Preferred Agent(s)</th><th>Non-Preferred Agent(s)</th></tr>
<tr><td>Avonex (interferon β-1a)
Betaseron (interferon β-1b)
dimethyl fumarate
fingolimod
glatiramer
Glatopa (glatiramer)
Kesimpta (ofatumumab)
Mavenclad (cladribine)
Mayzent (siponimod)
Plegridy (peginterferon β-1a)
Rebif (interferon β-1a)
teriflunomide
Vumerity (diroximel fumarate)
Zeposia (ozanimod)**</td><td>Aubagio (teriflunomide)*
Bafiertam (monomethyl fumarate)
Copaxone (glatiramer)*
Extavia (interferon β-1b)
Gilenya (fingolimod)*
Ponvory (ponesimod)
Tascenso ODT (fingolimod)
Tecfidera (dimethyl fumarate)*</td></tr>
</table>
*generic available
**target in a different program

<table>
<tr><th>FDA Labeled Indication</th><th>FDA Approved Agent(s)</th></tr>
<tr><td>Clinically Isolated Syndrome (CIS)</td><td>Aubagio, Avonex, Bafiertam, Betaseron, Copaxone, Extavia, Gilenya, Glatopa, Kesimpta, Mayzent,</td></tr>
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</td></tr>
</table>

Module	Clinical Criteria for Approval

	Plegridy, Ponvory, Rebif, Tascenso ODT, Tecfidera, Vumerity
Relapsing Remitting Multiple Sclerosis (RRMS)	Aubagio, Avonex, Bafiertam, Betaseron, Copaxone, Extavia, Gilenya, Glatopa, Kesimpta, Mavenclad, Mayzent, Plegridy, Ponvory, Rebif, Tascenso ODT, Tecfidera, Vumerity
Active Secondary Progressive Multiple Sclerosis (SPMS)	Aubagio, Avonex, Bafiertam, Betaseron, Copaxone, Extavia, Gilenya, Glatopa, Kesimpta, Mavenclad, Mayzent, Plegridy, Ponvory, Rebif, Tascenso ODT, Tecfidera, Vumerity

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Agents Eligible for Continuation of Therapy
All target agents except the following are eligible for continuation of therapy: Brand Aubagio Brand Copaxone Brand Gilenya 0.5 mg Brand Tecfidera

   1. The patient has been treated with the requested agent within the past 90 days **OR**
   2. The prescriber states the patient has been treated with the requested agent within the past 90 days AND is at risk if therapy is changed **OR**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
B. BOTH of the following:
1. ONE of the following:
A. The patient has a diagnosis of a relapsing form of MS AND ALL of the following:
1. ONE of the following:
A. The requested agent is a preferred agent OR
B. The requested agent is a non-preferred agent AND ONE of the following:
1. The patient is 17 years of age or younger AND ONE of the following:
A. The requested agent is one of the following brand agents that does NOT have an equipotent preferred generic strength OR
<table>
<tr><th>Agents that do NOT have an equipotent preferred generic strength</th></tr>
<tr><td>Gilenya 0.25 mg
Tascenso ODT 0.25 mg</td></tr>
</table>
B. The patient has tried and had an inadequate response to generic fingolimod (medical records required) OR
C. The patient has an intolerance (defined as an intolerance to the drug or its excipients, NOT to the route of administration) or hypersensitivity to generic fingolimod (medical records required) OR
D. The patient has an FDA labeled contraindication to generic fingolimod (medical records required) OR
E. If the requested agent is Tascenso ODT 0.5 mg, there is support for the use of the requested agent over
</td></tr>
</table>

Module	Clinical Criteria for Approval
	generic fingolimod (e.g., swallowing difficulties) **OR** 2. The patient is 18 years of age or older AND BOTH of the following: A. ONE of the following: 1. The patient has tried and had an inadequate response to TWO preferred agents that are FDA labeled for the treatment of the requested indication (medical records required) **OR** 2. The patient has an intolerance (defined as an intolerance to the drug or its excipients, NOT to the route of administration) or hypersensitivity to TWO preferred agents FDA labeled for the treatment of the requested indication **OR** 3. The patient has an FDA labeled contraindication to ALL preferred agents FDA labeled for the treatment of the requested indication **AND** B. If the requested agent is Tascenso ODT 0.5 mg, ONE of the following: 1. The patient has tried and had an inadequate response to generic fingolimod (medical records required) **OR** 2. The patient has an intolerance or hypersensitivity to generic fingolimod that is NOT expected to occur with the requested agent **OR** 3. The patient has an FDA labeled contraindication to generic fingolimod that is

Module	Clinical Criteria for Approval
	NOT expected to occur with the requested agent **OR** 4. There is support for the use of the requested agent over generic fingolimod (e.g., swallowing difficulties) **OR** 3. The patient has highly active MS disease activity AND BOTH of the following: (medical records including chart notes required) A. The patient has greater than or equal to 2 relapses in the previous year **AND** B. ONE of the following: 1. The patient has greater than or equal to 1 gadolinium enhancing lesion of MRI **OR** 2. The patient has significant increase in T2 lesion load compared with a previous MRI **OR** 4. The patient has been treated with at least 3 MS agents from different drug classes (medical records including chart notes required) (see MS disease modifying agents drug class table) **AND** 2. If the requested agent is Aubagio (teriflunomide), the prescriber has obtained transaminase and bilirubin levels within 6 months prior to initiating treatment **AND** 3. If the requested agent is Gilenya (fingolimod) or Tascenso ODT the prescriber has performed an electrocardiogram within 6 months prior to initiating treatment **OR** B. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
2. If the requested agent is a brand product with an available generic equivalent (listed below) ONE of the following: (Medical records required)

<table>
<tr><th>Non-Preferred Agents</th><th>Generic Equivalent</th></tr>
<tr><td>Aubagio</td><td>teriflunomide</td></tr>
<tr><td>Copaxone</td><td>Glatopa/glatiramer</td></tr>
<tr><td>Gilenya 0.5 mg</td><td>fingolimod</td></tr>
<tr><td>Tecfidera</td><td>dimethyl fumarate</td></tr>
</table>

A. The patient has an intolerance or hypersensitivity to the generic equivalent that is NOT expected to occur with the requested agent **OR**
B. The patient has an FDA labeled contraindication to the generic equivalent that is NOT expected to occur with the requested agent **OR**
C. There is support for the use of the requested agent over the generic equivalent **AND**

3. The prescriber is a specialist in the area of the patient's diagnosis (i.e., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**
4. ONE of the following:
   A. The patient will NOT be using the requested agent in combination with an additional disease modifying agent (DMA) for the requested indication **OR**
   B. The patient will be using the requested agent in combination with another DMA used for the treatment of the requested indication AND BOTH of the following:
      1. The requested agent will be used in combination with Mavenclad (cladribine) **AND**
      2. There is support for the use of the requested agent in combination with Mavenclad (e.g., relapse between cycles of Mavenclad) **AND**
5. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 12 months. NOTE: For agents requiring a starter dose for initial use, the starter dose can be approved for the FDA labeled starting dose and the maintenance dose can be approved for the remainder of 12 months.

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND**
2. If the requested agent is a brand product with a generic equivalent (listed below) AND ONE of the following:

<table>
<tr><th>Non-preferred Agents</th><th>Generic Equivalent</th></tr>
<tr><td>Aubagio</td><td>teriflunomide</td></tr>
<tr><td>Copaxone</td><td>Glatopa/glatiramer</td></tr>
<tr><td>Gilenya 0.5 mg</td><td>fingolimod</td></tr>
<tr><td>Tecfidera</td><td>dimethyl fumarate</td></tr>
</table>

   A. The patient has an intolerance to hypersensitivity to the generic equivalent that is NOT expected to occur with the requested agent **OR**
   B. The patient has an FDA labeled contraindication to the generic equivalent that is NOT expected to occur with the requested agent **OR**
   C. There is support for the use of the requested agent over the generic equivalent **AND**
3. The patient has had clinical benefit with the requested agent **AND**
4. The prescriber is a specialist in the area of the patient's diagnosis (i.e., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**
5. ONE of the following:
   A. The patient will NOT be using the requested agent in combination with an additional disease modifying agent (DMA) for the requested indication **OR**
   B. The patient will be using the requested agent in combination with another DMA used for the requested indication AND BOTH of the following:
      1. The requested agent will be used in combination with Mavenclad (cladribine) AND
      2. There is support for the use of the requested agent in combination with Mavenclad (e.g., relapse between cycles of Mavenclad) **AND**

</td></tr>
</table>

Module	Clinical Criteria for Approval
	6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL Standalone	**Quantity Limit for Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does not have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months NOTE: For agents requiring a starter dose for initial use, the starter dose can be approved for the FDA labeled starting dose and the maintenance dose can be approved for the remainder of 12 months
QL with PA - All agents	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met:

Module	Clinical Criteria for Approval
excluding Mavenclad	1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months. **NOTE**: For agents requiring a starter dose for initial use, the starter dose can be approved for the FDA labeled starting dose and the maintenance dose can be approved for the remainder of 12 months.
QL with PA Mavenclad	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does not exceed the program quantity limit **OR** 2. BOTH of the following A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) cannot be achieved with a lower quantity of packs and a higher pack size (e.g., two 10 tablet packs instead of four 5 tablet packs) that does not exceed the program quantity limit **Length of Approval:** Initial: up to 36 weeks for new starts OR if patient is currently taking the requested agent, approve for remainder of the annual course (1 course consists of 2 cycles of 4-5 days); Renewal: up to 3 months

CONTRAINDICATION AGENTS

Contraindicated as Concomitant Therapy
Examples of Contraindicated Concomitant Disease Modifying Agents (DMAs) **Aubagio** (teriflunomide)* **Avonex** (interferon β-1a) **Bafiertam** (monomethyl fumarate) **Betaseron** (interferon β-1b) **Briumvi** (ublituximab-xiiy)

Contraindicated as Concomitant Therapy
Copaxone (glatiramer)* dimethyl fumarate **Extavia** (interferon β-1b) fingolimod **Gilenya** (fingolimod)* **Glatopa** (glatiramer) glatiramer **Kesimpta** (ofatumumab) **Lemtrada** (alemtuzumab) **Mavenclad** (cladribine) **Mayzent** (siponimod) **Ocrevus** (ocrelizumab) **Plegridy** (peginterferon β-1a) **Ponvory** (ponesimod) **Rebif** (interferon β-1a) **Tascenso ODT** (fingolimod) **Tecfidera** (dimethyl fumarate)* teriflunomide **Tysabri** (natalizumab) **Vumerity** (diroximel fumarate) **Zeposia** (ozanimod) * -generic available

CLASS AGENTS

Class	Class Drug Agents
Class Ia antiarrhythmics	
Class Ia antiarrhythmics	NORPACE*Disopyramide Phosphate Cap
Class Ia antiarrhythmics	Pronestyl (procainamide)
Class Ia antiarrhythmics	quinidine
Class III antiarrhythmics	

Class	Class Drug Agents
Class III antiarrhythmics	BETAPACE*Sotalol HCl Tab
Class III antiarrhythmics	Cordarone, Pacerone (amiodarone)
Class III antiarrhythmics	CORVERT*Ibutilide Fumarate Inj
Class III antiarrhythmics	MULTAQ*Dronedarone HCl Tab
Class III antiarrhythmics	TIKOSYN*Dofetilide Cap
MS Disease Modifying Agents drug class: CD20 monoclonal antibody	
MS Disease Modifying Agents drug class: CD20 monoclonal antibody	BRIUMVI*ublituximab-xiiy soln for iv infusion
MS Disease Modifying Agents drug class: CD20 monoclonal antibody	KESIMPTA*Ofatumumab Soln Auto-Injector
MS Disease Modifying Agents drug class: CD20 monoclonal antibody	OCREVUS*Ocrelizumab Soln For IV Infusion
MS Disease Modifying Agents drug class: CD52 monoclonal antibody	
MS Disease Modifying Agents drug class: CD52 monoclonal antibody	LEMTRADA*Alemtuzumab IV Inj
MS Disease Modifying Agents drug class: Fumarates	
MS Disease Modifying Agents drug class: Fumarates	BAFIERTAM*Monomethyl Fumarate Capsule Delayed Release
MS Disease Modifying Agents drug class: Fumarates	TECFIDERA*Dimethyl Fumarate Capsule Delayed Release

Class	Class Drug Agents
MS Disease Modifying Agents drug class: Fumarates	VUMERITY*Diroximel Fumarate Capsule Delayed Release
MS Disease Modifying Agents drug class: Glatiramer	
MS Disease Modifying Agents drug class: Glatiramer	COPAXONE*Glatiramer Acetate Soln Prefilled Syringe
MS Disease Modifying Agents drug class: Glatiramer	GLATOPA*Glatiramer Acetate Soln Prefilled Syringe
MS Disease Modifying Agents drug class: IgG4k monoclonal antibody	
MS Disease Modifying Agents drug class: IgG4k monoclonal antibody	TYSABRI*Natalizumab for IV Inj Conc
MS Disease Modifying Agents drug class: Interferons	
MS Disease Modifying Agents drug class: Interferons	AVONEX*Interferon beta-1a injection
MS Disease Modifying Agents drug class: Interferons	BETASERON*Interferon beta-1b injection
MS Disease Modifying Agents drug class: Interferons	EXTAVIA*Interferon beta-1b injection
MS Disease Modifying Agents drug class: Interferons	PLEGRIDY*Peginterferon beta-1a injection
MS Disease Modifying Agents drug class: Interferons	REBIF*Interferon Beta-

Class	Class Drug Agents
MS Disease Modifying Agents drug class: Purine antimetabolite	
MS Disease Modifying Agents drug class: Purine antimetabolite	MAVENCLAD*Cladribine Tab Therapy Pack
MS Disease Modifying Agents drug class: Pyrimidine synthesis inhibitor	
MS Disease Modifying Agents drug class: Pyrimidine synthesis inhibitor	AUBAGIO*Teriflunomide Tab
MS Disease Modifying Agents drug class: Sphingosine 1-phosphate (SIP) receptor modulator	
MS Disease Modifying Agents drug class: Sphingosine 1-phosphate (SIP) receptor modulator	GILENYA*Fingolimod HCl Cap
MS Disease Modifying Agents drug class: Sphingosine 1-phosphate (SIP) receptor modulator	MAYZENT*Siponimod Fumarate Tab
MS Disease Modifying Agents drug class: Sphingosine 1-phosphate (SIP) receptor modulator	PONVORY*Ponesimod Tab
MS Disease Modifying Agents Drug Class: Sphingosine 1-phosphate (SIP) receptor modulator	
MS Disease Modifying Agents Drug Class: Sphingosine 1-phosphate (SIP) receptor modulator	TASCENSO*fingolimod lauryl sulfate tablet disintegrating
MS Disease Modifying Agents drug class: Sphingosine 1-phosphate (SIP) receptor modulator	

Class	Class Drug Agents
MS Disease Modifying Agents drug class: Sphingosine 1-phosphate (SIP) receptor modulator	ZEPOSIA*Ozanimod capsule

Myalept (metreleptin)

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Myalept® (metreleptin) Subcutaneous injection	Adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy Limitations of Use: • Safety and effectiveness for the treatment of complications of partial lipodystrophy have not been established • Safety and effectiveness for the treatment of liver disease, including nonalcoholic steatohepatitis (NASH), have not been established • Not indicated for use in patients with HIV-related lipodystrophy • Not indicated for use in patients with metabolic disease, including diabetes mellitus and hypertriglyceridemia, without concurrent evidence of congenital generalized lipodystrophy (CGL) or acquired generalized lipodystrophy (AGL)		1

CLINICAL RATIONALE

Lipodystrophy	Lipodystrophy is a rare, heterogeneous group of syndromes characterized by the complete or partial loss or absence of subcutaneous adipose tissue. The loss or absence of adipose tissue results in decreased levels of leptin, which is an important hormone regulating appetite. Lipodystrophy is often, although not always, accompanied by metabolic abnormalities, including insulin resistance, diabetes mellitus, hepatic steatosis or steatohepatitis, and dyslipidemia. Metabolic abnormalities associated with lipodystrophy can be severe and lead to substantial comorbidities, including acute pancreatitis (due to severe

	hypertriglyceridemia), hepatic cirrhosis, and premature cardiovascular disease.(2-5) Lipodystrophy can generally be classified based on extent or pattern of fat loss (generalized or partial) and whether the disease is genetic or acquired. There are 4 major lipodystrophy subtypes: congenital generalized lipodystrophy (CGL), acquired generalized lipodystrophy (AGL), familial partial lipodystrophy (FPL), and acquired partial lipodystrophy (APL).(2-4) Initial treatment of metabolic disturbances associated with lipodystrophy (e.g., diabetes, hypertriglyceridemia) is the same as in patients without lipodystrophy. Diabetes is treated with hyperglycemic drugs as well as insulin (although high doses are often required). Hypertriglyceridemia may be treated with statins, fibric acid derivatives, or omega-3 fatty acids. Individuals with CGL and AGL are encouraged to maintain a healthy weight by following a low-fat diet and engaging in regular exercise. If metabolic disturbances persist, metreleptin is recommended, along with careful monitoring, in these patients.(2,3,5)
Efficacy	Metreleptin is a recombinant human leptin analog that functions by binding to and activating the human leptin receptor which studies suggest causes an increase in insulin sensitivity and a reduction in food intake.(1) The efficacy of metreleptin was evaluated in an open label single arm study of 48 patients with congenital (n=32) or acquired (n=16) generalized lipodystrophy who also had at least one of the metabolic abnormalities (diabetes mellitus, hypertriglyceridemia > 200 mg/dL, and/or increased fasting insulin [greater than or equal to 30 microU/mL]). At baseline, 37 (77%) patients had HbA1c values of 7% or greater, 19 (40%) had HbA1c values of 9% or greater, 33 (69%) had fasting plasma glucose values of 126 mg/dL or greater, 17 (35%) had fasting triglyceride values of 500 mg/dL or greater, and 11 (23%) had fasting triglyceride values of 1000 mg/dL or greater. The metreleptin treatment duration was 3.6 months to 10.9 years (median = 2.7 years) and metreleptin was administered either once or twice daily. At year 1, patients treated with metreleptin had mean/median reductions in HbA1c (-2%), fasting glucose (-49 mg/dL), and triglycerides (-55%). Concomitant anti-hyperglycemic and lipid-altering medications dosing regimens were not held constant throughout the study.(1)
Safety	Metreleptin has the following boxed warning for risk of anti-metreleptin antibodies with neutralizing activity and risk of lymphoma:(1) • Anti-metreleptin antibodies with neutralizing activity have been identified in patients treated with metreleptin. The consequences are not well characterized but could include inhibition of endogenous leptin action

	and loss of metreleptin efficacy. Worsening metabolic control and/or severe infection have been reported. Test for anti-metreleptin antibodies with neutralizing activity in patients who develop severe infections or show signs suspicious for loss of efficacy during metreleptin treatment • T-cell lymphoma has been reported in patients with acquired generalized lipodystrophy, both treated and not treated with metreleptin. Carefully consider the benefits and risks of treatment with metreleptin in patients with significant hematologic abnormalities and/or acquired generalized lipodystrophy Metreleptin is available only through a restricted risk evaluation and mitigation strategy (REMS) program.(1) Metreleptin is contraindicated in the following:(1) • Patients with general obesity not associated with congenital leptin deficiency. It has not been shown to be effective in treating general obesity and the development of anti-metreleptin antibodies with neutralizing activity has been reported in obese patients treated with metreleptin • Patients with prior severe hypersensitivity reactions to metreleptin or to any of the product components

REFERENCES

Number	Reference
1	Myalept prescribing information. Aegerion Pharmaceuticals, Inc. February 2022.
2	Handelsman Y, Oral EA, Bloomgarden ZT. et al. The Clinical Approach to the Detection of Lipodystrophy An AACE Consensus Statement. *Endocrine Practice* 2013;19(1):107-116. doi:10.4158/endp.19.1.v767575m65p5mr06
3	Brown RJ, Araujo-Vilar D, Cheung PT, et al. The Diagnosis and Management of Lipodystrophy Syndromes: A Multi-Society Practice Guideline. *Journal of Clinical Endocrinology & Metabolism* 2016;101(12):4500-4511. doi:10.1210/jc.2016-2466
4	Araujo-Vilar D, Santini F. Diagnosis and Treatment of Lipodystrophy: A Step-By-Step Approach. *Journal of Endocrinological Investigation.* 2018;42(1):61-73. doi:10.1007/s40618-018-0887-z

Number	Reference
5	National Organization for Rare Disorders (NORD). *The Physician's Guide to Lipodystrophy Disorders*; 2012. https://www.rareconnect.org/uploads/documents/the-physician-s-guide-to-lipodystrophy-disorders.pdf

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of either congenital generalized lipodystrophy (CGL) or acquired generalized lipodystrophy (AGL) **AND** 2. The patient has a diagnosis of leptin deficiency AND The patient does NOT have any of the following: partial lipodystrophy, liver disease (including non-alcoholic steatohepatitis [NASH]), HIV-related lipodystrophy, or metabolic disease (e.g., diabetes mellitus, hypertriglyceridemia) without evidence of generalized lipodystrophy **AND** 3. The patient has baseline HbA1c, triglycerides, and fasting insulin levels measured prior to initiating the requested agent AND The patient has complications related to lipodystrophy (e.g., diabetes mellitus, hypertriglyceridemia [greater than or equal to 200 mg/dL], and/or high fasting insulin [greater than or equal to 30 microU/mL]) **AND** 4. The patient has tried and had an inadequate response to maximum tolerable dose of a conventional agent for complications related to lipodystrophy **AND** 5. The patient has had an inadequate response to lifestyle modification (i.e., diet modification and exercise) AND will continue lifestyle modifications with the requested agent **AND** 6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 8. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **Length of Approval:** 12 months **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met:

Module	Clinical Criteria for Approval
	1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had stabilization and/or reduction from baseline in at least ONE of the following: HbA1c, triglycerides, and/or fasting insulin **AND** 3. The patient will continue lifestyle modifications (i.e., diet and exercise) with the requested agent **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 6. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **Length of Approval:** 12 months

Nasal Antiepileptics

Quantity Limit

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Nasal Inhalers

Quantity Limit

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** B. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Neurotrophic Keratitis

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Oxervate® (cenegermin-bkbj) Ophthalmic solution	Treatment of neurotrophic keratitis		1

CLINICAL RATIONALE

Neurotrophic Keratitis	Neurotrophic keratitis (NK) is a rare corneal degenerative disease that is characterized by a reduction or absence of corneal sensitivity, due to impaired innervation by the trigeminal nerve. The lack of innervation leads to corneal epithelial breakdown, impairment of healing, and development of corneal ulceration, melting, and perforation.(2,3) There are numerous underlying ocular and systemic conditions associated with NK, with the most common causes including herpetic keratitis (zoster and simplex), topical anesthetic abuse, chemical and thermal burns, contact lends abuse, and topical drug toxicity. Corneal procedures have been linked to NK such as LASIK, corneal transplantation surgery, and specifically penetrating keratoplasty (PK) as well as non-corneal ocular surgeries (vitrectomy for retinal detachment and photocoagulation to treat diabetic retinopathy). Additional non-ocular or systemic causes include neurosurgical procedures or trauma damaging the fifth cranial nerve, stroke, aneurysms, multiple sclerosis, intracranial masses, diabetes, leprosy, vitamin A deficiency, and drugs (e.g., narcoleptics, antipsychotics).(2) Diagnosing NK requires clinical ocular and systemic history, complete eye examination, and assessment of corneal sensitivity. The hallmark of NK is a decrease or absence of corneal sensation.(2,3) Corneal sensitivity testing is recommended using a cotton swab, the Cochet-Bonnet contact esthesiometer, or the CRCERT-Belmonte non-contact esthesiometer. If sensitivity testing indicates reduced sensitivity, then corneal staining, Schirmer testing, microbiology exams,

	lid evaluation, nerve imaging, and limbal evaluation are recommended to determine disease staging and determine underlying etiology.(3) The clinical classification of NK is broken down into three stages. Stage 1 is characterized by corneal epithelial changes with dry and cloudy epithelium, the presence of superficial punctate keratopathy, and corneal edema. Stage 2 is characterized by recurrent and/or PED with an oval or circular shape, mostly localized at the superior half of the cornea. Stage 3 is characterized by corneal ulcer with stromal involvement that may be complicated by stromal melting and progression to corneal perforation.(2) Management of NK aims to promote corneal healing and avoid complications. Patients with NK should use preservative-free medications, as epithelial drug toxicity can complicate the disease. All ocular surface-associated diseases (i.e., dry eye, blepharitis, exposure keratopathy, limbal stem cell deficiency) should be treated. Topical NSAIDs should be avoided in NK as they do not show any benefit and they can decrease corneal sensitivity. Treatment options are determined based on staging. Stage 1 is treated with preservative-free artificial tears and lubricant ointments. Therapeutic soft contact lenses, punctal plugs, and autologous serum could also be options in some cases. Oxervate can be considered in patients that fail to respond to these therapies. Stage 2 treatment includes continuing preservative-free artificial tears and lubricant ointments with prophylactic antibiotic drops. Additional treatment options for stage 2 are therapeutic soft contact lenses, topical autologous serum application, amniotic membrane grafting, conjunctival flap, tarsorrhaphy or botulinum induced ptosis, and topical nerve growth factor application. Treatment for stage 3 includes all of the treatments for stage 1 and 2 with the addition of N-acetylcysteine, oral tetracycline, and medroxyprogesterone can be prescribed in case of stromal melting. Surgical treatments are typically reserved for refractory cases.(2,3) Corneal perforations require immediate treatment with either cyanoacrylate glue and soft bandage contact lenses, or amniotic membrane grafting. Tectonic perforating or lamellar keratoplasty can be performed for larger perforations.(3)
Efficacy	Cenegermin ophthalmic solution contains cenegermin, a recombinant form of human nerve growth factor produced in Escherichia coli. Nerve growth factor is an endogenous protein involved in the differentiation and maintenance of neurons, which acts through specific high-affinity (i.e., TrkA) and low-affinity (i.e., p75NTR) nerve growth factor receptors in the anterior segment of the eye to support corneal innervation and integrity. Efficacy and safety of Oxervate (cenegermin 20 mcg/mL) for treatment of patients with NK (N=151) was evaluated in two Phase 2, 8-week, randomized, multi-center, double-masked,

	vehicle-controlled studies (Study NGF0212 and Study NGF0214). In both studies, cenegermin was dosed 6 times daily in the affected eye(s) for 8 weeks. Results for the primary endpoint, "complete corneal healing" (i.e., absence of corneal lesion staining and no persistent staining in the rest of the cornea after 8 weeks of treatment) were as follows:(1) • Study NGF0214- cenegermin 20 mcg/mL (65.2%); vehicle (16.7%) [treatment difference: 48.6%; 95% CI: 24%, 73.1%; p-value less than 0.01] • Study NGF0212- cenegermin 20 mcg/mL (72.0%); vehicle (33.3%) [treatment difference: 38.7%; 95% CI: 20.7%, 56.6%; p-value less than 0.01] In patients healed after 8 weeks of Oxervate (cenegermin 20 mcg/mL) therapy, recurrences occurred in about 20% of patients in Study NGF0212 and 14% of patients in Study NGF0214. Least square mean changes (improvement) from baseline in corneal sensitivity inside the lesion after 8 weeks of treatment were not clinically significant in either study:(1) • Study NGF0214- cenegermin 20 mcg/mL (1.6); vehicle (0.7) [treatment difference: 0.9; 95% CI: 0.2, 1.7] • Study NGF0212- cenegermin 20 mcg/mL (1.1); vehicle (0.8) [treatment difference: 0.3; 95% CI: -0.4, 0.9] Inclusion criteria required patients to be 18 years of age with Stage 2 (persistent epithelial defect [PED]) or Stage 3 (corneal ulcer) NK (involving one eye for NGF0212 and involving both eyes for NGF0214); PED or corneal ulceration of greater than 2 weeks duration refractory to greater than 1 conventional non-surgical treatments for NK (e.g., preservative-free artificial tears, gels or ointments; discontinuation of preserved topical drops and medications that can decrease corneal sensitivity; therapeutic contact lenses); evidence of decreased corneal sensitivity (less than or equal to 4 cm on Cochet-Bonnet aesthesiometer) within area of the PED or corneal ulcer and outside of the area of the defect in greater than 1 corneal quadrant; best corrected distance visual acuity (BCDVA) score less than or equal to 75 Early Treatment Diabetic Retinopathy Study (ETDRS) letters, (greater than or equal to +0.2 log MAR, less than or equal to 20/32 Snellen or less than or equal to 0.625 decimal fraction) in the affected eye; and no objective clinical evidence of improvement in PED or corneal ulceration within the 2 weeks prior to study enrollment.(4) Exclusion criteria included any active ocular infection or active ocular inflammation not related to NK in the affected eye; any other ocular disease requiring topical ocular treatment in the affected eye during study treatment

	period; severe vision loss in the affected eye with no potential for visual improvement; Schirmer's test without anesthesia less than or equal to 3 mm/ 5 minutes in the affected eye; severe blepharitis and/or severe meibomian gland disease in the affected eye; history of any ocular surgery in affected eye within 3 months before study enrollment (allowed if the ocular surgery was the cause of Stage 2 or 3 NK); prior surgical procedure(s) for treatment of NK (e.g., complete tarsorrhaphy, conjunctival flap, etc.) in affected eye; previous Botox treatment; botulinum injections used to induce pharmacologic blepharoptosis eligible only if last injection was greater than 90 days prior to enrollment; use of contact lenses during study treatment periods in the eye with NK; anticipated need for punctal occlusion during study treatment period (patients with punctal occlusion or punctal plugs inserted prior to study were eligible for enrollment if the punctal occlusion was maintained during the study); evidence of corneal ulceration involving posterior third of the corneal stroma, corneal melting or perforation in the affected eye; presence/history of any ocular or systemic disorder or condition that might have hindered efficacy of the study treatment or its evaluation; need for or anticipated change in dose of systemic medications known to impair function of the trigeminal nerve (e.g., neuroleptics, antipsychotic and antihistamine drugs [these treatments were allowed during the study if initiated prior to 30 days before study enrollment provided they remained stable throughout the course of the study treatment periods]); known hypersensitivity to study or procedural medications (e.g., fluorescein); history of drug, medication or alcohol abuse or addiction; use of any investigational agent within 4 weeks of baseline visit; and participation in another clinical study at the same time as the present study.(4)
Safety	Oxervate has no FDA labeled contraindications for use.(1)

REFERENCES

Number	Reference
1	Oxervate prescribing information. Dompé farmaceutici S.p.A. October 2023.
2	Neurotrophic keratitis - EyeWiki. Published December 29, 2023. http://eyewiki.aao.org/Neurotrophic_Keratitis
3	Sacchetti M, Lambìase A. Diagnosis and management of neurotrophic keratitis. *Clinical Ophthalmology*. Published online March 1, 2014:571. doi:10.2147/opth.s45921

Number	Reference
4	Bonini S, Lambìase A, Rama P, et al. Phase II randomized, Double-Masked, Vehicle-Controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. *Ophthalmology*. 2018;125(9):1332-1343. doi:10.1016/j.ophtha.2018.02.022

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of neurotrophic keratitis (NK) **AND** 2. The patient has stage 2 (persistent epithelial defect [PED]) or stage 3 (corneal ulcer) NK **AND** 3. ONE of the following: A. The patient has NOT been previously treated with the requested agent in the affected eye(s) AND ALL of the following: 1. The patient's PED and/or corneal ulcer have been present for at least 2 weeks **AND** 2. ONE of the following: A. The patient's NK has been refractory to at least ONE conventional non-surgical treatment (i.e., preservative-free lubricant eye drops or ointment, discontinuation of preserved topical agents that can decrease corneal sensitivity, therapeutic soft contact lenses, topical autologous serum application, botulinum A toxin treatment) **OR** B. The patient has an intolerance or hypersensitivity to at least ONE conventional non-surgical treatment for NK **OR** **C.** The patient has an FDA labeled contraindication to ALL conventional non-surgical treatments for NK **AND** 3. The patient has decreased corneal sensitivity within the area of the PED or ulcer and outside the area of defect in at least one corneal quadrant **OR** B. The patient has been previously treated with the requested agent in the affected eye(s) AND BOTH of the following: 1. The patient had complete corneal healing in the previously treated eye(s) (medical records required) **AND** 2. The patient has a recurrence of NK that requires another treatment course (medical records required) **AND** 4. ONE of the following: A. The patient does NOT have ocular surface disease associated with or in conjunction with NK **OR**

Module	Clinical Criteria for Approval
	B. BOTH of the following: 1. The patient has ocular surface disease associated with or in conjunction with NK **AND** 2. The ocular surface disease has been properly treated **AND** 5. The patient will NOT be using the requested agent in combination with a topical ophthalmic NSAID **AND** 6. The patient does NOT have any of the following: A. Active ocular infection or active ocular inflammation not related to NK in the affected eye **OR** B. Severe blepharitis and/or severe Meibomian gland disease in the affected eye **OR** C. History of any ocular surgery in the affected eye within the past 90 days that has not been determined to be the cause of NK **OR** D. Corneal perforation, ulceration involving the posterior third of the corneal stroma, or corneal melting **AND** 7. The prescriber is a specialist in the area of the patient's diagnosis (e.g., optometrist, ophthalmologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 8. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 8 weeks NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND BOTH of the following: A. The patient has bilateral neurotrophic keratitis (NK) (medical records required) **AND** B. The requested quantity (dose) does NOT exceed TWICE the program quantity limit **Length of Approval**: up to 8 weeks

Coverage Exception Net Results

OBJECTIVE

These criteria apply to any request for agents that are included in the clients Lockout/Excluded Agents list and is not otherwise excluded from coverage under the member's pharmacy benefit.

For any agent which has additional clinical review criteria specific to the agent and/or disease state/medical condition, the additional clinical review criteria will also be applied.

CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	A coverage exception will be granted when BOTH of the following are met: 1. The requested agent is NOT restricted for coverage under the patient's medical benefit **AND** A. ALL of the following: 1. ONE of the following: A. The requested agent is in an ACA Preventative Care category AND did NOT meet the preventative service requirements **OR** B. BOTH of the following: 1. ONE of the following: A. The requested agent is NOT in an ACA Preventative Care category **OR** B. The member's benefit does NOT include ACA Preventative Care for the category requested **AND** 2. The requested agent is not excluded from coverage under the pharmacy benefit **AND** 2. The patient has an FDA labeled indication, or an indication supported in AHFS, DrugDex with 1 or 2a level of evidence, or NCCN with 1 or 2a level of evidence for the requested agent **AND** 3. ONE of the following: A. The requested agent has formulary alternatives (any formulary tier) for the diagnosis being treated by the requested agent AND BOTH of the following: 1. If the requested agent is a brand product with an available formulary generic equivalent AND ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient has tried and had an inadequate response to one or more available formulary generic equivalent to the requested agent **OR** B. There is support that ALL available formulary (any formulary tier) generic equivalent to the requested agent are contraindicated, are likely to be less effective, or will cause an adverse reaction or other harm for the patient **AND** 2. ONE of the following A. The patient has tried and had an inadequate response to at least two formulary alternatives (any formulary tier), if available, for the diagnosis being treated with the requested agent **OR** B. There is support that ALL available formulary (any formulary tier) alternatives are contraindicated, likely to be less effective, or cause an adverse reaction or other harm for the patient **OR** B. The requested agent does NOT have formulary (any formulary tier) alternatives for the diagnosis being treated with the requested agent **OR** C. The prescriber states that the patient is currently receiving the requested agent and is at risk if the therapy is changed **ACA Length of Approval:** • Aspirin 81 mg: 9 months • Infant eye appointment: 3 months • All other indications: 12 months • Apply $0 copay if ACA criteria met **Coverage Exception length of approval:** • 12 months

Northera (droxidopa)

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Northera® (droxidopa) Capsule*	Treatment of orthostatic dizziness, lightheadedness, or the "feeling that you are about to black out" in adult patients with symptomatic neurogenic orthostatic hypotension (nOH) caused by primary autonomic failure (Parkinson's disease [PD], multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy. Effectiveness beyond 2 weeks of treatment has not been established. The continued effectiveness should be assessed periodically.	* Generic available	1

CLINICAL RATIONALE

Orthostatic Hypotension	Orthostatic hypotension (OH) is defined as a blood pressure decrease greater than or equal to 20mmHg systolic or greater than or equal to 10mmHg diastolic recorded within 3 minutes after that patient stands.(2-6) OH can impair perfusion to organs above the heart, resulting in symptoms of hypoperfusion in these tissues. OH is a frequent problem in the general population, especially in the elderly.(2-4,6) The overall prevalence of OH in patients greater than 65 years is approximately 20%.(2) It can result from a variety of medical conditions, such as IV volume depletion, blood pooling from varicose veins, severe anemia, medications, and physical deconditioning. In these cases, OH usually improves once the underlying cause is treated. In a minority of patients, OH occurs due to decreased norepinephrine release from sympathetic nerves, which leads to defective vasoconstriction when in the upright position. This is referred to as neurogenic orthostatic hypotension (nOH). nOH occurs frequently in patients with neurodegenerative disorders such as Parkinson's disease, Lewy Body dementia, multiple system atrophy, pure autonomic failure, dopamine beta-hydroxylase deficiency and nondiabetic autonomic neuropathy.(2-6) An estimated 30-50% of Parkinson's disease patients have nOH.(2,4) When present, symptoms are similar to those observed with OH. However, in contrast to

	vasovagal (neutrally mediated) syncope, syncope in nOH occurs without signs of autonomic activation such as diaphoresis, tachycardia, nausea, or abdominal discomfort.(2) The goal of nOH treatment is not to normalize standing blood pressure, but to reduce symptom burden so as to improve quality of life. The steps in management include: 1) correcting aggravating factors, 2) implementing non-pharmacological measures, and 3) drug therapies. The correction of aggravating factors includes management of medications contributing to the nOH through the reduction of IV volume, induction of vasodilation, and interference with norepinephrine. The correction of anemia and vitamin deficiencies is also included. Non-pharmacological management includes insuring proper blood volume, adjusting sodium intake, physical conditioning, avoid increased core body temperature, compression garments, and head-up position while sleeping.(2) Pharmacological options include midodrine and droxidopa, as well as off-label use of fludrocortisone and pyridostigmine for nOH.(2-6) One of the challenges associated with treating nOH pharmacologically is the limited availability of clinical evidence and lack of comparative effectiveness studies. Once initial therapy has begun, symptomatic benefit, including impact on activities of daily living, and changes in blood pressure need to be assessed frequently. Little data exists to determine efficacy and safety of different combinations of therapy compared to monotherapy for nOH. Based on the experience of the consensus panel, the recommendation is to appropriately titrate to maximum tolerable dose of a single agent and then, if symptomatic benefit is not obtained, consider switching to a different therapy or adding a second agent and titrate from its lowest starting dose.(3)
Efficacy	Clinical studies examined the efficacy of Northera in the short-term (1-2 weeks) and over longer-term periods (8 weeks; 3 months). Studies 301 and 306B showed a treatment effect of Northera at Week 1, but none of the studies demonstrated continued efficacy beyond two weeks of treatment.(1) Study 301: Patients with symptomatic neurogenic orthostatic hypotension (nOH) participated in this multicenter, multinational, double-blind, randomized, placebo-controlled, parallel-group study. Patients were required to have a clinical diagnosis of symptomatic nOH due to one of the following: Parkinson's disease, pure autonomic failure, multiple system atrophy, non-diabetic autonomic neuropathy, or dopamine-beta-hydroxylase deficiency. After the initial screening, patients went through open-label dose titration period followed by a seven-day wash-out period (n=263).(1,7)

	Of the 263 patients who participated in dose randomization, 162 (61.6%) were identified as responders and entered the double-blind phase of the study. Responders were defined as demonstrating improvement on the Orthostatic Hypotension Symptom Assessment (OHSA) Item #1 score by at least one point and an increase in systolic blood pressure of at least 10 mmHg upon standing. The OHSA Item #1 referred to dizziness, lightheadedness, feeling faint, and feeling like you might black out (see monograph appendix for more information). Responders were then randomized to a seven-day treatment period with droxidopa (n=82) or placebo (n=80).(1,7) Patients in the treatment period had an average age of 60 years and a primary diagnosis of Parkinson's disease (n=60), pure autonomic failure (n=36) or multiple system atrophy (n=26). Patients were allowed to continue taking dopa-decarboxylase inhibitors (45% of patients) and fludrocortisones (29% of patients).(1) Efficacy was measured utilizing the Orthostatic Hypotension Questionnaire (OHQ, see monograph appendix for more information), which measures the symptoms of nOH and their impact on the patient's daily activities. The OHQ was administered at baseline, randomization, and at the end of the study. The pre-specified primary efficacy endpoint was the change in overall composite score from randomization to end of study. Secondary endpoints were individual OHQ items and changes in symptom and symptom impact scores. Blood pressure was also measured throughout the study.(1,7) Results revealed a statistically significant improvement in the OHQ composite score from randomization to the end of the study (p=0.003). Several symptom items revealed differences between droxidopa and placebo including dizziness/lightheadedness (item 1 for randomization), vision disturbance, weakness, and fatigue. Differences from placebo were also observed on all symptom-impact items. Standing systolic blood pressures increased an average of 11.2 mmHg in patients receiving droxidopa versus 3.9 mmHg with placebo.(7) The mean baseline dizziness score on OHSA Item #1 ("dizziness, lightheadedness, feeling faint, and feeling like you might black out") was 5.2 units on an 11-point scale. At week one of treatment, patients showed a mean 0.7 unit decrease in dizziness with NORTHERA versus placebo (P=0.06).(1) Study 306B: Study 306B was a multi-center, double-blind, randomized, placebo-controlled, parallel-group study that consisted of an initial dose titration period followed by an 8-week treatment period. Patients (n=171) in the study had

	symptomatic nOH and Parkinson's disease, and were required to have a decrease of at least 20 mmHg or 10 mmHg, respectively, in systolic or diastolic blood pressure within three minutes after standing. Dosing was titrated to patient response and ranged from 100 mg to 600 mg three times daily. Data was collected throughout an eight-week treatment period. At week one, patients demonstrated a statistically significant decrease (0.9-unit) in dizziness as reported on the OHSA Item #1 11-point scale (p=0.028). This effect did not continue beyond week one.(1)
Safety	Northera has a Boxed Warning for supine hypertension. Supine blood pressure should be monitored prior to and during treatment and more frequently when increasing doses. Elevating the head of the bed lessens the risk of supine hypertension, and blood pressure should be measured in this position. If supine hypertension cannot be managed by elevation of the head of the bed, reduce or discontinue droxidopa.(1)

REFERENCES

Number	Reference
1	Northera prescribing information. Lundbeck LLC. July 2019.
2	Palma JA, Kaufmann H. Epidemiology, Diagnosis, and Management of Neurogenic Orthostatic Hypotension. Mov Disord Clin Pract. 2017 May-Jun;4(3):298-308.
3	Gibbons CH, Schmidt P, Biaggioni I, et al. The Recommendations of a Consensus Panel for the Screening, Diagnosis, and Treatment of Neurogenic Orthostatic Hypotension and Associated Supine Hypertension. J Neurol. 2017;264(8):1567-1582.
4	2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients with Syncope: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines, and the Heart Rhythm Society. J Am Coll Cardiol. 2017 Aug;70(5):e39-e110.
5	Brignole M, Moya A, de Lange FJ, et al. 2018 European Society of Cardiology (ESC) Guidelines for the Diagnosis and Management of Syncope. Eur Heart J. 2018 June;39(21):1883-1948.
6	Kalra DK, Raina A, Sohal S. Neurogenic Orthostatic Hypotension: State of the Art and Therapeutic Strategies. Clin Med Insights Cardiol. 2020;14:1-12.

Number	Reference
7	A Clinical Study for Patients With Neurogenic Orthostatic Hypotension (NOH) Using Droxidopa (NOH301). Chelsea Therapeutics. https://clinicaltrials.gov/study/NCT00782340?term=northera&page=4&rank=36&a=12. September 2010.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of neurogenic orthostatic hypotension (nOH) AND ALL of the following: 1. The prescriber has performed baseline (prior to therapy with the requested agent) blood pressure readings while the patient is sitting or supine (laying face up) AND also within 3 minutes of standing from a supine position **AND** 2. The patient has a decrease of at least 20 mmHg in systolic blood pressure or 10 mmHg diastolic blood pressure within three minutes after standing **AND** 3. The patient has persistent and consistent symptoms of neurogenic orthostatic hypotension (nOH) caused by ONE of the following: A. Primary autonomic failure (Parkinson's disease [PD], multiple system atrophy, or pure autonomic failure) **OR** B. Dopamine beta-hydroxylase deficiency **OR** C. Non-diabetic autonomic neuropathy **AND** 4. The prescriber has assessed the severity of the patient's baseline (prior to therapy with the requested agent) symptoms of dizziness, lightheadedness, feeling faint, or feeling like the patient may black out **AND** 5. The prescriber has assessed and adjusted, if applicable, any medications known to exacerbate orthostatic hypotension (e.g., diuretics, vasodilators, beta-blockers) **AND** 6. ONE of the following: A. The patient has tried and had an inadequate response to midodrine **OR** B. The patient has an intolerance or hypersensitivity to therapy with midodrine **OR** C. The patient has an FDA labeled contraindication to midodrine **OR**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
B. The patient has another FDA labeled indication for the requested agent AND
2. If the patient has an FDA labeled indication, then ONE of the following:
A. The patient's age is within FDA labeling for the requested indication for the requested agent OR
B. There is support for using the requested agent for the patient's age for the requested indication AND
3. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:
<table>
<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Northera</td><td>droxidopa</td></tr>
</table>
A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
C. There is support for the use of the requested brand agent over the generic equivalent AND
4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND
5. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 1 month

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [NOTE: Patients not previously approved for the requested agent will require initial evaluation review] AND
2. ONE of the following:
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
A. The patient has a diagnosis of neurogenic orthostatic hypotension (nOH) AND BOTH of the following:
1. The patient has had improvement in severity from baseline symptoms (prior to therapy with the requested agent) of dizziness, lightheadedness, feeling faint, or feeling like the patient may black out AND
2. The patient had an increase in systolic blood pressure from baseline (prior to therapy with the requested agent) of at least 10 mmHg upon standing from a supine (laying face up) position OR
B. BOTH of the following:
1. The patient has another FDA labeled indication for the requested agent AND
2. The patient has had clinical benefit with the requested agent AND
3. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:
<table>
<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Northera</td><td>droxidopa</td></tr>
</table>
A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
C. There is support for the use of the requested brand agent over the generic equivalent AND
4. The prescriber is a specialist in the area of the patient’s diagnosis (e.g., cardiologist, neurologist) or the prescriber has consulted with a specialist in the area of the patient’s diagnosis AND
5. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 3 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
</td></tr>
</table>

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support for therapy with a higher dose for the requested indication **Length of Approval**: Initial - Up to 1 month; Renewal - Up to 3 months

Ophthalmic Pilocarpine

Quantity Limit

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Ophthalmic Prostaglandins

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Iyuzeh™ (latanoprost) Ophthalmic Solution	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension		14
Lumigan® (bimatoprost)* Ophthalmic solution	The reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	*generic available	1
Travatan Z® (travoprost)* Ophthalmic solution	The reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	*generic available	2
Vyzulta® (latanoprostene bunod) Ophthalmic solution	The reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension		5
Xalatan*®, Latanoprost (latanoprost)* Ophthalmic solution	The reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension	*generic available	3
Xelpros® (latanoprost) Ophthalmic emulsion	The reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension		4

Agent(s)	FDA Indication(s)	Notes	Ref#
Zioptan® (tafluprost)* Ophthalmic solution	The reduction of elevated intraocular pressure in patients with open angle glaucoma or ocular hypertension	*generic available	6

CLINICAL RATIONALE

Open Angle Glaucoma	Glaucoma describes a group of conditions in which there is characteristic cupping of the optic disc with corresponding visual field defects, due to retinal ganglion cell loss. It is a progressive condition and is the most common cause of irreversible blindness worldwide. Primary open angle glaucoma (POAG) is a subset of the glaucomas defined by an open, normal appearing anterior chamber angle and raised intraocular pressure (IOP), with no other underlying disease. IOP is considered the most important risk factor for the progression to POAG from ocular hypertension (OHT) and remains the only known modifiable risk factor.(13) Visual loss from glaucoma is irreversible, and therefore early diagnosis and treatment is a key strategy to preventing morbidity from this condition.(7,13) The American Academy of Ophthalmology (AAO) guidelines for open angle glaucoma indicate that medical therapy is presently the most common initial intervention to lower intraocular pressure (IOP). There are many drugs available for initial therapy and medication choice may be influenced by potential cost, side effects, dosing schedules, and degree of pressure lowering needed. If target IOP is not achieved by one medication, then either switching or adding medications should be considered depending on whether the individual patient has responded to the first medication. The first medication should not be continued in the regimen if there is no response to lowering IOP.(7) Prostaglandin analogs are the most frequently prescribed eye drops for lowering IOP in patients with glaucoma because they are most efficacious, well tolerated, and instilled only once daily. Other glaucoma agents include topical beta-blockers, topical alpha-2 adrenergic agonists, topical parasympathomimetics, topical rho-kinase inhibitors, and topical and oral carbonic anhydrase inhibitors. Guidelines recommend prostaglandin analogs as first-line therapy, but do not recommend one medication over another.(7) The AAO guidelines note that adequate treatment of glaucoma requires a high

	level of adherence to therapy to achieve goal IOP. The guidelines also note that patients have relatively poor adherence (nearly 45% of patients in one study administered less than 75% of prescribed doses). Dosing frequency, difficulty in administration, comorbidities, cost, and patients running out of medication prior to being able to refill their prescription are the leading causes of poor adherence.(7)
Drops/Bottle and Days of Supply	The drop size dispensed is dependent on a number of factors for these ophthalmic solutions which include the viscosity, surface tension, design of the dropper tip, the angle the bottle is held when the drop is dispensed, and the manufacturer. A number of studies have been completed evaluating the number of drops per bottle for the prostaglandin analogs. These studies have determined that overfilling the bottles is a common occurrence for the prostaglandin analogs with an average of roughly 30 drops/mL for each 2.5 mL bottle.(8-12) With the average of 30 drops/mL, a 2.5 mL bottle should last 37.5 days if patients are treating both eyes.
Safety	The combined use of two or more prostaglandins or prostaglandin analogs is not recommended. It has been shown that administration of these prostaglandin agents more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.(3,4) Iyuzeh, Lumigan, and Xelpros are contraindicated in patients with a known hypersensitivity to any ingredients in the product.(1,4,14) Xalatan is contraindicated in patients with a known hypersensitivity to latanoprost, benzalkonium chloride, or any other ingredients in the product.(3) Travatan Z, Vyzulta, and Zioptan have no FDA labeled contraindications for use.(2,5,6)

REFERENCES

Number	Reference
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2	Travatan Z prescribing information. Alcon Laboratories, Inc. May 2020.

Number	Reference
3	Xalatan prescribing information. Pfizer Inc/Pharmacia & Upjohn Company. December 2022.
4	Xelpros prescribing information. Sun Pharmaceutical Industries, Inc. June 2022.
5	Vyzulta prescribing information. Bausch & Lomb Incorporated. January 2024.
6	Zioptan prescribing information. Akorn Inc. November 2018.
7	Primary Open-Angle Glaucoma PPP 2020. American Academy of Ophthalmology. Published October 5, 2022. https://www.aao.org/education/preferred-practice-pattern/primary-open-angle-glaucoma-ppp
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10	Rylander NR, Vold SD. Cost analysis of glaucoma medications. American Journal of Ophthalmology. 2008;145(1):106-113. doi:10.1016/j.ajo.2007.08.041
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12	Moore DB, Beck J, Kryscio RJ. An objective assessment of the variability in number of drops per bottle of glaucoma medication. BMC Ophthalmology. 2017;17(1). doi:10.1186/s12886-017-0473-8
13	Primary Open-Angle glaucoma - EyeWiki. Published March 20, 2023. https://eyewiki.aao.org/Primary_Open-Angle_Glaucoma
14	Iyuzeh prescribing information. Thea Pharma Inc. December 2022.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Opioid Immediate Release (IR) Morphine Milliequivalents

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Apadaz, Benzhydrocodone/Acetaminophen Tablet	Short-term (no more than 14 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate		
butalbital/aspirin/caffeine/codeine Capsule*	Management of the symptom complex of tension (or muscle contraction) headache when non-opioid analgesic and alternative treatments are inadequate	* generic available	
butorphanol Nasal spray*	Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate	* generic available	
Codeine Tablet*	Management of mild to moderate pain, where treatment with an opioid is appropriate and for which alternative treatments are inadequate	* generic available	
Meperidine Tablet*	Management of acute pain severe enough to require an opioid analgesic and for which	* generic available	

Agent(s)	FDA Indication(s)	Notes	Ref#
Solution	alternative treatments are inadequate		
Dilaudid (hydromorphone) Tablet* Liquid*	Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate	* generic available	
Fioricet/Codeine (butalbital/acetaminophen/caffeine/codeine) Capsule*	Management of the symptom complex of tension (or muscle contraction) headache when non-opioid analgesic and alternative treatments are inadequate	* generic available	
Hydrocodone/Ibuprofen Tablet*	Short-term management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate	* generic available	
Levorphanol Tablet*	Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate	* generic available	
Lortab, Xoldol (hydrocodone/acetaminophen) Tablet* Solution*	Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate	* generic available	
Methadose, Methadone	Management of pain severe enough to require daily, around-the-clock, long-term opioid	* generic available	

Agent(s)	FDA Indication(s)	Notes	Ref#
Tablet* Soluble tablet* Solution* Concentrate*	treatment and for which alternative treatment options are inadequate		
Morphine sulfate Tablet* Solution* Concentrate*	Management of acute and chronic pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate	* generic available	
Nucynta (tapentadol)	Management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate in adults and pediatric patients aged 6 years and older with a body weight of at least 40 kg	* generic available	
Oxaydo, Roxybond, Roxicodone (oxycodone) Capsule* Tablet* Solution* Concentrate*	Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate	* generic available	
oxymorphone Tablet*	Management of acute pain severe enough to require an opioid analgesic and for which	* generic available	

Agent(s)	FDA Indication(s)	Notes	Ref#
	alternative treatments are inadequate		
pentazocine/acetaminophen Tablet*	Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate	* generic available	
Percocet, Nalocet, Endocet, Prolate, Oycodone/Acetaminophen Tablet* Solution	Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate	* generic available	
Seglentis (celecoxib/tramadol) Tablet	Management of acute pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate		
Trezix, Acetaminophen/Caffeine/Dihydrocodeine Capsule Tablet	Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate		
Tylenol/Codeine, Acetaminophen/Codeine Tablet* Oral Solution*	Management of mild to moderate pain, where treatment with an opioid is appropriate and for which alternative treatments are inadequate	* generic available	
Ultracet (tramadol/acetaminophen) Tablet*	Management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate	* generic available	

Agent(s)	FDA Indication(s)	Notes	Ref#
Ultram, Odolo, Tramadol Tablet* Oral solution	Management of pain in adults that is severe enough to require an opioid analgesic and for which alternative treatments are inadequate	* generic available	

CLINICAL RATIONALE

	The Centers for Disease Control and Prevention (CDC) guidelines define acute pain as pain with abrupt onset and caused by an injury or other process that is not ongoing. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids.(1) Use of tramadol or codeine containing products in pediatric patients has caused life-threatening respiratory depression, with some of the reported cases occurring post-tonsillectomy and/or adenoidectomy. Ultra-rapid metabolizers are at increased risk of life-threatening respiratory depression due to a CYP2D6 polymorphism. Use in children under 12 years of age is contraindicated for these products, and for those between the ages of 12 and 18 years when used for post-operative pain management following tonsillectomy and/or adenoidectomy.(3) The CDC defines chronic pain as pain that continues or is expected to continue more than three months or past the time of normal tissue healing. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids. The FDA modified labeling of ER/LA opioids, indicating they should be reserved for management of severe, continuous pain requiring daily, around-the-clock, long term opioid treatment. The CDC indicates ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who have received immediate-release opioids daily for at least 1 week. Assessment should be done to determine if continued opioid therapy is needed.(1) The American Society of Interventional Pain Physicians (ASIPP) 2017 Guideline for Responsible, Safe, and Effective Prescription of Opioids for Chronic Non-Cancer Pain states that there is similar effectiveness for long and short-acting

	opioids, with increased adverse consequences of long-acting opioids. Long-acting agents should only be used in the management of severe, intractable pain. The guidelines recommend the following for the treatment of chronic non-cancer pain:(2)
	
	• Initiating therapy with an opioid:
	  ○ Complete a comprehensive assessment and document comprehensive history, general medical condition, psychosocial history, psychiatric status, and substance use history
	  ○ Screen for opioid abuse, utilize prescription drug monitoring programs (PDMPs), and utilize urine drug testing (UDT) to identify opioid abusers, reduce opioid abuse, and potentially reduce doctor shopping. Utilize at initiation of therapy and to monitor adherence
	  ○ Establish appropriate physical and psychological diagnoses prior to initiating therapy
	  ○ Complete a pain management consultation, for non-pain physicians, if use of chronic opioids is planned or in patients where the total daily dose will exceed the recommended CDC morphine equivalent therapy
	  ○ Establish medical necessity prior to initiation or maintenance of opioid therapy based on average, moderate, or severe (greater than or equal to 4 on a scale of 0-10) pain and/or disability
	  ○ Establish treatment goals of opioid therapy with regard to pain relief and improvement in function
	  ○ Obtain a robust agreement prior to initiating and maintaining opioid therapy. Agreements reduce over-use, misuse, abuse, and diversion
	• Assessing improvement:
	  ○ Assess improvement based on analgesia, activity, aberrant behavior, and adverse effects. Clinicians should document at least a 30% improvement in pain or disability without adverse consequences
	  ○ Therapy must be started with short-acting opioids and should be maintained with lowest effective doses

	○ Evidence of effectiveness is similar for long-acting and short-acting opioids with increased prevalence of adverse consequences of long-acting opioids ○ Long-acting opioids in high doses are recommended only in specific circumstances with severe intractable pain that is not amenable to short-acting opioids or moderate doses of long-acting opioids ○ Low dose should be considered up to 40 morphine milligram equivalents (MME), 41-90 MME should be considered moderate dose, and greater than 91 MME as high dose ○ Long-acting opioids should not be utilized for initial opioid therapy ○ Monitor adherence via UDT and PDMP to identify patients who are non-compliant or abusing prescription or illicit drugs ○ Chronic opioid therapy may be continued, with continuous adherence monitoring, and modified in conjunction with or after failure of other modalities of treatments. The 2022 CDC guidelines for Prescribing Opioids for Pain recommend the following for prescribing opioids for acute, subacute, and chronic pain:(1) • When to initiate or continue opioids for chronic pain: ○ Clinicians should maximize use of non-pharmacologic and non-opioid pharmacologic therapies prior to initiating opioid therapy as appropriate for the specific condition and patient ○ Clinicians should consider opioids only if expected benefits for both pain and function are anticipated to outweigh risks to the patients ○ Clinicians should establish treatment goals with all patients prior to starting opioid therapy for chronic pain. Goals should include realistic goals for pain and function, and how to discontinue therapy if benefits do not outweigh the risks. Clinicians should only continue therapy with opioids if there is clinically meaningful improvement in pain and function that outweigh the risks to patient safety ○ Clinicians should discuss the risks and realistic benefits of opioid therapy prior to starting and periodically during therapy

	• Opioid selection, dosage, duration, follow-up, and discontinuation:
	  ○ Clinicians should prescribe immediate release opioids instead of extended release/long-acting opioids when starting opioid therapy for acute, subacute, or chronic pain
	  ○ The lowest effective dose should be prescribed when opioids are started. Clinicians should use caution when prescribing opioids, should reassess evidence of benefits and risks when increasing doses to greater than or equal to 50 MME/day, as many patients do not experience benefit in pain or function when doses are increased beyond 50 MME/day. Exposure to doses over 50 MME/day put patients at increased risk of harm, including opioid misuse
	  ○ Opioids for acute pain should be prescribed at the lowest effective dose of immediate release opioids and should be prescribed at a quantity no greater than necessary for the expected duration of pain. Benefits and risks should be evaluated at least every 2 weeks if patients after initiating opioid therapy, and if opioid use is required beyond 1 month, clinicians should ensure reversible causes of pain are addressed and that opioid prescribing for acute pain does not become long-term opioid therapy simply due to lack of appropriate reassessment
	  ○ Benefits and risks should be evaluated within 1 to 4 weeks after starting opioid therapy for subacute or chronic pain or of dose escalations. Benefits and risks of continued therapy should be evaluated every 3 months or more frequently
	  ○ Clinicians should re-evaluate patients at higher risk for opioid use disorder (e.g., patients with mental health conditions or depression, patients with a history of substance abuse, history of overdose, taking more than 50 MME/day, or taking other central nervous system depressants with opioids) more frequently than every 3 months
	• Assessing Risk and addressing Harms of Opioid use:
	  ○ Clinicians should incorporate into the management plan strategies to mitigate risk, including offering naloxone when there is increased risk of opioid overdose, such as history of overdose, history of substance abuse disorder, higher opioid dosages

	(greater than or equal to 50 MME/day), or concurrent benzodiazepine use ○ When initiating opioid therapy for acute, subacute, or chronic pain, and periodically during opioid therapy for subacute or chronic pain, clinicians should review a patient's history of controlled substance prescriptions using the states prescription drug monitoring program (PDMP) data to determine if the patient is receiving opioid dosages or dangerous combinations that put the patient at high risk for overdose. ○ Clinicians should consider the benefits and risks of toxicology testing when prescribing opioids for subacute or chronic pain ○ Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible The CDC guideline for opioid prescribing note that patients with cancer, sickle cell disease, and patients receiving palliative or end of life care are exempt from these recommendations. The guideline also states that although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. Clinicians should continue to use non-pharmacologic and non-opioid pharmacologic pain treatments as appropriate and consider consulting a pain specialist as needed to provide optimal pain management.(1)

References

Number	Reference
1	Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1
2	Manchikanti L, Kaye AM, Knezevic NN, et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. Pain Physician 2017;20:S3-S92.

Number	Reference
3	FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. April 2017.
4	Acetaminophen/caffeine/dihydrocodeine prescribing information. Xspire Pharma, LLC. January 2021.
5	Acetaminophen/codeine solution prescribing information. Akorn. November 2022.
6	Apadaz prescribing information. KVK Tech Inc. March 2021.
7	Butorphanol tartrate nasal solution prescribing information. Apotex Corp. September 2023.
8	Codeine prescribing information. Hikma Pharmaceuticals USA Inc. February 2023.
9	Dilaudid prescribing information. Rhodes Pharmaceuticals . January 2023.
10	Fioricet with Codeine prescribing information. Actavis Pharma, Inc. March 2023.
11	Butalbital, Aspirin, Caffeine, Codeine prescribing information. Breckenridge Pharmaceutical, Inc. April 2021.
12	Hydrocodone/Acetaminophen 300 mg prescribing information. Lupin Pharmaceuticals. December 2021.
13	Hydrocodone/Acetaminophen oral solution prescribing information. Eywa Pharma Inc. October 2022.
14	Hydrocodone/ibuprofen prescribing information. Amneal Pharmaceuticals, LLC. November 2022.
15	Levorphanol prescribing information. Lannett Company, Inc. January 2022.
16	Lortab prescribing information. Akorn, Inc. September 2022.
17	Meperidine prescribing information. West-Ward Pharmaceuticals Corp. December 2022.
18	Methadone prescribing information. VistaPharm, Inc. June 2021.
19	Methadose prescribing information. VistaPharm, Inc. July 2021.

Number	Reference
20	Morphine prescribing information. Hikma Pharmaceuticals USA Inc. April 2022.
21	Hydrocodone/Acetaminophen tablet prescribing information. Amneal Pharmaceuticals, LLC. November 2022.
22	Nucynta prescribing information. Collegium Pharm, Inc. July 2023.
23	Oxaydo prescribing information. Zyla Life Sciences US Inc. July 2023.
24	Oxycodone prescribing information. ANI Pharmaceuticals Inc. August 2021.
25	Oxycodone/acetaminophen 300 mg prescribing information. FH2 Pharma LLC. April 2023.
26	Oxycodone/acetaminophen 5/325 solution prescribing information. Nostrum Laboratories, Inc. September 2021.
27	Reference no longer used.
28	Oxymorphone prescribing information. Hikma Pharmaceuticals USA. April 2023.
29	Pentazocine/naloxone prescribing information. Actavis Pharma, Inc. July 2020.
30	Percocet prescribing information. Endo Pharmaceuticals Inc. July 2022.
31	Prolate prescribing information. Forte Bio-Pharma LLC. September 2021.
32	Qdolo prescribing information. Athena Bioscience, LLC. September 2021.
33	Roxicodone prescribing information. Specgx LLC. January 2023.
34	Seglentis prescribing information. Kowa Pharmaceuticals America, Inc. October 2021.
35	Trezix prescribing information. Wraser Pharms LLC. February 2021.
36	Tylenol with codeine prescribing information. A-S Medication Solutions. April 2019.
37	Ultracet prescribing information. Jassen Pharma. February 2022.

Number	Reference
38	Ultram prescribing information Janssen Pharms. February 2021.
39	Roxybond prescribing information. Protega Pharms. March 2021.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
MME With Daily Quantity Limit	**Target Agent(s)** will be approved when ONE of the following is met: 1. The request exceeds 50 morphine milligram equivalent per day limit AND ALL of the following: A. ONE of the following: 1. Information has been provided that indicates the patient has been treated with the requested agent at the requested dose within the past 90 days **OR** 2. The prescriber states the patient is currently being treated with the requested agent at the requested dose within the past 90 days AND is at risk if therapy is changed **OR** 3. The patient has a claim for an oncology agent in the past 120 days **OR** 4. BOTH of the following: A. ONE of the following: 1. The patient has a diagnosis of chronic cancer pain due to an active malignancy **OR** 2. The patient is eligible for hospice OR palliative care **OR** 3. The patient has a diagnosis of sickle cell disease **OR** 4. The patient is undergoing treatment of non-cancer pain and ALL of the following: A. There is support for use of immediate-release single or combination opioids at a dose greater than a 50 morphine milligram equivalents (MME) per day **AND** B. A formal, consultative evaluation which includes BOTH of the following was conducted: 1. Diagnosis **AND** 2. A complete medical history which includes previous and current pharmacological and non-pharmacological therapy **AND**

Module	Clinical Criteria for Approval
	C. A patient-specific pain management plan is on file for the patient **AND** D. The prescriber has reviewed the patient's records in the state's prescription drug monitoring program (PDMP) AND has determined that the opioid dosages and combinations within the patient's records do NOT indicate the patient is at high risk for overdose **AND** B. ONE of the following: 1. The patient is not concurrently using buprenorphine or buprenorphine/naloxone agent for opioid dependence treatment **OR** 2. There is support for use of opioids with buprenorphine or buprenorphine/naloxone agent for opioid dependence treatment **AND** B. If the requested agent contains acetaminophen, then the requested dose of acetaminophen does NOT exceed 4 g/day **AND** C. If the requested agent contains tramadol, dihydrocodeine, OR codeine, then ONE of the following: 1. The patient is 12 to less than 18 years of age AND the requested agent will NOT be used for post-operative pain management following a tonsillectomy and/or adenoidectomy **OR** 2. The patient is 18 years of age or over **AND** D. ONE of the following: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND BOTH of the following: A. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **AND** B. There is support for therapy with a higher dose for the requested indication **OR** 2. The request does NOT exceed 50 morphine milligram equivalent per day limit; but the requested dose is greater than the program quantity daily limit AND ALL of the following: A. ONE of the following:

Module	Clinical Criteria for Approval
	1. The patient has a diagnosis of chronic cancer pain due to an active malignancy **OR** 2. The patient is eligible for hospice OR palliative care **OR** 3. The patient has a diagnosis of sickle cell disease **OR** 4. The patient is undergoing treatment of non-cancer pain and ALL of the following: A. A formal, consultative evaluation which includes BOTH of the following was conducted: 1. Diagnosis **AND** 2. A complete medical history which includes previous and current pharmacological and non-pharmacological therapy **AND** B. A patient-specific pain management plan is on file for the patient **AND** C. The prescriber has reviewed the patient's records in the state's prescription drug monitoring program (PDMP) AND has determined that the opioid dosages and combinations within the patient's records do NOT indicate the patient is at high risk for overdose **AND** B. ONE of the following: 1. The patient is not concurrently using buprenorphine or buprenorphine/naloxone agent for opioid dependence treatment **OR** 2. The prescriber has provided information in support of use of opioids with buprenorphine or buprenorphine/naloxone agent for opioid dependence treatment **AND** C. If the requested agent contains acetaminophen, then the requested dose of acetaminophen does NOT exceed 4 g/day **AND** D. If the requested agent contains tramadol, dihydrocodeine, OR codeine, then ONE of the following: 1. The patient is 12 to less than 18 years of age AND the requested agent will NOT be used for post-operative pain management following a tonsillectomy and/or adenoidectomy **OR** 2. The patient is 18 years of age or over **AND** E. BOTH of the following: 1. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **AND**

Module	Clinical Criteria for Approval
	2. There is support for therapy with a higher dose for the requested indication **OR** 3. The request does NOT exceed 50 morphine milligram equivalent per day limit nor the program quantity daily limit AND BOTH of the following: A. If the requested agent contains tramadol, dihydrocodeine, OR codeine, then ONE of the following: 1. The patient is 12 to less than 18 years of age AND the requested agent will NOT be used for post-operative pain management following a tonsillectomy and/or adenoidectomy **OR** 2. The patient is 18 years of age or over **AND** B. If the requested agent contains acetaminophen, then the requested dose of acetaminophen does NOT exceed 4 g/day **Length of Approval:** 6 months NOTE: If other programs (e.g., Step Therapy) also applies, please refer to program specific documents

Opioids ER

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Belbuca® (buprenorphine) Buccal film	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Limitations of Use: • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve product for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • Product is not indicated as an as-needed (prn) analgesic.		5
Butrans® (buprenorphine) Transdermal patch*	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Limitations of Use: • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve product for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be	*generic available	6

Agent(s)	FDA Indication(s)	Notes	Ref#
	otherwise inadequate to provide sufficient management of pain. • Product is not indicated as an as-needed (prn) analgesic.		
Conzip®, Tramadol Sustained Release Capsule Extended Release Tablet	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Limitations of Use: • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve product for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • Product is not indicated as an as-needed (prn) analgesic.		7,19
fentanyl Transdermal patch*	Management of pain in opioid tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Limitations of Use: • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve product for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or	*generic available	10

Agent(s)	FDA Indication(s)	Notes	Ref#
	would be otherwise inadequate to provide sufficient management of pain. • Product is not indicated as an as-needed (prn) analgesic.		
hydromorphone Extended-Release Tablet*	Management of pain in opioid tolerant patients severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Limitations of Use: • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve product for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • Product is not indicated as an as-needed (prn) analgesic.	* generic available	9
Hysingla ER® (hydrocodone Extended-Release) Tablet*	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Limitations of Use: • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve product for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be	*generic available	11

Agent(s)	FDA Indication(s)	Notes	Ref#
	otherwise inadequate to provide sufficient management of pain. • Product is not indicated as an as-needed (prn) analgesic.		
Morphine Sulfate Extended-Release Capsule*	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Limitations of Use: • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve product for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • Product is not indicated as an as-needed (prn) analgesic.	*generic available	12,14
MS Contin® (morphine sulfate Extended-Release) Tablet*	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Limitations of Use: • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve product for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be	*generic available	15

Agent(s)	FDA Indication(s)	Notes	Ref#
	otherwise inadequate to provide sufficient management of pain. • Product is not indicated as an as-needed (prn) analgesic.		
Nucynta ER® (tapentadol Extended-Release) Tablet	Pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Limitations of Use: • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve tapentadol ER for use in patients for whom alternative treatment options (e.g., nonopioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • Product is not indicated as an as-needed (prn) analgesic.		16
Oxycontin®, Oxycodone Extended-Release Tablet	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Limitations of Use: • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended		17

Agent(s)	FDA Indication(s)	Notes	Ref#
	doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve product for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • Product is not indicated as an as-needed (prn) analgesic.		
Oxymorphone Extended-Release Tablet	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Limitations of Use: • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve product for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • Product is not indicated as an as-needed (prn) analgesic.		18
Xtampza ER® (oxycodone Extended-Release) Capsule	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Limitations of Use: • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of		20

Agent(s)	FDA Indication(s)	Notes	Ref#
	overdose and death with extended-release opioid formulations, reserve product for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • Product is not indicated as an as-needed (prn) analgesic.		
Hydrocodone Extended-Release Abuse Deterrent Capsule	Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate. Limitations of Use: • Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve product for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain. • Product is not indicated as an as-needed (prn) analgesic.		21

CLINICAL RATIONALE

Chronic Pain	The Centers for Disease Control and Prevention (CDC) guidelines define acute pain as pain with abrupt onset and caused by an injury or other process that is not ongoing. Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater

	quantity than needed for the expected duration of pain severe enough to require opioids.(1)
	
	Use of tramadol or codeine containing products in pediatric patients has caused life-threatening respiratory depression, with some of the reported cases occurring post-tonsillectomy and/or adenoidectomy. Ultra-rapid metabolizers are at increased risk of life-threatening respiratory depression due to a CYP2D6 polymorphism. Use in children under 12 years of age is contraindicated for these products, and for those between the ages of 12 and 18 years when used for post-operative pain management following tonsillectomy and/or adenoidectomy.(3)
	
	The CDC defines chronic pain as pain that continues or is expected to continue more than three months or past the time of normal tissue healing. When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids. The FDA modified labeling of ER/LA opioids, indicating they should be reserved for management of severe, continuous pain requiring daily, around-the-clock, long term opioid treatment. The CDC indicates ER/LA opioids should be reserved for severe, continuous pain and should be considered only for patients who have received immediate-release opioids daily for at least 1 week. Assessment should be done to determine if continued opioid therapy is needed.(1)
	
	The American Society of Interventional Pain Physicians (ASIPP) 2017 Guideline for Responsible, Safe, and Effective Prescription of Opioids for Chronic Non-Cancer Pain states that there is similar effectiveness for long and short-acting opioids, with increased adverse consequences of long-acting opioids. Long-acting agents should only be used in the management of severe, intractable pain. The guidelines recommend the following for the treatment of chronic non-cancer pain:(2)
	
	• Initiating therapy with an opioid:
	  ○ Complete a comprehensive assessment and document comprehensive history, general medical condition, psychosocial history, psychiatric status, and substance use history
	  ○ Screen for opioid abuse, utilize prescription drug monitoring programs (PDMPs), and utilize urine drug testing (UDT) to identify opioid abusers, reduce opioid abuse, and potentially reduce doctor shopping. Utilize at initiation of therapy and to monitor adherence
	  ○ Establish appropriate physical and psychological diagnoses prior to initiating therapy
	  ○ Complete a pain management consultation, for non-pain physicians, if use of chronic opioids is planned or in patients

	where the total daily dose will exceed the recommended CDC morphine equivalent therapy ○ Establish medical necessity prior to initiation or maintenance of opioid therapy based on average, moderate, or severe (greater than or equal to 4 on a scale of 0-10) pain and/or disability ○ Establish treatment goals of opioid therapy with regard to pain relief and improvement in function ○ Obtain a robust agreement prior to initiating and maintaining opioid therapy. Agreements reduce over-use, misuse, abuse, and diversion • Assessing improvement: ○ Assess improvement based on analgesia, activity, aberrant behavior, and adverse effects. Clinicians should document at least a 30% improvement in pain or disability without adverse consequences ○ Therapy must be started with short-acting opioids and should be maintained with lowest effective doses ○ Evidence of effectiveness is similar for long-acting and short-acting opioids with increased prevalence of adverse consequences of long-acting opioids ○ Long-acting opioids in high doses are recommended only in specific circumstances with severe intractable pain that is not amenable to short-acting opioids or moderate doses of long-acting opioids ○ Low dose should be considered up to 40 MME, 41-90 MME should be considered moderate dose, and greater than 91 morphine milligram equivalents (MME) as high dose ○ Long-acting opioids should not be utilized for initial opioid therapy ○ Monitor adherence via UDT and PDMP to identify patients who are non-compliant or abusing prescription or illicit drugs ○ Chronic opioid therapy may be continued, with continuous adherence monitoring, and modified in conjunction with or after failure of other modalities of treatments. The 2022 CDC guidelines for Prescribing Opioids for Pain recommend the following for prescribing opioids for acute, subacute, and chronic pain:(1) • When to initiate or continue opioids for chronic pain: ○ Clinicians should maximize use of non-pharmacologic and non-opioid pharmacologic therapies prior to initiating opioid therapy as appropriate for the specific condition and patient

	○ Clinicians should consider opioids only if expected benefits for both pain and function are anticipated to outweigh risks to the patients ○ Clinicians should establish treatment goals with all patients prior to starting opioid therapy for chronic pain. Goals should include realistic goals for pain and function, and how to discontinue therapy if benefits do not outweigh the risks. Clinicians should only continue therapy with opioids if there is clinically meaningful improvement in pain and function that outweigh the risks to patient safety ○ Clinicians should discuss the risks and realistic benefits of opioid therapy prior to starting and periodically during therapy • Opioid selection, dosage, duration, follow-up, and discontinuation: ○ Clinicians should prescribe immediate release opioids instead of extended release/long-acting opioids when starting opioid therapy for acute, subacute, or chronic pain ○ The lowest effective dose should be prescribed when opioids are started. Clinicians should use caution when prescribing opioids, should reassess evidence of benefits and risks when increasing doses to greater than or equal to 50 MME/day, as many patients do not experience benefit in pain or function when doses are increased beyond 50 MME/day. Exposure to doses over 50 MME/day put patients at increased risk of harm, including opioid misuse ○ Opioids for acute pain should be prescribed at the lowest effective dose of immediate release opioids and should be prescribed at a quantity no greater than necessary for the expected duration of pain. Benefits and risks should be evaluated at least every 2 weeks if patients after initiating opioid therapy, and if opioid use is required beyond 1 month, clinicians should ensure reversible causes of pain are addressed and that opioid prescribing for acute pain does not become long-term opioid therapy simply due to lack of appropriate reassessment ○ Benefits and risks should be evaluated within 1 to 4 weeks after starting opioid therapy for subacute or chronic pain or of dose escalations. Benefits and risks of continued therapy should be evaluated every 3 months or more frequently ○ Clinicians should re-evaluate patients at higher risk for opioid use disorder (e.g., patients with mental health conditions or depression, patients with a history of substance abuse, history of overdose, taking more than 50 MME/day, or taking other central

	nervous system depressants with opioids) more frequently than every 3 months
	• Assessing Risk and addressing Harms of Opioid use:
	  ○ Clinicians should incorporate into the management plan strategies to mitigate risk, including offering naloxone when there is increased risk of opioid overdose, such as history of overdose, history of substance abuse disorder, higher opioid dosages (greater than or equal to 50 MME/day), or concurrent benzodiazepine use
	  ○ When initiating opioid therapy for acute, subacute, or chronic pain, and periodically during opioid therapy for subacute or chronic pain, clinicians should review a patient's history of controlled substance prescriptions using the states prescription drug monitoring program (PDMP) data to determine if the patient is receiving opioid dosages or dangerous combinations that put the patient at high risk for overdose.
	  ○ Clinicians should consider the benefits and risks of toxicology testing when prescribing opioids for subacute or chronic pain
	  ○ Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible
	
	The CDC guideline for opioid prescribing note that patients with cancer, sickle cell disease, and patients receiving palliative or end of life care are exempt from these recommendations. The guideline also states that although identification of an opioid use disorder can alter the expected benefits and risks of opioid therapy for pain, patients with co-occurring pain and substance use disorder require ongoing pain management that maximizes benefits relative to risks. Clinicians should continue to use non-pharmacologic and non-opioid pharmacologic pain treatments as appropriate and consider consulting a pain specialist as needed to provide optimal pain management.(1)

Safety	The concurrent use of opioid agonists with buprenorphine or buprenorphine/naloxone should be avoided. Such concurrent use may reduce analgesic effect and/or may precipitate withdrawal symptoms.(5-7, 9-12, 14-21) All agents contain the following boxed warnings:(5-7, 9-12, 14-21) • Addiction, Abuse, and Misuse: Product exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing product and monitor all patients regularly for the development of these behaviors and conditions

	• Opioid Analgesic Risk Evaluation and Mitigation Strategy (REMS): To ensure that the benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse, the Food and Drug Administration (FDA) has required a REMS for these products. Under the requirements of the REMS, drug companies with approved opioid analgesic products must make REMS-compliant education programs available to healthcare providers. Healthcare providers are strongly encouraged to:
	  ○ complete a REMS-compliant education program,
	  ○ counsel patients and/or their caregivers, with every prescription, on safe use, serious risks, storage, and disposal of these products,
	  ○ emphasize to patients and their caregivers the importance of reading the Medication Guide every time it is provided by their pharmacist, and
	  ○ consider other tools to improve patient, household, and community safety.
	• Life-Threatening Respiratory Depression: Serious, life-threatening, or fatal respiratory depression may occur with use of product. Monitor for respiratory depression, especially during initiation of product or following a dose increase
	  ○ Oral products: Instruct patients to swallow product whole (for some capsules, contents may be sprinkled on applesauce and swallowed immediately without chewing); crushing, chewing, or dissolving product can cause rapid release and absorption of a potentially fatal dose of product
	  ○ Belbuca, Butrans: Misuse or abuse of Belbuca by chewing, swallowing, snorting, or injecting buprenorphine extracted from the film/patch will result in uncontrolled delivery of buprenorphine and pose a significant risk of overdose and death
	  ○ Fentanyl transdermal patches: Due to risk of respiratory depression, patches are contraindicated for use as an as-needed analgesic, in non-opioid tolerant patients, in acute pain, and in postoperative pain
	• Accidental Ingestion/Exposure: Accidental ingestion/exposure of even one dose of product, especially by children, can result in a fatal overdose of product
	  ○ Fentanyl products also note deaths due to an overdose have occurred when children and adults were accidentally exposed. Strict adherence to the recommended handling and disposal instructions is of the utmost importance to prevent accidental exposure

	• Neonatal Opioid Withdrawal Syndrome: Prolonged use of product during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available
	• Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants: Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death:
	  ○ Reserve concomitant prescribing of product and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
	  ○ Limit dosages and durations to the minimum required.
	  ○ Follow patients for signs and symptoms of respiratory depression and sedation.
	
	Tramadol products contain the following additional boxed warnings:(7,19)
	
	• Ultra-Rapid Metabolism Of Tramadol And Other Risk Factors For Life-Threatening Respiratory Depression In Children: Life-threatening respiratory depression and death have occurred in children who received tramadol. Some of the reported cases occurred following tonsillectomy and/or adenoidectomy, and at least one case, the child had evidence of being an ultra-rapid metabolizer of tramadol due to a CYP2D6 polymorphism. Tramadol is contraindicated in children younger than 12 years of age and in children younger than 18 years of age following tonsillectomy and/or adenoidectomy. Avoid the use of tramadol in adolescents 12 to 18 years of age who have other risk factors that may increase their sensitivity to the respiratory depressant effects of tramadol
	• Interactions with Drugs Affecting Cytochrome P450 Isoenzymes: The effects of concomitant use or discontinuation of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol are complex. Use of cytochrome P450 3A4 inducers, 3A4 inhibitors, or 2D6 inhibitors with tramadol requires careful consideration of the effects on the parent drug, tramadol, and the active metabolite, M1
	
	Fentanyl products contain the following additional boxed warnings:(10)
	
	• Cytochrome P450 3A4 Interaction: The concomitant use of fentanyl with all cytochrome P450 3A4 inhibitors may result in an increase in fentanyl

	plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in fentanyl plasma concentration. Monitor patients receiving fentanyl and any CYP3A4 inhibitor or inducer • Risk of Increased Fentanyl Absorption with Application of External Heat: Exposure of the fentanyl application site and surrounding area to direct external heat sources, such as heating pads or electric blankets, heat or tanning lamps, sunbathing, hot baths, saunas, hot tubs, and heated water beds may increase fentanyl absorption and has resulted in fatal overdose of fentanyl. Warn patients to avoid exposing the application site and surrounding area to direct external heat sources Oxycodone and hydrocodone products contain the following additional boxed warning:(11,17,20,21) • Cytochrome P450 3A4 Interaction: The concomitant use of oxycodone/hydrocodone with all cytochrome P450 3A4 inhibitors may result in an increase in oxycodone/hydrocodone plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in oxycodone/hydrocodone plasma concentration. Monitor patients receiving oxycodone/hydrocodone and any CYP3A4 inhibitor or inducer Oxymorphone, Morphine sulfate ER capsules, Nucynta contain the following additional boxed warning:(12,14,15,16,18) • Interaction with Alcohol: Instruct patients not to consume alcoholic beverages or use prescription or non-prescription products that contain alcohol while taking product. The co-ingestion of alcohol with product may result in increased plasma levels and a potentially fatal overdose Morphine ER products have the following contraindications for use:(12,14,15) • Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment • Concurrent use of monoamine oxidase inhibitors (MAOIs) or use within 14 days • Known or suspected gastrointestinal obstruction, including paralytic ileus

	• Hypersensitivity to morphine Buprenorphine products have the following contraindications for use:(5,6) • Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment • Known or suspected gastrointestinal obstruction, including paralytic ileus • Hypersensitivity (e.g., anaphylaxis) to buprenorphine Tramadol products have the following contraindications for use:(7,19) • Hypersensitivity to tramadol • Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment • All children younger than 12 years of age • Post-operative pain management in children younger than 18 years of age following tonsillectomy and/or adenoidectomy • Concurrent use of monoamine oxidase inhibitors (MAOIs) or use of MAOIs within the last 14 days • Known or suspected gastrointestinal obstruction, including paralytic ileus Fentanyl products have the following contraindications for use:(10) • Opioid non-tolerant patients • Acute or intermittent pain, postoperative pain, mild pain • Known or suspected GI obstruction, including paralytic ileus • Known hypersensitivity to fentanyl or any of the components of the transdermal system • Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment Hydromorphone ER has the following contraindications for use:(9) • Opioid non-tolerant patients. • Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment • Known or suspected gastrointestinal obstruction, including paralytic ileus • Surgical procedures and/or underlying disease resulting in narrowing of the gastrointestinal tract, or have “blind loops” of the gastrointestinal tract or gastrointestinal obstruction

	• Hypersensitivity (e.g., anaphylaxis) to hydromorphone or sulfite-containing medications Hydrocodone ER products have the following contraindications for use:(11,21) • Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment • Known or suspected gastrointestinal obstruction, including paralytic ileus • Hypersensitivity to any component or hydrocodone bitartrate Nucynta ER has the following contraindications for use:(16) • Acute or severe bronchial asthma • Known or suspected paralytic ileus • Hypersensitivity to tapentadol or to any other ingredients of the product • Concurrent use of monoamine oxidase inhibitors (MAOI) or use within the last 14 days Oxycodone ER products have the following contraindications for use:(17,20) • Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment • Known or suspected gastrointestinal obstruction, including paralytic ileus • Hypersensitivity (e.g., anaphylaxis) to oxycodone Oxymorphone ER products have the following contraindications for use:(18) • Acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment • Known or suspected gastrointestinal obstruction, including paralytic ileus • Moderate and severe hepatic impairment • Hypersensitivity (e.g., anaphylaxis) to oxymorphone, any other ingredients in oxymorphone ER

REFERENCES

Number	Reference
1	Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. DOI: http://dx.doi.org/10.15585/mmwr.rr7103a1
2	Manchikanti L, Kaye AM, Knezevic NN, et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. Pain Physician 2017;20:S3-S92.
3	FDA Drug Safety Communication: FDA restricts use of prescription codeine pain and cough medicines and tramadol pain medicines in children; recommends against use in breastfeeding women. April 2017.
4	Reference no longer used.
5	Belbuca prescribing information. BioDelivery Sciences International Inc, June 2022.
6	Butrans prescribing information. Purdue Pharma LP. June 2022.
7	Conzip prescribing information. Vertical Pharmaceuticals Inc. September 2021.
8	Reference No longer used.
9	Hydromorphone ER prescribing information. Ascent Pharmaceuticals, Inc. September 2020.
10	Fentanyl patch prescribing information. SpecGx, LLC. May 2023.
11	Hysingla ER prescribing information. Purdue Pharma LP. March 2021.
12	Morphine sulfate ER capsule prescribing information. Upsher-Smith Laboratories, LLC. September 2023.
13	Reference no longer used.
14	Morphine sulfate ER prescribing information. Actavis Pharma, Inc. August 2021.
15	MS Contin prescribing information. Rhodes Pharmaceuticals L.P. May 2023.

Number	Reference
16	Nucynta ER prescribing information. Janssen Pharmaceuticals Inc. March 2021.
17	OxyContin prescribing information. Purdue Pharma L.P. October 2021.
18	Oxymorphone prescribing information. Amneal Pharmaceuticals LLC. June 2022.
19	Tramadol ER prescribing information. Sun Pharmaceuticals Industries, Inc. June 2023.
20	Xtampza prescribing information. Collegium Pharmaceuticals, Inc. March 2021.
21	Zohydro ER prescribing information. Alvogen Inc. March 2021.

ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
65100095107 5		tramadol hcl tab er	100 MG ; 200 MG ; 300 MG	a			
65100095107 0	Conzip	tramadol hcl cap er	100 MG ; 200 MG ; 300 MG	a			

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** All target agents are eligible for continuation of therapy 1. Information has been provided that the patient has been treated with the requested agent within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent within the past 90 days AND is at risk if therapy is changed **OR** B. ALL of the following: 1. ONE of the following: A. The patient has a diagnosis of chronic cancer pain due to an active malignancy **OR** B. The patient is eligible for hospice OR palliative care **OR** C. The patient has a diagnosis of sickle cell disease **OR** D. The patient is undergoing treatment of chronic non-cancer pain and ALL of the following: 1. A formal, consultative evaluation which includes ALL of the following has been conducted: A. Diagnosis **AND** B. A complete medical history which includes previous and current pharmacological and non-pharmacological therapy **AND** C. The need for continued opioid therapy has been assessed **AND** 2. The requested agent is not prescribed as an as-needed (prn) analgesic **AND** 3. ONE of the following:

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
A. The patient's medication history includes a trial of at least 7 days of an immediate-acting opioid OR
B. The patient has an intolerance or hypersensitivity to therapy with immediate-acting opioids that is not expected to occur with the requested agent OR
C. The patient has an FDA labeled contraindication to ALL immediate-acting opioids that is not expected to occur with the requested agent AND
4. A patient-specific pain management plan is on file for the patient AND
5. The prescriber has reviewed the patient's records in the state's prescription drug monitoring program (PDMP) AND has determined that the opioid dosages and combinations of opioids and other controlled substances within the patient's records do NOT indicate the patient is at high risk for overdose AND
2. ONE of the following:
A. The patient is not concurrently using buprenorphine or buprenorphine/naloxone for opioid dependence treatment OR
B. The prescriber has provided information in support of use of concurrent use of opioids with buprenorphine or buprenorphine/naloxone for opioid dependence treatment AND
3. If the client has preferred agent(s), then ONE of the following:
<table>
<tr><th>Preferred Agent(s)</th><th>Non-Preferred Agent(s)</th></tr>
<tr><td></td><td></td></tr>
</table>
A. The requested agent is a preferred agent OR
B. The patient has tried and had an inadequate response to a preferred agent OR
C. The patient has an intolerance or hypersensitivity to a preferred agent OR
D. The patient has an FDA labeled contraindication to ALL preferred agents AND
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
2. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:
<table>
<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Butrans</td><td>Buprenorphine patch</td></tr>
<tr><td>Hysingla</td><td>Hydrocodone ER tabs</td></tr>
<tr><td>MS Contin</td><td>Morphine sulfate ER tabs</td></tr>
</table>
A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
C. The prescriber has provided information to support the use of the requested brand agent over the generic equivalent AND
3. If the requested agent contains tramadol, dihydrocodeine, or codeine, then ONE of the following:
A. The patient is 12 to less than 18 years of age AND the requested agent will NOT be used for post-operative pain management following a tonsillectomy and/or adenoidectomy OR
B. The patient is 18 years of age or over AND
4. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 6 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
</td></tr>
</table>

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td>QL Standalone</td><td>
Program Maximum Daily Doses
<table>
<tr><th>Agent(s)</th><th>Program Maximum Daily Dose</th></tr>
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</td></tr>
</table>

Module	Clinical Criteria for Approval	
	Belbuca (buprenorphine buccal film)	1800 mcg
	Butrans (buprenorphine transdermal system)	20 mcg/hr system/week
	ConZip, Tramadol SR (tramadol ER) capsules	300 mg
	fentanyl transdermal patch	100 mcg/hr patch/2 days
	Hysingla (hydrocodone ER) tablets	120 mg
	Morphine Sulfate ER (generic Kadian) capsules	400 mg
	Morphine Sulfate ER capsules (beads)	240 mg
	MS Contin (morphine sulfate ER) tablets	600 mg
	Nucynta ER (tapentadol ER) tablets	500 mg
	OxyContin (oxycodone ER) tablets	160 mg
	Oxymorphone ER tablets	80 mg
	tramadol ER tablets	300 mg
	Xtampza ER (oxycodone ER) capsules	288 mg
	Zohydro ER (hydrocodone ER) capsules	100 mg

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met: 1. BOTH of the following: A. The requested quantity (dose) does NOT exceed the program quantity limit **AND** B. If the requested agent contains tramadol, dihydrocodeine, or codeine, then ONE of the following: 1. The patient is 12 to less than 18 years of age AND the requested opioid will NOT be used for post-operative pain management following a tonsillectomy and/or adenoidectomy **OR** 2. The patient is 18 years of age or over **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. The requested quantity (dose) is less than or equal to the Program Maximum Daily dose (maximum mg allowed with highest dosage strength) AND ALL of the following: 1. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **AND** 2. The prescriber has provided information in support of therapy with a higher dose for the intended diagnosis **AND** 3. If the requested agent contains tramadol, dihydrocodeine, or codeine, then ONE of the following: A. The patient is 12 to less than 18 years of age AND the requested opioid will NOT be used for post-operative pain management following a tonsillectomy and/or adenoidectomy **OR** B. The patient is 18 years of age or over **OR** B. The requested quantity (dose) is greater than the Program Maximum Daily Dose (maximum mg allowed with highest dosage strength) AND ALL of the following: 1. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **AND** 2. ONE of the following: A. The patient has a diagnosis of active cancer pain due to an active malignancy **OR** B. The patient is eligible for hospice OR palliative care **OR** C. The patient has a diagnosis of sickle cell disease **OR** D. The patient is undergoing treatment of chronic non-cancer pain and ALL of the following: 1. A formal, consultative evaluation which includes ALL of the following has been conducted: A. Diagnosis **AND**

Module	Clinical Criteria for Approval
	B. A complete medical history which includes previous and current pharmacological and non-pharmacological therapy **AND** C. The need for continued opioid therapy has been assessed **AND** 2. A patient-specific pain management plan is on file for the patient **AND** 3. The prescriber has reviewed the patient's records in the state's prescription drug monitoring program (PDMP) **AND** has determined that the opioid dosages and combinations of opioids and other controlled substances within the patient's records do NOT indicate the patient is at high risk for overdose **AND** 3. The prescriber has provided information in support of therapy with a higher dose for the requested indication **AND** 4. If the requested agent contains tramadol, dihydrocodeine, or codeine, then ONE of the following: A. The patient is 12 to less than 18 years of age AND the requested opioid will NOT be used for post-operative pain management following a tonsillectomy and/or adenoidectomy **OR** B. The patient is 18 years of age or over **Length of Approval:** 1 month for dose titration requests and up to 6 months for all other requests
QL with PA	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND BOTH of the following: A. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **AND** B. The prescriber has provided information in support of therapy with a higher dose for the requested indication **Length of Approval:** 6 months

Opzelura (ruxolitinib)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Opzelura® (ruxolitinib) Cream	Topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable Topical treatment of nonsegmental vitiligo in adult and pediatric patients 12 years of age and older Limitation of Use: • Use of Opzelura in combination with therapeutic biologics, other Janus kinase (JAK) inhibitors, or potent immunosuppressants such as azathioprine or cyclosporine is not recommended		1

CLINICAL RATIONALE

Atopic Dermatitis	Atopic dermatitis (AD), also known as atopic eczema, is a chronic, pruritic inflammatory dermatosis affecting up to 25% of children and 1-5% of adults. AD follows a relapsing course and is associated with elevated serum immunoglobulin (IgE) levels and a personal or family history of type I allergies, allergic rhinitis, and/or asthma. Onset is most common between 3 and 6 months of age, with approximately 60% of patients developing the eruption in the first year of life and 90% by age 5. While the majority of affected individuals have resolution of disease by adulthood, 10 to 30% do not, and a smaller percentage first develop symptoms as adults. AD has a complex pathogenesis involving genetic, immunologic, and environmental factors, which lead to a dysfunctional skin barrier and dysregulation of the immune system. Clinical findings include erythema, edema, xerosis, erosions/excoriations, oozing and crusting, and

	lichenification. These clinical findings vary by patient age and chronicity of lesions. Pruritus is a hallmark of the condition that is responsible for much of the disease burden borne by patients and their families. Typical patterns include facial, neck and extensor involvement in infants and children; flexure involvement in any age group, with sparing of groin and axillary regions.(2) Goals of treatment are to reduce symptoms (pruritus and dermatitis), prevent exacerbations, and minimize therapeutics risks.(3) Despite its relapsing and remitting nature, the majority of patients with AD can achieve clinical improvement and disease control with topical emollient/moisturizer use and conventional topical therapies (including corticosteroids and calcineurin inhibitors).(3,5) Moisturizers reduce signs, symptoms, and inflammation in AD, and can improve severity while also increasing time between flares. Moisturizers are considered generally safe and are strongly recommended to be used as part of a treatment regimen for AD, either as monotherapy or as concurrent use with pharmacologic treatments.(4) Topical therapies remain the mainstay of treatment due to their proven track record and generally favorable safety profile. They can be utilized individually or in combination with other topical, physical, and/or systemic treatments; as different classes of treatment have different mechanisms of action, combining therapies allows for the targeting of AD via multiple disease pathways. The American Academy of Dermatology (AAD) strongly recommends the following topical agents:(4) • Topical corticosteroids (TCS) • Calcineurin inhibitors (TCIs) (e.g., tacrolimus, pimecrolimus) • Topical PDE-4 inhibitors (e.g., crisaborole) [mild to moderate AD] • Topical JAK inhibitors (e.g., ruxolitinib) [mild to moderate AD] TCS are the most commonly utilized FDA-approved therapies in AD and are commonly used as first-line treatment for mild-to severe dermatitis in all skin regions. TCS target a variety of immune cells and suppress the release of proinflammatory cytokines. High to very high (super) potency TCS can be used to control flares and treat severe disease, while medium potency TCS are utilized for longer courses and as maintenance therapy. Lower potency TCS may be used, and it is important to consider the anatomical site (i.e., using lower potency agents on the face, neck, genitals, and body folds) and severity of the disease when choosing a steroid potency. Most studies of TCS in AD management involve twice daily application, but some studies (particularly for potent TCS) suggest once daily use may be sufficient. Traditionally, TCS were stopped once

	AD signs and symptoms of an AD flare were controlled. Maintenance in between AD flares with once to twice weekly use of TCS is another approach.(4) TCIs are a safe anti-inflammatory option for mild-to-severe AD, particularly when there is concern for adverse events secondary to corticosteroid use. Both tacrolimus and pimecrolimus have been shown to be effective in treating AD, but pimecrolimus may be more appropriate for patients who have milder disease or are sensitive to local reactions.(4) Prescribing information for pimecrolimus cream and tacrolimus ointment indicate evaluation after 6 weeks if symptoms of AD do not improve for adults and pediatrics.(7,8)
Vitiligo	Vitiligo is an acquired skin pigmentation disorder characterized by well defined, depigmented areas of the skin. The depigmentation is due to a loss of epidermal melanocytes. Vitiligo can present in a localized or generalized distribution, with the lesions coalescing into larger depigmented areas. The underlying cause of vitiligo is yet unknown.(10) Vitiligo is commonly classified into two different forms, segmental and non-segmental. Non-segmental vitiligo (NSV) tends to evolve over time in both distribution and extension patterns. NSV is an umbrella term for a number of different subtypes of vitiligo. These include acrofacial, generalized, mucosal (multifocal), and universal. NSV is characterized by depigmented lesions that vary in size and often involve both sides of the body. Involvement of the scalp and other hair-bearing areas may manifest with patches of gray or white hairs, while body hair is generally spared. Segmental vitiligo (SV) tends to have an earlier age of onset, that rapidly progresses but has a limited course. Depigmentation spreads within a segment within 6-24 months and then stops. Hair follicles are more frequently involved early in the disease course with SV, with up to 50% of patients exhibiting poliosis, a localized cluster of white hair shafts, in affected areas.(11) The diagnosis of vitiligo is based off of clinical presentation and with a Woods lamp, which is a handheld ultraviolet device. The Woods lamp is also used to track progression of lesions over time. There are a number of other indications that can mimic vitiligo and it is important to rule those out with a close examination of the skin. Vitiligo does not cause scaling or textural changes in the skin.(10) Topical corticosteroids (TCS) are recommended as first line treatment for vitiligo.(6,12) TCS have been found to be effective in areas of the face and neck, extrafacial locations, and limited treatment areas.(6,14) A (medium) potent to very potent TCS should be used for treatment.(12,14) Mometasone furoate, a medium potency TCS, is often recommended due to a decreased risk of side effects.(6,9) The risk of local side effects, including skin atrophy, should be

	evaluated when determining an appropriate treatment regimen.(6,14) When using TCS on the face, the periocular area should be avoided.(12) TCS should also be used with caution in areas of thinner skin, such as the axillar region and genital area. Although once daily dosing is used for the treatment of vitiligo, using an intermittent dosing regimen can reduce the risk of side effects. Intermittent dosing regimens of 1 week on and at least 1 week off, or 2 weeks on and 2 weeks off, have been suggested.(12,14) Topical calcineurin inhibitors (TCIs) can be considered as an alternative treatment to TCS for areas of the face, neck, groin, and axillary.(14) TCIs have been noted to be less effective or not effective at all for extrafacial regions.(6,14) The topical safety profile of TCIs is advantageous compared to TCS, especially the risk of skin atrophy.(9,14) This allows them to be used long term and in areas where the use of potent TCS may not be appropriate.(6,14) The minimal treatment period for evaluation of efficacy has not been established, but the treatment duration in studies ranged from 10 weeks to 18 months.(9) Topical therapies should be evaluated every 3 to 6 months to check for improvement.(12) Both TCS and TCIs can be considered for maintenance treatment in vitiligo after successful repigmentation, although a less frequent dosing regimen should be used. Ruxolitinib, a topical JAK-inhibitor, is the first FDA approved drug for non-segmental vitiligo. At this time, there is no sufficient data to support the use of topical ruxolitinib as a maintenance therapy.(13)
Efficacy	*Atopic Dermatitis*(1) Two double-blind, randomized, vehicle-controlled trials of identical design (TRuE-AD1 and TRuE-AD2, NCT03745638 and NCT03745651, respectively) enrolled a total of 1249 adult and pediatric subjects aged 12 and older. Subjects had affected body surface area (BSA) of 3 to 20%, and an Investigator's Global Assessment (IGA) score of 2 (mild) to 3 (moderate) on a severity scale of 0 to 4. The baseline Itch Numerical Rating Scale (Itch NRS), defined as the 7-day average of the worst level of itch intensity in the last 24 hours, was 5 on a scale of 0 to 10. In both trials, subjects were randomized 2:2:1 to treatment with Opzelura, ruxolitinib cream, 0.75%, or vehicle cream twice daily (BID) for 8 weeks. The primary efficacy endpoint was the proportion of subjects at week 8 achieving IGA treatment success (IGA-TS) defined as a score of 0 (clear) or 1 (almost clear) with greater than or equal to 2 grade improvement from baseline. Efficacy was also assessed using a greater than or equal to 4-point improvement in Itch NRS. Opzelura was 38.9% and 44.1% more effective than placebo for IGA-TS, and

	36.7% and 35.8% more effective than placebo for Itch NRS in TRuE-AD1 and TRuE-AD2 respectively. Patients should stop using Opzelura when signs and symptoms (e.g., itch, rash, and redness) of atopic dermatitis resolve. If signs and symptoms do not improve within 8 weeks, patients should be re-examined by their healthcare provider. *Nonsegmental Vitiligo*(1) Two double-blind, randomized, vehicle-controlled trials of identical design (TRuE-V1 and TRuE-V2, NCT04052425 and NCT04057573, respectively) enrolled a total of 674 adult and pediatric subjects aged 12 years and older. Subjects had depigmented areas affecting greater than or equal to 0.5% facial body surface area (F-BSA), greater than or equal to 3% non-facial BSA, and total body vitiligo area (facial and non-facial, including hands, feet, upper and lower extremities, and trunk body areas) of up to 10% BSA. In both trials, subjects were randomized 2:1 to treatment with Opzelura or vehicle cream twice daily (BID) for 24 weeks followed by an additional 28 weeks of treatment with Opzelura twice daily for all subjects. Lesions on the face were assessed with the facial Vitiligo Area Scoring Index (F-VASI) and lesions on the total body (including the face) were assessed with the total body Vitiligo Area Scoring Index (T-VASI). The primary efficacy endpoint was the proportion of subjects achieving at least 75% improvement in F-VASI (F-VASI75) at week 24, and the proportion of participants achieving at least 90% improvement in F-VASI (F-VASI90) was also evaluated. Opzelura was 22.5% and 16.9% more effective than placebo for F-VASI75, and 13.3% and 13.5% more effective than placebo for F-VASI90 in TRuE-V1 and TRuE-V2 respectively. Satisfactory patient response may require treatment with Opzelura for more than 24 weeks. If the patient does not find the repigmentation meaningful by 24 weeks, the patient should be re-evaluated by the healthcare provider.

Safety	Opzelura carries the following boxed warnings:(1)
	
	• Serious infections leading to hospitalization or death have occurred in patients receiving oral Janus kinase (JAK) inhibitors for inflammatory conditions
	  ○ Reported infections include:
	  ▪ Active tuberculosis, which may present with pulmonary or extrapulmonary disease
	  ▪ Invasive fungal infections, including cryptococcosis and pneumocystosis

	▪ Bacterial, viral, and other infections due to opportunistic pathogens ○ Avoid use of Opzelura in patients with an active, serious infection, including localized infections. If a serious infection develops, interrupt Opzelura until the infection is controlled. The risks and benefits of treatment with Opzelura should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with Opzelura. • A higher rate of all-cause mortality, including sudden cardiovascular death, was observed in patients 50 years of age and older with at least one cardiovascular risk factor treated with an oral JAK inhibitor compared with a TNF blocker for RA. • Malignancies, including non-melanoma skin cancer (NMSC), were reported in patients treated with Opzelura. Lymphoma and other malignancies (excluding NMSC) have occurred at a higher rate in patients receiving oral JAK inhibitors used to treat inflammatory conditions compared to TNF blockers. Patients who are current or past smokers are at additional increased risk. • In patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of major adverse cardiovascular events (MACE) (defined as cardiovascular death, myocardial infarction, and stroke) was observed in patients treated with an oral JAK inhibitor compared with a TNF blocker for RA. Patients who are current or past smokers are at additional increased risk. Discontinue Opzelura in patients that have experienced a myocardial infarction or stroke. • Thromboembolic events were observed in clinical trials with Opzelura. Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis have occurred in patients treated with JAK inhibitors for inflammatory conditions. Many of these adverse reactions were serious and some resulted in death. In patients 50 years of age and older with at least one cardiovascular risk factor, a higher rate of thrombosis was observed in patients treated with an oral JAK inhibitor compared with a TNF blocker for RA. Avoid Opzelura in patients at increased risk of thrombosis. If symptoms of thrombosis occur, discontinue Opzelura and treat appropriately. Opzelura has no FDA labeled contraindications for use.(1)

	Opzelura for the treatment of atopic dermatitis may be applied to affected areas of up to 20% body surface area. Opzelura for the treatment of nonsegmental vitiligo may be applied to affected areas of up to 10% body surface area.(1) Do not use more than one 60 gram tube per week or one 100 gram tube per 2 weeks.(1)

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of mild to moderate atopic dermatitis (AD) AND ALL of the following: 1. The patient's affected body surface area (BSA) is less than or equal to 20% **AND** 2. The patient is NOT immunocompromised **AND** 3. ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient has tried and had an inadequate response to at least a low-potency topical corticosteroid used in the treatment of AD after at least a 4-week duration of therapy **OR** B. The patient has an intolerance or hypersensitivity to at least a low-potency topical corticosteroid used in the treatment of AD **OR** C. The patient has an FDA labeled contraindication to ALL topical corticosteroids used in the treatment of AD **AND** 4. ONE of the following: A. The patient has tried and had an inadequate response to a topical calcineurin inhibitor used in the treatment of AD after at least a 6-week duration of therapy **OR** B. The patient has an intolerance or hypersensitivity to a topical calcineurin inhibitor used in the treatment of AD **OR** C. The patient has an FDA labeled contraindication to ALL topical calcineurin inhibitors used in the treatment of AD **AND** 5. BOTH of the following: A. The patient is currently treated with topical emollients and practicing good skin care **AND** B. The patient will continue the use of topical emollients and good skin care practices in combination with the requested agent **OR** B. The patient has a diagnosis of nonsegmental vitiligo AND ALL of the following: 1. Vitiligo is NOT restricted from coverage under the patient's benefit **AND** 2. The patient's affected body surface area (BSA) is less than or equal to 10% **AND** 3. ONE of the following: A. The patient has vitiligo impacting areas OTHER THAN the face, neck, axillary, or groin AND ONE of the following: 1. The patient has tried and had an inadequate response to at least a medium-potency topical corticosteroid used in the treatment of nonsegmental vitiligo after at least a 2-week duration of therapy **OR** 2. The patient has an intolerance or hypersensitivity to at least a medium-potency topical corticosteroid used in the treatment of nonsegmental vitiligo **OR** 3. The patient has an FDA labeled contraindication to ALL medium-, high-, and super-potency topical corticosteroids used in the treatment of nonsegmental vitiligo **OR** B. The patient has vitiligo on the face, neck, axillary, or groin AND ONE of the following:

Module	Clinical Criteria for Approval
	1. The patient has tried and had an inadequate response to at least a medium-potency topical corticosteroid used in the treatment of nonsegmental vitiligo after at least a 2-week duration of therapy **OR** 2. The patient has tried and had an inadequate response to a topical calcineurin inhibitor used in the treatment of nonsegmental vitiligo **OR** 3. The patient has an intolerance or hypersensitivity to at least a medium-potency topical corticosteroid OR a topical calcineurin inhibitor used in the treatment of nonsegmental vitiligo **OR** 4. The patient has an FDA labeled contraindication to ALL medium-, high-, and super-potency topical corticosteroids AND ALL topical calcineurin inhibitors used in the treatment of nonsegmental vitiligo **OR** C. The patient has another FDA labeled indication for the requested agent **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., dermatologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. ONE of the following (Please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (submitted copy of clinical trials, phase III studies, guidelines required) **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 3 months for atopic dermatitis and 6 months for nonsegmental vitiligo NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

CONTRAINDICATION AGENTS

Contraindicated as Concomitant Therapy
Agents NOT to be used Concomitantly Abrilada (adalimumab-afzb) Actemra (tocilizumab) Adalimumab Adbry (tralokinumab-ldrm) Amjevita (adalimumab-atto) Arcalyst (rilonacept) Avsola (infliximab-axxq) Benlysta (belimumab) Bimzelx (bimekizumab-bkzx) Cibinqo (abrocitinib) Cimzia (certolizumab)

Contraindicated as Concomitant Therapy
Cinqair (reslizumab)
Cosentyx (secukinumab)
Cyltezo (adalimumab-adbm)
Dupixent (dupilumab)
Enbrel (etanercept)
Entyvio (vedolizumab)
Fasenra (benralizumab)
Hadlima (adalimumab-bwwd)
Hulio (adalimumab-fkjp)
Humira (adalimumab)
Hyrimoz (adalimumab-adaz)
Idacio (adalimumab-aacf)
Ilaris (canakinumab)
Ilumya (tildrakizumab-asmn)
Inflectra (infliximab-dyyb)
Infliximab
Kevzara (sarilumab)
Kineret (anakinra)
Leqselvi (deuruxolitinib)
Litfulo (ritlecitinib)
Nemluvio (nemolizumab-ilto)
Nucala (mepolizumab)
Olumiant (baricitinib)
Omvoh (mirikizumab-mrkz)
Opzelura (ruxolitinib)
Orencia (abatacept)
Otezla (apremilast)
Pyzchiva (ustekinumab-ttwe)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rinvoq (upadacitinib)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Saphnelo (anifrolumab-fnia)
Selarsdi (ustekinumab-aekn)
Siliq (brodalumab)
Simlandi (adalimumab-ryvk)

Contraindicated as Concomitant Therapy
Simponi (golimumab)
Simponi ARIA (golimumab)
Skyrizi (risankizumab-rzaa)
Sotyktu (deucravacitinib)
Spevigo (spesolimab-sbzo) subcutaneous injection
Stelara (ustekinumab)
Taltz (ixekizumab)
Tezspire (tezepelumab-ekko)
Tofidence (tocilizumab-bavi)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tyenne (tocilizumab-aazg)
Tysabri (natalizumab)
Velsipity (etrasimod)
Wezlana (ustekinumab-auub)
Xeljanz (tofacitinib)
Xeljanz XR (tofacitinib extended release)
Xolair (omalizumab)
Yuflyma (adalimumab-aaty)
Yusimry (adalimumab-aqvh)
Zeposia (ozanimod)
Zymfentra (infliximab-dyyb)

Oral Inhalers

Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
ADVAIR DISKUS® (fluticasone propionate and salmeterol)* Inhalation powder	Twice-daily treatment of asthma in patients 4 years of age and older. Maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). • Limitations of use: not indicated for relief of acute bronchospasm.	*generic available	1
Alvesco® (ciclesonide) Inhalation aerosol	Maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients 12 years of age and older. • Limitations of use: not indicated for the relief of acute bronchospasm.		2
Arnuity Ellipta® (fluticasone furoate) Inhalation powder	Maintenance treatment of asthma in adult and pediatric patients aged 5 years and older. • Limitations of use: not indicated for the relief of acute bronchospasm.		3
Asmanex HFA® (mometasone furoate) Inhalation aerosol	Maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older. • Limitations of use: not indicated for the relief of acute bronchospasm.		4

Agent(s)	FDA Indication(s)	Notes	Ref#
Asmanex Twisthaler® (mometasone furoate) Inhalation powder	Maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients 4 years of age and older. • Limitations of use: not indicated for the relief of acute bronchospasm.		5
Flovent Diskus® (fluticasone propionate) Inhalation powder	Maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older. • Limitations of use: not indicated for the relief of acute bronchospasm.		6
Flovent HFA® (fluticasone propionate) Inhalation aerosol	Maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients aged 4 years and older. • Limitations of use: not indicated for the relief of acute bronchospasm.		7
QVAR RediHaler® (beclomethasone dipropionate HFA) Inhalation aerosol	Maintenance treatment of asthma as prophylactic therapy in adult and pediatric patients 4 years of age and older. • Limitations of use: not indicated for the relief of acute bronchospasm.		8

CLINICAL RATIONALE

Asthma	Asthma is a respiratory disease of chronic airway inflammation that is characterized by variable symptoms of wheezing, shortness of breath, chest tightness and/or cough, and expiratory airflow due to bronchoconstriction, airway wall thickening, and increased mucus. Asthma affects an estimated 300 million people worldwide of all ages and imposes a substantial burden on patients, their families, the community and on healthcare systems. The long-term goals of asthma management from a clinical perspective are to achieve good symptom control and maintain normal activity levels along with minimizing the

	risk of asthma-related death, exacerbations, persistent airflow limitation and side-effects. It is also important to determine the patient's own goals regarding their asthma.(9,10) For the best outcomes, inhaled corticosteroid (ICS)-containing treatment should be started as soon as possible after the diagnosis of asthma is made. Current guidelines provide no preference on the specific type of ICS to use and note that recommendations for broad populations will be different compared to individual patients that need to consider their own goals and preferences, characteristics and phenotype, along with practical issues such as cost, adherence, and availability.(9,10)
Asthma	Asthma is a respiratory disease of chronic airway inflammation that is characterized by variable symptoms of wheezing, shortness of breath, chest tightness and/or cough, and expiratory airflow due to bronchoconstriction, airway wall thickening, and increased mucus. Asthma affects an estimated 300 million people worldwide of all ages and imposes a substantial burden on patients, their families, the community and on healthcare systems. The long-term goals of asthma management from a clinical perspective are to achieve good symptom control and maintain normal activity levels along with minimizing the risk of asthma-related death, exacerbations, persistent airflow limitation and side-effects. It is also important to determine the patient's own goals regarding their asthma.(9,10) For the best outcomes, inhaled corticosteroid (ICS)-containing treatment should be started as soon as possible after the diagnosis of asthma is made. Current guidelines provide no preference on the specific type of ICS to use and note that recommendations for broad populations will be different compared to individual patients that need to consider their own goals and preferences, characteristics and phenotype, along with practical issues such as cost, adherence, and availability.(9,10)
COPD	Long-term monotherapy with an inhaled corticosteroid (ICS) in not recommended for the treatment of chronic obstructive pulmonary disease (COPD). If there is an indication for an ICS, the preferred combination is long-acting-beta2 agonist (LABA) + long-acting muscarinic antagonist (LAMA) + ICS which can be administered as single or multiple inhaler therapy. If patients with COPD have features of asthma, treatment should always include an ICS. Guidelines do not recommend one type of ICS over another. Guidelines recommend the patient and the prescriber to make the decision together based on the patient's abilities, goals, and preferences with an emphasis on adherence to therapy.(11)

COPD	Long-term monotherapy with an inhaled corticosteroid (ICS) in not recommended for the treatment of chronic obstructive pulmonary disease (COPD). If there is an indication for an ICS, the preferred combination is long-acting-beta2 agonist (LABA) + long-acting muscarinic antagonist (LAMA) + ICS which can be administered as single or multiple inhaler therapy. If patients with COPD have features of asthma, treatment should always include an ICS. Guidelines do not recommend one type of ICS over another. Guidelines recommend the patient and the prescriber to make the decision together based on the patient's abilities, goals, and preferences with an emphasis on adherence to therapy.(11)
Safety	ADVAIR DISKUS is contraindicated in the following:(1) • Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required. • Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone propionate, salmeterol, or any of the excipients. Alvesco is contraindicated in the following:(2) • Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. • Patients with known hypersensitivity to ciclesonide or any of the ingredients of Alvesco. Rare cases of hypersensitivity reactions with manifestations such as angioedema, with swelling of the lips, tongue and pharynx, have been reported. Arnuity Ellipta is contraindicated in the following:(3) • Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. • Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate or any of the excipients. Asmanex HFA is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.(4) Asmanex Twisthaler is contraindicated in the following:(5) • Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

	• Patients with known hypersensitivity to milk proteins or any ingredients of Asmanex Twisthalers. Flovent Diskus is contraindicated in the following:(6) • Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. • Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone propionate. Flovent HFA is contraindicated in the following:(7) • Primary treatment of status asthmaticus or acute episodes of asthma requiring intensive measures. • Hypersensitivity to any ingredient. QVAR RediHaler is contraindicated in the following:(8) • Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. • Patients with known hypersensitivity to beclomethasone dipropionate or any of the ingredients in QVAR RediHaler.
Safety	ADVAIR DISKUS is contraindicated in the following:(1) • Primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required. • Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone propionate, salmeterol, or any of the excipients. Alvesco is contraindicated in the following:(2) • Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. • Patients with known hypersensitivity to ciclesonide or any of the ingredients of Alvesco. Rare cases of hypersensitivity reactions with manifestations such as angioedema, with swelling of the lips, tongue and pharynx, have been reported. Arnuity Ellipta is contraindicated in the following:(3)

	• Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. • Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone furoate or any of the excipients. Asmanex HFA is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.(4) Asmanex Twisthaler is contraindicated in the following:(5) • Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. • Patients with known hypersensitivity to milk proteins or any ingredients of Asmanex Twisthalers. Flovent Diskus is contraindicated in the following:(6) • Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. • Severe hypersensitivity to milk proteins or demonstrated hypersensitivity to fluticasone propionate. Flovent HFA is contraindicated in the following:(7) • Primary treatment of status asthmaticus or acute episodes of asthma requiring intensive measures. • Hypersensitivity to any ingredient. QVAR RediHaler is contraindicated in the following:(8) • Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. • Patients with known hypersensitivity to beclomethasone dipropionate or any of the ingredients in QVAR RediHaler.

REFERENCES

Number	Reference
1	ADVAIR DISKUS prescribing information. GlaxoSmithKline. October 2020.
2	Alvesco prescribing information. Covis Pharma. February 2023.
3	Arnuity Ellipta prescribing information. GlaxoSmithKline. March 2023.
4	Asmanex HFA prescribing information. Organon Global Inc. June 2021
5	Asmanex Twisthaler prescribing information. Merck & CO., INC. February 2021.
6	Flovent Diskus prescribing information. GlaxoSmithKline. June 2022.
7	Flovent HFA prescribing information. GlaxoSmithKline. August 2021.
8	QVAR RediHaler prescribing information. Teva Respiratory, LLC. September 2022.
9	Cloutier, M. M., Baptist, A. P., Blake, K. V., Brooks, E. G., Bryant-Stephens, T., DiMango, E., Dixon, A. E., Elward, K. S., Hartert, T., Krishnan, J. A., Lemanske Jr., R. F., Ouellette, D. R., Pace, W. D., Schatz, M., Skolnik, N. S., Stout, J. W., Teach, S. J., Umscheid, C. A., & Walsh, C. G. (2020, December). 2020 Focused updates to the Asthma Management Guidelines. National Heart Lung and Blood Institute (NHLBI). https://www.nhlbi.nih.gov/health-topics/asthma-management-guidelines-2020-updates
10	Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, 2023. www.ginasthma.org
11	Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease, 2023. https://goldcopd.org

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** B. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Oral Anticoagulant

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Eliquis® (apixaban) Tablet	*Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation* *Prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery* *Treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy*		1
PRADAXA® (dabigatran) Capsule*	To reduce the risk of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation For the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in adult patients who have been treated with a parenteral anticoagulant for 5-10 days To reduce the risk of recurrence of DVT and PE in adult patients who have been previously treated For the prophylaxis of DVT and PE in adult patients who have undergone hip replacement surgery For the treatment of venous thromboembolic events (VTE) in pediatric patients 8 to less than 18 years of age who have been treated with a parenteral anticoagulant for at least 5 days To reduce the risk of recurrence of VTE in pediatric patients 8 to less than 18 years of age who have previously been treated	* generic available	2
PRADAXA® (dabigatran) Oral Pellets	For the treatment of venous thromboembolic events (VTE) in pediatric patients aged 3 months to less than 12 years of age who have been treated with a parenteral anticoagulant for at least 5 days.		5

Agent(s)	FDA Indication(s)	Notes	Ref#
	To reduce the risk of recurrence of VTE in pediatric patients aged 3 months to less than 12 years of age who have been previously treated		
Savaysa® (edoxaban) Capsule	To reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF) For the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant.		3
Xarelto® (rivaroxaban) Tablet Suspension	To reduce risk of stroke and systemic embolism in nonvalvular atrial fibrillation Treatment of deep vein thrombosis (DVT) Treatment of pulmonary embolism (PE) Reduction in the risk of recurrence of DVT or PE Prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery Prophylaxis of venous thromboembolism (VTE) in acutely ill medical patients Reduction of risk of major cardiovascular events in patients with coronary artery disease (CAD) Reduction of risk of major thrombotic vascular events in patients with peripheral artery disease (PAD), including patients after recent lower extremity revascularization due to symptomatic PAD Treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years Thromboprophylaxis in pediatric patients 2 years and older with congenital heart disease after the Fontan procedure		4

REFERENCES

Number	Reference
1	Eliquis prescribing information. Cardinal Health 107, LLC. November 2021.
2	PRADAXA Capsule prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. November 2023.
3	Savaysa prescribing information. Daiichi Sankyo Co., LTD. October 2023.
4	Xarelto prescribing information. Janssen Pharmaceuticals, Inc. February 2023.
5	PRADAXA Oral Pellets prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. November 2023.

ALLOWED EXCEPTIONS QUANTITY LIMIT

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Allowed Exceptions	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
83370010000330	Eliquis	apixaban tab	5 MG	2 tablets/day for maintenance			

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Eliquis and Savaysa	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR**

Module	Clinical Criteria for Approval
	2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: 12 months or as requested by the prescriber, whichever is shorter
Pradaxa	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The indicated use is prophylaxis of DVT and PE in an adult patient who has undergone hip replacement surgery **AND** the prescriber has provided information in support of therapy with a higher quantity (duration) for the requested indication **OR** 3. The indicated use is to reduce the risk of stroke and systemic embolism in an adult patient with nonvalvular atrial fibrillation OR treatment of DVT and PE OR reduction in the risk of recurrence of DVT and PE **AND** BOTH of the following: A. The requested dosage form is NOT 110 mg **AND** B. ONE of the following: 1. BOTH of the following: i. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** ii. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 2. BOTH of the following: i. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	ii. There is support for therapy with a higher dose for the requested indication **OR** 4. The indicated use is other than those listed above **AND** there is support for therapy with a higher quantity (dose) for the requested indication **Length of Approval**: 12 months or as requested by the prescriber, whichever is shorter
Xarelto	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The indicated use is prophylaxis of DVT which may lead to PE in a patient undergoing hip or knee replacement surgery **AND** the prescriber has provided information in support of therapy with a higher quantity (duration) for the requested indication **OR** 3. The indicated use is reduction of risk of stroke and systemic embolism in a patient with nonvalvular atrial fibrillation OR treatment of DVT/PE **AND** ONE of the following: A. BOTH of the following: i. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** ii. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** B. BOTH of the following: i. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** ii. There is support for therapy with a higher dose for the requested indication **OR** 4. The indicated use is other than those listed above **AND** there is support for therapy with a higher quantity (dose) for the requested indication **Length of Approval:** 12 months or as requested by the prescriber, whichever is shorter

Oral Immunotherapy

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Grastek® (Timothy Grass Pollen Allergen Extract) Sublingual tablet	Treatment of persons 5 through 65 years of age with grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens		2
Odactra® (House Dust Mite [*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*] Allergen Extract) Sublingual tablet	Immunotherapy in persons 12 through 65 years of age for the treatment of house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or by positive skin testing to licensed house dust mite allergen extracts		4
Oralair® (Sweet Vernal, Orchard, Perennial Rye, Timothy, and Kentucky Blue Grass Mixed Pollens Alergen Extract) Sublingual tablet	Treatment of persons 5 through 65 years of age with grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for any of the five grass species contained in this product		1
Ragwitek®	Treatment of patients 5 through 65 years of age with short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or *in vitro*		3

Agent(s)	FDA Indication(s)	Notes	Ref#
(Short Ragweed Pollen Allergen Extract) Sublingual tablet	testing for pollen-specific IgE antibodies for short ragweed pollen		

CLINICAL RATIONALE

Allergic Rhinoconjunctivitis	Allergic rhinoconjunctivitis (AR) is an allergic disorder of the nose and eyes with symptoms that can be controlled with allergen avoidance measures and pharmacotherapy. Conventional pharmacotherapy for allergic rhinitis include oral or intranasal antihistamines, intranasal corticosteroids, and leukotriene inhibitors.(6,7) Intranasal corticosteroids are considered the most effective conventional pharmacotherapy.(7) However, many patients continue to have ongoing symptoms and an impaired quality of life. Allergen immunotherapy represents the only currently available treatment that targets the underlying pathophysiology, and it may have a disease-modifying effect. Either the subcutaneous (SCIT) or sublingual (SLIT) routes may be used.(6,7) Per guidelines, allergen immunotherapy should be considered for patients with evidence of IgE sensitization (i.e., positive skin prick test and/or serum-specific IgE) to one or more clinically relevant allergens, who continue to experience symptoms despite conventional pharmacotherapy and allergen avoidance measures.(5-7) Patients receiving SLIT therapy should have regularly scheduled care with a healthcare professional skilled in the assessment and management of patients with allergic conditions.(8)
Safety	All four oral immunotherapy agents carry the same boxed warning:(1,2,3,4) • Can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal edema/restriction. • Do not administer to patients with severe, unstable or uncontrolled asthma. • Observe patients in the office for at least 30 minutes following the initial dose. • Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use.

	• May not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. • May not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. All four oral immunotherapy agents carry the same contraindications:(1,2,3,4) • Severe, unstable or uncontrolled asthma. • History of any severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy. • A history of eosinophilic esophagitis. • Hypersensitivity to any of the inactive ingredients contained in this product. Grastek, Odactra, Oralair, and Ragwitek have not been studied in subjects who are receiving concomitant allergen immunotherapy. Concomitant dosing with other allergen immunotherapy may increase the likelihood of local or systemic adverse reactions to either subcutaneous or sublingual allergen immunotherapy.(1,2,3,4)

REFERENCES

Number	Reference
1	Oralair prescribing information. Stallergenes SAS. January 2021.
2	Grastek prescribing information. ALK-Abelló, Inc. December 2019.
3	Ragwitek prescribing information. ALK-Abelló, Inc. April 2021.
4	Odactra prescribing information. ALK-Abelló, Inc. January 2023.
5	Global Initiative for Asthma (GINA) 2023 guidelines. Global Strategy for Asthma Management and Prevention. Available at: https://ginasthma.org/gina-reports/.
6	EAACI Guidelines on Allergen Immunotherapy: Allergic Rhinoconjunctivitis. *Allergy*. 2018;73:765-798.
7	2019 ARIA Care Pathways for Allergen Immunotherapy. *Allergy*. 2019;74(11):2087-2102.

Number	Reference
8	Greenhawt M, Oppenheimer J, Nelson M, et al. Sublingual Immunotherapy: A Focused Allergen Immunotherapy Practice Parameter Update. *Ann Allergy Asthma Immunol*. 2017;118:276-282.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The patient has a diagnosis of allergic rhinitis, with or without conjunctivitis **AND** 2. The patient's diagnosis is confirmed with ONE of the following: A. Positive skin test to ONE of the pollen extracts included in the requested agent (Grastek, Oralair, or Ragwitek) or licensed house dust mite allergen extracts (Odactra) **OR** B. IgE specific antibodies to ONE of the extracts included in the requested agent: 1. Grastek: Timothy grass or cross-reactive grass 2. Odactra: *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* 3. Oralair: Sweet vernal, orchard, perennial rye, Timothy, or Kentucky blue grass 4. Ragwitek: Short Ragweed **AND** 3. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergy or immunology) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. ONE of the following: A. The patient has tried and had an inadequate response to an intranasal corticosteroid AND one other standard allergy agent (e.g., oral or intranasal antihistamines, oral or intranasal corticosteroids, leukotriene inhibitors; note: two separate intranasal corticosteroids meet this criteria) **OR** B. The patient has an intolerance or hypersensitivity to therapy with an intranasal corticosteroid AND one other standard allergy agent **OR** C. The patient has an FDA labeled contraindication to ALL intranasal corticosteroids AND other standard allergy therapies **AND** 6. The patient will NOT be using the requested agent in combination with subcutaneous injectable immunotherapy for the requested indication **AND**

Module	Clinical Criteria for Approval
	7. If the requested agent is Grastek, Oralair, or Ragwitek: The product will be started, or has already been started, 3 to 4 months before the expected onset of the applicable pollen season **AND** 8. The first dose is given in the clinic/hospital under direct supervision from the provider for a period of at least 30 minutes **AND** 9. The patient has been prescribed epinephrine auto-injector for at home emergency use **AND** 10. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. The prescriber has provided information in support of therapy with a higher dose for the requested indication **Length of Approval**: 12 months

Otezla (apremilast)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Otezla® (apremilast) Tablets	Treatment of adult patients with active psoriatic arthritis Treatment of adult patients with plaque psoriasis who are candidates for phototherapy or systemic therapy Treatment of pediatric patients 6 years of age and older and weighing at least 20 kg with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy Treatment of adult patients with oral ulcers associated with Behcet's disease		1

CLINICAL RATIONALE

Psoriasis (PS)	Psoriasis (PS) is a chronic inflammatory skin condition that is often associated with systemic manifestations, especially arthritis. Diagnosis is usually clinical, based on the presence of typical erythematous scaly patches, papules, and plaques that are often pruritic and sometimes painful. Treatment goals for psoriasis include improvement of skin, nail, and joint lesions plus enhanced quality of life.(2) The American Academy of Family Physicians (AAFP) categorizes psoriasis severity into mild to moderate (less than 5% of body surface area [BSA]) and moderate to severe (5% or more of BSA). The AAFP psoriasis treatment guidelines recommend basing treatment on disease severity:(2) • Mild to moderate (less than 5% of BSA and sparing the genitals, hands, feet, and face): ○ Candidate for intermittent therapy: topical corticosteroids, vitamin D analogs (calcipotriene and calcitriol), or tazarotene (Tazorac)

	○ Candidate for continuous therapy: calcineurin inhibitors (tacrolimus and pimecrolimus) • Severe (5% or more of BSA or involving the genitals, hands, feet, and face): ○ Less than 20% of BSA affected: vitamin D analogs (calcipotriene and calcitriol) with or without phototherapy. These agents have a slower onset of action but a longer disease-free interval than topical corticosteroids ○ 20% or more of BSA affected: systemic therapy with MTX, cyclosporine, acitretin, or biologics. Biologics are recommended for those with concomitant PsA • Less commonly used topical therapies include non-medicated moisturizers, salicylic acid, coal tar, and anthralin The American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) categorize psoriasis severity as limited or mild (less than 3% of BSA), moderate (3% to 10% of BSA), or severe (greater than 10% of BSA). The AAD/NPF guidelines also note that psoriasis can be considered severe irrespective of BSA when is occurs in select locations (e.g., hands, feet, scalp, face, or genital area) or when it causes intractable pruritus.(5) The AAD psoriasis treatment guidelines recommend the following*:(3,4,5,9,10) • Mild to moderate disease (less than 5% of BSA): ○ Topical corticosteroids strength of recommendation A ○ Off-label use of 0.1% tacrolimus for psoriasis involving the face as well as inverse psoriasis strength of evidence B ○ Long-term use (up to 52 weeks) of topical vitamin D analogs including calcipotriene, calcitriol, tacalcitol, and maxacalcitol strength of recommendation A ○ Use of calcipotriene foam and calcipotriene plus betamethasone dipropionate gel for the treatment of mild to moderate scalp psoriasis level of recommendation A ○ Use of tacalcitol ointment or calcipotriene combined with hydrocortisone for facial psoriasis strength of recommendation B ○ Vitamin D analogs in combination with topical corticosteroids strength of recommendation A ○ Topical tazarotene alone or in combination with narrowband ultraviolet B (NB-UVB) strength of recommendation B, or topical corticosteroids strength of recommendation A ○ Topical salicylic acid alone or in combination with topical corticosteroids strength of recommendation B ○ Coal tar preparations strength of evidence A

- Moderate to severe disease without PsA (5% or more of BSA or psoriasis in vulnerable areas [e.g., face, genitals, hands, and feet] that adversely affects quality of life):
  - Methotrexate (adults) strength of evidence A
  - Methotrexate is less effective than TNF-inhibitors strength of evidence B
  - Combination therapy with methotrexate and NB-UVB (adult patients) strength of evidence B
  - Cyclosporine for patients with severe, recalcitrant strength of recommendation A , erythrodermic, generalized pustular, and/or palmoplantar psoriasis strength of recommendation B
  - Acitretin as monotherapy or in combination with psoralen plus ultraviolet light (PUVA) or broad band ultraviolet light (BB-UVA strength of evidence B
  - If UV-therapy is unavailable, first line therapies include MTX, cyclosporine, acitretin, and biologics
  - Apremilast strength of recommendation A
  - TNF-α inhibiters monotherapy strength of evidence A or in combination with topical corticosteroids with or without a vitamin D analogue strength of evidence B or in combination with acitretin strength of evidence C
  - TNF-α inhibitors should be considered as a preferred treatment option for patients concomitant PsA
  - Infliximab strength of evidence A
  - IL-12/IL-23 Inhibitors monotherapy strength of evidence A or in combination with topical corticosteroids with or without a vitamin D analogue strength of evidence C or in combination with acitretin or methotrexate strength of evidence B
  - IL-12/IL-23 inhibitors in combination with apremilast or cyclosporine strength of evidence C
  - IL-17 inhibitors monotherapy strength of evidence A
  - IL-23 inhibitors monotherapy for moderate to severe plaque psoriasis or as monotherapy for generalized pustular psoriasis strength of evidence B

* Strength of recommendation and descriptions

Strength of recommendation	Description

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<tr><td>A</td><td>Recommendation based on consistent and good-quality patient-oriented evidence</td></tr>
<tr><td>B</td><td>Recommendation based on inconsistent or limited-quantity patient-orientated evidence</td></tr>
<tr><td>C</td><td>Recommendation based on consensus, opinion, case studies, or disease-orientated evidence</td></tr>
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Biologics are routinely used when one or more traditional systemic agents fail to produce adequate response, but are considered first line in patients with moderate to severe psoriasis with concomitant severe PsA. Primary failure is defined as initial nonresponse to treatment. Primary failure to a TNF-α inhibitor does not preclude successful response to a different TNF-α inhibitor. Failure of another biologic therapy does not preclude successful response to ustekinumab.(9)

The National Psoriasis Foundation (NPF) medical board recommend a treat-to-target approach to therapy for psoriasis that include the following:(6)

• The preferred assessment instrument for determining disease severity is BSA
• Target response after treatment initiation should be BSA less than or equal to 1% after 3 months
• Acceptable response is either a BSA less than or equal to 3% or a BSA improvement greater than or equal to 75% from baseline at 3 months after treatment initiation</td>
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<tr>
<td>Psoriatic Arthritis (PsA)</td>
<td>Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease associated with psoriasis, most commonly presenting with peripheral arthritis, dactylitis, enthesitis, and spondylitis. Treatment involves the use of a variety of interventions, including many agents used for the treatment of other inflammatory arthritis, particularly spondyloarthritis and RA, and other management strategies of the cutaneous manifestations of psoriasis.(7)

The American Academy of Dermatology (AAD) recommends initiating MTX in most patients with moderate to severe PsA. After 12 to 16 weeks of MTX therapy</td>
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	with appropriate dose escalation, the AAD recommends adding or switching to a TNF inhibitor if there is minimal improvement on MTX monotherapy.(3)
	
	The American College of Rheumatology (ACR) and the National Psoriasis Foundation (NPF) guidelines for PsA recommend a treat-to-target approach in therapy, regardless of disease activity, and the following:(7)
	
	• Active PsA is defined as symptoms at an unacceptably bothersome level as reported by the patient and health care provider to be due to PsA based on the presence of one of the following:
	  ○ Actively inflamed joints
	  ○ Dactylitis
	  ○ Enthesitis
	  ○ Axial disease
	  ○ Active skin and/or nail involvement
	  ○ Extraarticular manifestations such as uveitis or inflammatory bowel disease
	• Disease severity includes level of disease activity at a given time point and the presence/absence of poor prognostic factors and long-term damage
	• Severe PsA disease includes the presence of 1 or more of the following:
	  ○ Erosive disease
	  ○ Elevated markers of inflammation (ESR, CRP) attributable to PsA
	  ○ Long-term damage that interferes with function (i.e., joint deformities)
	  ○ Highly active disease that causes a major impairment in quality of life
	  ○ Active PsA at many sites including dactylitis, enthesitis
	  ○ Function limiting PsA at a few sites
	  ○ Rapidly progressive disease
	• Symptomatic treatments include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, local glucocorticoid injections
	• Treatment recommendations for active disease:
	  ○ Treatment naïve patients first line options include oral small molecules (OSM), TNF biologics, IL-17 inhibitor, and IL-12/23 inhibitor
	  ▪ OSM (i.e., methotrexate [MTX], sulfasalazine, cyclosporine, leflunomide, apremilast) should be considered if the patient does not have severe PsA, does not have severe psoriasis, prefers oral therapy, has concern over starting a biologic, or has contraindications to TNF inhibitor

	▪ Biologics (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) are recommended as a first line option in patients with severe PsA and/or severe psoriasis o Previous treatment with OSM and continued active disease: ▪ Switch to a different OSM (except apremilast) in patients without severe PsA or severe PS, contraindications to TNF biologics, prefers oral therapy OR add on apremilast to current OSM therapy ▪ May add another OSM (except apremilast) to current OSM therapy for patients that have exhibited partial response to current OSM in patients without severe PsA or severe PS, contraindications to TNF biologics, or prefers oral therapy ▪ Biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) monotherapy o Previous treatment with a biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor) and continued active disease: ▪ Switch to another biologic (i.e., TNF biologic, IL-17 inhibitor, IL-12/23 inhibitor, abatacept, or tofacitinib) monotherapy or add MTX to the current TNF biologic
Behcet's Disease (BD)	Behcet's disease (BD) is a type of vasculitis that involves numerous organ systems, such as the skin, mucosa, joints, eyes, veins, arteries, nervous system, and gastrointestinal system. BD runs a relapsing and remitting course and a multidisciplinary approach is necessary for optimal care. The goal of treatment is to suppress inflammatory exacerbations and recurrences to prevent irreversible organ damage.(8) Chronic oral ulceration can cause scaring requiring vigorous treatment to prevent oropharyngeal narrowing. The European League Against Rheumatism recommends topical measures, such as steroids, for the treatment of oral and genital ulcers. Colchicine is recommended for the prevention of recurrent mucocutaneous lesions. Patients with lesions that continue to recur despite colchicine may use immunomodulatory or immunosuppressive agents, such as azathioprine, tumor necrosis factor (TNF) inhibitors, or apremilast.(8)
Efficacy	The efficacy of Otezla for the treatment of oral ulcers associated with BD was established in a multicenter, randomized, placebo-controlled trial. Patients were required to have active oral ulcers at the time of enrollment, have had at least 3 occurrences of oral ulcers within the previous 12 months, and have received treatment with at least one non-biologic therapy. All subjects had a history of recurrent oral ulcers that were currently active. Otezla had a greater reduction in

	the number of oral ulcers and patient reported ulcer pain when compared to placebo.(1)
Safety	Otezla is contraindicated in patients with a known hypersensitivity to apremilast or to any of the excipients in the formulation.(1)

REFERENCES

Number	Reference
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4	Menter, Alan et al. (2019). Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. Journal of the American Academy of Dermatology. doi: https://doi.org/10.1016/j.jaad.2018.11.057.
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6	Armstrong AW, Siegel MP, Bagel J, et al. From the medical board of the National Psoriasis Foundation: treatment targets for plaque psoriasis. Journal of the American Academy of Dermatology. 2017;76(2):290-298. doi: 10.1016/j.jaad.2016.10.017.
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9	Elmets CA, et al. Joint AAD-NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. J Am Acad Dermatol Volume 84 Number 2:432-470.

Number	Reference
10	Menter A, Cordoro KM, Davis DMR, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients. *Journal of the American Academy of Dermatology*. 2020;82(1):161-201. doi:10.1016/j.jaad.2019.08.049

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when the ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** All target agents are eligible for continuation of therapy 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. ONE of the following: A. The patient has a diagnosis of active psoriatic arthritis (PsA) AND ONE of the following: 1. The patient has tried and had an inadequate response to ONE conventional agent (i.e., cyclosporine, leflunomide, methotrexate, sulfasalazine) used in the treatment of PsA for at least 3 months **OR** 2. The patient has an intolerance or hypersensitivity to ONE conventional agent used in the treatment of PsA **OR**

Module	Clinical Criteria for Approval
	3. The patient has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of PsA **OR** 4. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of PsA **OR** B. The patient has a diagnosis of plaque psoriasis (PS) AND BOTH of the following: 1. ONE of the following: A. The patient is an adult with mild to severe plaque psoriasis **OR** B. The patient is a pediatric patient 6 years of age or older AND BOTH of the following: 1. The patient has moderate to severe plaque psoriasis **AND** 2. The patient weighs at least 20 kg **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to ONE conventional agent (i.e., acitretin, anthralin, calcipotriene, calcitriol, coal tar products, cyclosporine, methotrexate, pimecrolimus, PUVA [phototherapy], tacrolimus, tazarotene, topical corticosteroids) used in the treatment of PS for at least 3 months **OR** B. The patient has an intolerance or hypersensitivity to ONE conventional agent used in the treatment of PS **OR** C. The patient has an FDA labeled contraindication to ALL conventional agents used in the treatment of PS **OR** D. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of PS **OR** C. The patient has a diagnosis of Behcet's disease (BD) AND ALL of the following: 1. The patient has active oral ulcers associated with BD **AND** 2. The patient has had at least 3 occurrences of oral ulcers in the last 12-months **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response to ONE conventional agent (i.e., topical oral corticosteroids [i.e., triamcinolone dental paste], colchicine, azathioprine) used in the treatment of BD **OR**

Module	Clinical Criteria for Approval
	B. The patient has an intolerance or hypersensitivity to ONE conventional agent used in the treatment of BD **OR** C. The patient has an FDA labeled contraindication to ALL conventional agents used in the treatment of BD **OR** D. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of BD **OR** D. The patient has another FDA labeled indication for the requested agent not mentioned previously **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **OR** C. The patient has another indication that is supported in compendia for the requested agent not mentioned previously **AND** 2. ONE of the following (Please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (copy of support required, e.g., clinical trials, phase III studies, guidelines) **AND** 3. ONE of the following: A. The patient has a diagnosis of mild severity plaque psoriasis **OR** B. The prescriber is a specialist in the area of the patient's diagnosis (e.g., dermatologist, rheumatologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence **Length of approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Clinical Criteria for Approval
	Renewal Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. ONE of the following (Please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (copy of support required, e.g., clinical trials, phase III studies, guidelines) **AND** 4. ONE of the following: A. The patient has a diagnosis of mild severity plaque psoriasis **OR** B. The prescriber is a specialist in the area of the patient's diagnosis (e.g., dermatologist, rheumatologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support of therapy with a higher dose for the requested indication (e.g., clinical trials, phase III studies, guidelines required) **Length of Approval**: up to 12 months

CONTRAINDICATION AGENTS

Contraindicated as Concomitant Therapy
Agents NOT to be used Concomitantly Abrilada (adalimumab-afzb) Actemra (tocilizumab) Adalimumab Adbry (tralokinumab-ldrm) Amjevita (adalimumab-atto) Arcalyst (rilonacept) Avsola (infliximab-axxq) Benlysta (belimumab) Bimzelx (bimekizumab-bkzx) Cibinqo (abrocitinib) Cimzia (certolizumab) Cinqair (reslizumab) Cosentyx (secukinumab) Cyltezo (adalimumab-adbm) Dupixent (dupilumab) Enbrel (etanercept) Entyvio (vedolizumab) Fasenra (benralizumab) Hadlima (adalimumab-bwwd) Hulio (adalimumab-fkjp) Humira (adalimumab) Hyrimoz (adalimumab-adaz)

Contraindicated as Concomitant Therapy
Idacio (adalimumab-aacf)
Ilaris (canakinumab)
Ilumya (tildrakizumab-asmn)
Inflectra (infliximab-dyyb)
Infliximab
Kevzara (sarilumab)
Kineret (anakinra)
Leqselvi (deuruxolitinib)
Litfulo (ritlecitinib)
Nemluvio (nemolizumab-ilto)
Nucala (mepolizumab)
Olumiant (baricitinib)
Omvoh (mirikizumab-mrkz)
Opzelura (ruxolitinib)
Orencia (abatacept)
Otezla (apremilast)
Pyzchiva (ustekinumab-ttwe)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rinvoq (upadacitinib)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Saphnelo (anifrolumab-fnia)
Selarsdi (ustekinumab-aekn)
Siliq (brodalumab)
Simlandi (adalimumab-ryvk)
Simponi (golimumab)
Simponi ARIA (golimumab)
Skyrizi (risankizumab-rzaa)
Sotyktu (deucravacitinib)
Spevigo (spesolimab-sbzo) subcutaneous injection
Stelara (ustekinumab)
Taltz (ixekizumab)
Tezspire (tezepelumab-ekko)
Tofidence (tocilizumab-bavi)
Tremfya (guselkumab)
Truxima (rituximab-abbs)

Contraindicated as Concomitant Therapy
Tyenne (tocilizumab-aazg)
Tysabri (natalizumab)
Velsipity (etrasimod)
Wezlana (ustekinumab-auub)
Xeljanz (tofacitinib)
Xeljanz XR (tofacitinib extended release)
Xolair (omalizumab)
Yuflyma (adalimumab-aaty)
Yusimry (adalimumab-aqvh)
Zeposia (ozanimod)
Zymfentra (infliximab-dyyb)

Oxbryta

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Oxbryta® (voxelotor) Oral tablets Tablet for oral suspension	Treatment of sickle cell disease (SCD) in adults and pediatric patients 4 years of age and older		1

CLINICAL RATIONALE

Sickle cell disease	Sickle cell disease (SCD) is the name given to a group of lifelong inherited conditions that affect hemoglobin. People with SCD have atypical hemoglobin molecules called hemoglobin S, which can distort red blood cells into a sickle or crescent shape.(2) Signs and symptoms of SCD usually begin in early childhood. Characteristic features of SCD include anemia, repeated infections, and periodic episodes of pain. The severity of symptoms varies from person to person and can range from mild to requiring frequent hospitalizations.(2) SCD affects nearly every system in the body resulting in both acute and chronic complications. An episode of severe pain (acute vaso-occlusive crisis [VOC]) is the most common acute complication of SCD. In addition to VOCs, other common acute complications of SCD include fever related to infection, acute kidney injury (AKI), hepatobiliary complications, acute anemia, splenic sequestration, acute chest syndrome (ACS), and acute stroke. Certain acute complications often evolve into chronic phases. The most common chronic complications of SCD include chronic pain, chronic anemia, avascular necrosis,

	leg ulcers, pulmonary hypertension, renal complications, stuttering/recurrent priapism, and ophthalmologic complications.(2) Pain is the most common complication of SCD. People with SCD experience both nociceptive and neuropathic pain. Pain can be acute, chronic, or an acute episode superimposed on chronic pain. In SCD, pain is considered chronic if it lasts more than 3 months.(2) Recurrent and unpredictable episodes of vaso-occlusion are the hallmark of sickle cell disease. Discoveries over the past 2 decades have highlighted the important contributions of various cellular and soluble participants in the vaso-occlusive cascade. Although the molecular basis of SCD is well characterized, the complex mechanisms underlying VOC have not been fully elucidated. Based on direct observations in SCD mice, adhesive interactions of sickle cell-red blood cells (SS-RBC) and leukocytes to the endothelium play important roles in the initiation of VOC. It is thought that the activated adherent leukocytes, which are rigid and larger than SS-RBC, likely drive VOC in collecting venules, whereas the SS-RBCs may contribute in smaller vessels or in situations where there is no potent inflammatory trigger.(4) Triggers for VOC vary and can include inflammation, stress, increased viscosity, decreased flow, hemolysis, or a combination of the following factors:(4) • Endothelial activation by SS-RBCs and other inflammatory mediators • Recruitment of adherent leukocytes • Activation of recruited neutrophils and of other leukocytes (e.g., monocytes or iNKT cells) • Interactions of sickle erythrocytes with adherent neutrophils • Vascular clogging by heterotypic cell-cell aggregates composed of SS-RBCs, adherent leukocytes and possibly platelets • Increased transit time to greater than the delay time for deoxygenation-induced hemoglobin polymerization, propagating retrograde VOC • Ischemia as a result of the obstruction that creates a feedback loop of worsening endothelial activation Sickle hemoglobin can cause damage to the RBC membrane from deformation by polymer formation. In addition, the mutated globin can undergo autooxidation and precipitate on the inner surface of the RBC membrane, causing membrane damage via iron-mediated generation of oxidants. Both endothelial selectins, P-selectin and E-selectin, have been suggested to participate in VOC.(4)

	Nearly all people with SCD have chronic anemia, but individual baseline hemoglobin values vary widely depending upon hemoglobin genotype (HbSS, HbSC, HbSβ^+-thalassemia, HbSβ^0-thalassemia). It is important for the patient and the primary care provider to know the baseline or "steady state" hemoglobin value for ongoing monitoring and management during acute complications.(2) Hydroxyurea, a ribonucleotide reductase inhibitor, was identified as an option to increase fetal hemoglobin (HbF) levels in people with SCD. The initial clinical trial of hydroxyurea for the treatment of sickle cell anemia (SCA) involved two people. The results of this study showed favorable outcomes which lead to two extended studies with larger cohorts of people. Although HbF induction is the most powerful effect of hydroxyurea and provides the biggest direct benefit for people who have SCD, additional mechanisms of actions and benefits exist. Hydroxyurea lowers the number of circulating leukocytes and reticulocytes and alters the expression of adhesion molecules, all of which contribute to vaso-occlusion. Hydroxyurea also raises RBC volume (higher mean corpuscular volume [MCV]) and improves cellular deformability and rheology, which increases blood flow and reduces vaso-occlusion.(3) An expert panel report of evidence-based management of sickle cell disease supports the use of hydroxyurea with strong recommendations in the following:(3) • In adults with SCA who have three or more sickle cell-associated moderate to severe pain crises in a 12-month period • In adults with SCA who have sickle cell-associated pain that interferes with daily activity and quality of life • In adults with SCA who have a history of severe and/or recurrent acute coronary syndrome (ACS) • In adults with SCA who have severe symptomatic chronic anemia that interferes with daily activities or quality of life • In infants 9 months of age and older, children, and adolescents with SCA, offer treatment with hydroxyurea regardless of clinical severity to reduce SCD-related complications (e.g., pain, dactylitis, ACS, anemia) A clinical response to treatment with hydroxyurea may take 3-6 months. Therefore, the expert panel recommends a 6-month trial on the maximum tolerated dose prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy.(3) While hydroxyurea remains the first-line therapy for SCD, L-glutamine, crizanlizumab, and voxelotor have been approved as adjunctive or second-line

	treatments, and hematopoietic stem cell transplant with a matched sibling donor is now standard care for severe disease. The emergence of gene therapies for SCD now bring the potential for curative therapy without a matched donor.(5)
Efficacy	Oxbryta (voxelotor) is a hemoglobin S (HbS) polymerization inhibitor that binds HbS with a 1:1 stoichiometry and exhibits preferential partitioning to RBCs. By increasing the affinity of hemoglobin (Hb) for oxygen, voxelotor demonstrates dose-dependent inhibition of HbS polymerization. Nonclinical studies suggest that voxelotor may inhibit RBC sickling, improve RBC deformability, and reduce whole blood viscosity.(1) The efficacy and safety of Oxbryta in sickle cell disease was evaluated in HOPE, a randomized, double blind, placebo-controlled, multicenter trial involving 274 patients. Eligible patients on stable doses of hydroxyurea for at least 90 days could continue hydroxyurea therapy throughout the study. Patients were included if they had from 1 to 10 vaso-occlusive crisis events with 12 months prior to enrollment and baseline hemoglobin greater than or equal to 5.5 and less than or equal to 10.5 g/dL. The trial excluded patients who received red blood cell transfusions within 60 days and erythropoietin within 28 days of enrollment, had renal insufficiency, uncontrolled liver disease, were pregnant, or lactating.(1) Efficacy of the HOPE trial was based on Hb response rate defined as a Hb increase of greater than 1 g/dL from baseline to week 24 in patients treated with Oxbryta vs placebo. The response rate for Oxbryta 1,500 mg was 51% compared to 6.5% in the placebo group ($p < 0.001$).(1) Additional efficacy evaluation included change in Hb and percent change in indirect bilirubin and percent reticulocyte count from baseline to week 24. The results for Hb were 1.1 g/dL with Oxbryta 1,500 mg daily vs -0.1 g/dL with placebo. For indirect bilirubin, results were -29.1% with Oxbryta 1,500 mg daily vs -2.8% with placebo. For Percent reticulocyte count the results were -18% for Oxbryta 1,500 mg daily vs 6.8% with placebo.(1)b response rate, which is defined as a Hb increase of greater than 1 g/dL from baseline to Week 24. Hb response rate for Oxbryta in patients aged 4 to less than 12 years who took at least one dose of Oxbryta was 36% (95% CI).(1) Hb response rate, which is defined as a Hb increase of greater than 1 g/dL from baseline to Week 24. Hb response rate for Oxbryta in patients aged 4 to less than 12 years who took at least one dose of Oxbryta was 36% (95% CI).(1) The efficacy and safety of Oxbryta in patients 4 to less than 12 years with sickle cell disease was evaluated in an open-label, multi-center, Phase 2 trial (NCT 02850406). Patients were included if their baseline Hb was less than or

	equal to 10.5 g/dL. Eligible patients on stable doses of hydroxyurea for at least 90 days were allowed to continue hydroxyurea therapy throughout the study. The trial excluded patients who had a VOC event within 14 days prior to enrollment, received RBC transfusions within 30 days of enrollment, and had renal insufficiency or uncontrolled liver disease.(1) Efficacy was based on Hb response rate, which is defined as a Hb increase of greater than 1 g/dL from baseline to Week 24. Hb response rate for Oxbryta in patients aged 4 to less than 12 years who took at least one dose of Oxbryta was 36% (95% CI).(1)
Safety	Oxbryta (voxelotor) is contraindicated in patients with a history of serious drug hypersensitivity reaction drug hypersensitivity to voxelotor or excipients.(1)

REFERENCES

Number	Reference
1	Oxbryta Prescribing Information. Global Blood Therapeutics, Inc. August 2023.
2	U.S. National Library of Medicine. Genetics Home Reference. Sickle cell disease. November 2019.
3	U.S. Department of Health and Human Services. National Institute of Health. Evidence-Based Management of Sickle Cell Disease. Expert Panel Report, 2014.
4	Manwani D, Frenette PS, Vaso-occlusion in sickle cell disease: pathophysiology and novel targeted therapies. Blood. 2013 Dec 5; 122(24): 3892-3898.
5	Brandow AM, Liem RI. Advances in the diagnosis and treatment of sickle cell disease. Journal of Hematology & Oncology. 2022;15(1). doi:10.1186/s13045-022-01237-z.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met:

Module	Clinical Criteria for Approval
	1. The patient has a diagnosis of sickle cell disease **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. ONE of the following A. The patient has tried and had an inadequate response after at least 6 months duration of therapy with maximally tolerated hydroxyurea **OR** B. The patient has an intolerance or hypersensitivity to hydroxyurea **OR** C. The patient has an FDA labeled contraindication to hydroxyurea **AND** 4. ONE of the following: A. The patient's baseline (before treatment with the requested agent) hemoglobin is greater than or equal to 5.5 g/dL and less than or equal to 10.5 g/dL **OR** B. The patient's baseline (before treatment with the requested agent) hemoglobin is below the lab reference range for the patient's age and gender **AND** 5. ONE of the following: A. The patient will NOT be using the requested agent in combination with Adakveo (crizanlizumab-tmca) OR Endari (L-glutamine) for the requested indication **OR** B. There is support for the use of the requested agent in combination with Adakveo (crizanlizumab-tmca) or Endari (L-glutamine) for the requested indication **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent indicated by one of the following: A. The patient had an increase in hemoglobin level of greater than 1 g/dL from baseline (before treatment with the requested agent) **OR** B. The patient has a hemoglobin level within the normal range for age and gender **OR**

Module	Clinical Criteria for Approval
	C. There is support for continuation with the requested agent (medical records required) **AND** 3. ONE of the following: A. The patient will NOT be using the requested agent in combination with Adakveo (crizanlizumab-tmca) OR Endari (L-glutamine) for the requested indication **OR** B. There is support for the use of the requested agent in combination with Adakveo (crizanlizumab-tmca) or Endari (L-glutamine) for the requested indication **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND BOTH of the following: A. ONE of the following: 1. The requested agent is Oxbryta 500 mg tablets **OR** 2. The requested agent is Oxbryta 300 mg tablets AND there is support for why the patient cannot take 3 tablets of Oxbryta 500 mg strength **AND** B. ONE of the following: 1. BOTH of the following: A. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** B. There is support for therapy with a higher dose for the requested indication **OR** 2. BOTH of the following: A. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** B. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR**

Module	Clinical Criteria for Approval
	3. BOTH of the following: A. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** B. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Oxybate

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Lumryz™ (sodium oxybate extended release) Oral suspension	Treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy		11
Xyrem®, Sodium Oxybate Oral solution	Treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy		1, 10
Xywav® (calcium, magnesium, potassium, and sodium oxybate) Oral solution	Treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy Treatment of idiopathic hypersomnia (IH) in adults		2

CLINICAL RATIONALE

Narcolepsy	Narcolepsy is a chronic neurological disorder caused by the inability to regulate sleep-wake cycles. At various times throughout the day, patients with narcolepsy experience irresistible bouts of sleep and could fall asleep. If left undiagnosed or untreated, narcolepsy can interfere with psychological, social, and cognitive function and development and can inhibit academic, work, and social activities.(3) Symptoms may include excessive daytime sleepiness (EDS), cataplexy, sleep paralysis, and hallucinations. All patients diagnosed with narcolepsy will have excessive daytime sleepiness. However, sleepiness in narcolepsy is more like a “sleep attack”, where an overwhelming sense of sleepiness comes on quickly.(3) There is limited evidence to advise on treatment

	of special populations such as children, pregnant women, and breastfeeding mothers.(6)
	
	The American Family Physician recommends referral to a sleep clinic if narcolepsy is suspected.(4) The American Academy of Sleep Medicine indicates treatment goals should be to alleviate daytime sleepiness and produce the fullest possible return of normal function for patients at work, school, home, and socially.(5)
	
	Excessive daytime sleepiness (EDS) is characterized by persistent sleepiness regardless of how much sleep an individual gets at night. In between sleep attacks, individuals have normal levels of alertness, particularly if doing activities that keep their attention. The most common causes of EDS include narcolepsy, obstructive sleep apnea, shift work disorder, sleep deprivation, medication effects, and other medical and psychiatric conditions.(6) Narcolepsy has two types, narcolepsy with cataplexy and without cataplexy. Narcolepsy with cataplexy involves the sudden loss of voluntary muscle tone while awake. It is often triggered by sudden, strong emotions such as laughter, fear, anger, stress, or excitement. The symptoms of cataplexy may appear weeks or even years after the onset of EDS.(3) The American Academy of Sleep Medicine (AASM) 2021 guidelines combined the recommendations for narcolepsy with cataplexy and EDS associated with narcolepsy. The AASM recommend the following for the pharmacologic treatment of narcolepsy:(7)
	
	• Strong treatment recommendations:
	  ○ Modafinil
	  ○ Pitolisant
	  ○ Sodium oxybate
	  ○ Solriamfetol
	• Conditional treatment recommendations:
	  ○ Armodafinil
	  ○ Dextroamphetamine
	  ○ Methylphenidate
	• There was insufficient evidence to make recommendations for SSRI and SNRIs for the treatment of narcolepsy.(7)

Efficacy	*Lumryz* The effectiveness of Lumryz for the treatment of cataplexy or excessive daytime sleepiness (EDS) in adults with narcolepsy has been established based on a double-blind, randomized, placebo-controlled, two-arm multi-center study to assess the efficacy and safety of a once nightly administration of Lumryz in

	patients with narcolepsy. The three co-primary endpoints were the Maintenance of Wakefulness Test (MWT), Clinical Global Impression-Improvement (CGI-I), and mean change in weekly cataplexy attacks.(11) The mean number of cataplexy attacks per week at baseline was 18.9 in the Lumryz group and 19.8 in the placebo group. A statistically significant improvement was seen on the MWT, CGI-I, and mean weekly cataplexy attacks, for the 6 g (Week 3), 7.5 g (Week 8), and 9 g (Week 13) dose of Lumryz, compared to the placebo group.(11) *Xyrem* The effectiveness of sodium oxybate in the treatment of EDS in narcolepsy was established in two 8-week, randomized, double-blind, placebo-controlled trials in patients with narcolepsy. Patients were randomized to one of four groups: placebo, sodium oxybate 4.5 grams per night, sodium oxybate 6 grams per night, or sodium oxybate 9 grams per night. The primary efficacy was extent of sleepiness in everyday situations (determined using Epworth Sleepiness Scale) and change in symptoms of EDS (evaluated using Clinical Global Impression of Change tool). Sodium oxybate was associated with statistically significant differences for both primary outcomes when compared to placebo.(1) The effectiveness of sodium oxybate in the treatment of cataplexy was established in two 4-week, randomized, double-blind, placebo-controlled trials in patients with narcolepsy. Patients were randomized to receive placebo or sodium oxybate dosed at 3 grams to 9 grams nightly. The primary efficacy endpoint for both trials was frequency of cataplexy attacks. Both trials found that dose of 6 grams to 9 grams resulted in statistically significant reduction in frequency of cataplexy attacks. The trials also found that discontinuation of sodium oxybate in patient who had been treated with it long term resulted in a significant increase in cataplexy attacks.(1) *Xywav* Efficacy of Xywav for the treatment of cataplexy and excessive daytime sleepiness in adult patients with narcolepsy was established in a double-blind, placebo-controlled, randomized-withdrawal study (Study 1; NCT03030599). This study had two parts, consisting of the main study, followed by an optional 24-week open-label extension (OLE). The main study consisted of a 12-week open-label optimized treatment and titration period (OL OTTP), followed by a 2-week

	stable-dose period (SDP), and finally a 2-week double-blind randomized-withdrawal period (DB RWP).(2) Patients entering the study were taking a stable dosage of 1) Xyrem only, 2) Xyrem + another anticataplectic, 3) a non-Xyrem anticataplectic, or 4) were cataplexy-treatment naïve. The primary efficacy endpoint was the change in frequency of cataplexy attacks from the 2 weeks of the SDP to the 2 weeks of the DB RWP. The key secondary endpoint was the change in the Epworth Sleepiness Scale (ESS) score, as a measure of reduction in EDS from the end of the SDP to the end of the DB RWP. Patients taking stable doses of Xywav who discontinued Xywav treatment and were randomized to placebo during the DB RWP experienced a significant worsening in the average weekly number of cataplexy attacks and in ESS score, compared with patients randomized to continue treatment with Xywav.(2) The effectiveness of Xywav in pediatric patients is based upon a clinical study in patients treated with Xyrem.(2)

Idiopathic Hypersomnia	Idiopathic hypersomnia (IH) is a sleep disorder characterized by excessive daytime sleepiness despite adequate quantity and quality of sleep, and difficulty waking up from nocturnal sleep and daytime naps. IH often develops in adolescents and can be lifelong with some instances of remission. The pathogenesis is not well understood, with some cases associated with autoimmune etiologies or changes in inhibitory signaling through GABA receptor pathway. The diagnosis is one of exclusion by ruling out other causes, such as sleep apnea, restless leg syndrome, narcolepsy, periodic limb movement disorder, medications, substance use/abuse, or other medical, neurological, or psychiatric conditions. The diagnosis should be made by a sleep specialist and a sleep study completed.(8,9)
	
	Treatment focuses on the symptoms of sleepiness due to the underlying causes being unknown. The American Academy of Sleep Medicine recommend the following for the pharmacologic treatment of IH:(7)
	
	• Strong treatment recommendations:
	  ○ Modafinil
	• Conditional treatment recommendations:
	  ○ Clarithromycin
	  ○ Methylphenidate
	  ○ Pitolisant
	  ○ Sodium oxybate(7)

Efficacy	Xywav Efficacy of Xywav for the treatment of idiopathic hypersomnia (IH) in adult patients as a once or twice nightly regimen was established in a double-blind, placebo-controlled, randomized-withdrawal, study (Study 2, NCT03533114). This study consisted of a minimum of 10-week open-label treatment titration and optimization period (OL OTTP), (with up to 4 additional weeks) to allow for an optimally effective and tolerable dose and regimen followed by a 2-week stable dose period (SDP), a 2-week double-blind, randomized withdrawal period (DB RWP), and a 24-week open label safety extension period (OLE).(2) Study 2 enrolled 154 patients with idiopathic hypersomnia, 19 to 75 years of age. Of the 154 patients, 115 were evaluable for efficacy data and were randomized 1:1 to continue treatment with Xywav or to placebo in the 2-week DB RWP. The primary efficacy endpoint was the change in Epworth Sleepiness Scale (ESS) score, as a measure of reduction in EDS from the end of the SDP to the end of the DB RWP.(2) Patients in Study 2 taking stable doses of Xywav who were withdrawn from Xywav treatment and randomized to placebo during DB RWP experienced significant worsening in ESS score compared with patients randomized to continue treatment with Xywav ($p<0.0001$) across all dosing regimens.(2)
Safety	*Lumryz* Lumryz carries the following contraindications: • Use in combination with sedative hypnotics (i.e., benzodiazepines, butabarbital, eszopiclone, Rozerem [ramelteon], Silenor [doxepin], zaleplon, zolpidem) • Use in combination with alcohol • Use in patients with succinic semialdehyde dehydrogenase deficiency(11) Boxed warnings include: • Central Nervous System Depression. Lumryz is a CNS depressant and respiratory depression can occur with Lumryz use • Abuse and Misuse. Lumryz is the sodium salt of gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB is associated with CNS adverse reactions, including seizure, respiratory depression, decreased consciousness, coma, and death

	Lumryz is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) due to the risks of CNS depression, abuse, and misuse. This program is called the Lumryz REMS.(11) *Xyrem* Xyrem carries the following contraindications: • Use in combination with sedative hypnotics • Use in combination with alcohol • Use in patients with succinic semialdehyde dehydrogenase deficiency(1) Boxed warnings include: • Central Nervous System Depression. Sodium oxybate is a CNS depressant. Clinically significant respiratory depression occurred in adult patients treated with Xyrem at recommended doses • Abuse and Misuse. Sodium oxybate is the sodium salt of gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB, either alone or in combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death(1) Xyrem is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) due to the risks of CNS depression, abuse, and misuse. This program is called the Xywav and Xyrem REMS.(1) *Xywav* Xywav carries the following contraindications: • Use in combination with sedative hypnotics • Use in combination with alcohol • Use in patients with succinic semialdehyde dehydrogenase deficiency(2) Boxed warnings include: • Central Nervous System Depression. Xywav is a CNS depressant. Clinically significant respiratory depression and obtundation may occur in patients treated with Xywav at recommended doses • Abuse and Misuse. The active moiety of Xywav is oxybate or gamma-hydroxybutyrate (GHB). Abuse or misuse of illicit GHB, either alone or in

	combination with other CNS depressants, is associated with CNS adverse reactions, including seizure, respiratory depression, decreases in the level of consciousness, coma, and death(2) Xywav is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) due to the risks of CNS depression, abuse, and misuse. This program is called the Xywav and Xyrem REMS.(2)

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1	Xyrem prescribing information. Jazz Pharmaceuticals, Inc. April 2023.
2	Xywav prescribing information. Jazz Pharmaceuticals, Inc. April 2023.
3	National Institute of Neurological Disorders and Stroke. Narcolepsy. NIH Publication No. 17-1637. Available at:https://www.ninds.nih.gov/health-information/disorders/narcolepsy. Last updated September 2023. Accessed October 2023.
4	Ramar, Kannan MD and Olson, Eric MD. Management of Common Sleep Disorders. *Am Fam Physician*. 2013 Aug 15; 88(4): 231-238.
5	Krahn, Lois MD, et al. Quality Measures for the Care of Patients with Narcolepsy. Journal of Clinical Sleep Medicine. 2015; Vol. 11(3).
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7	Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2021;17(9):1881–1893.
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9	Chervin, R. D. (2022, January 31). Idiopathic Hypersomnia. UpToDate. Retrieved October 2023, from https://www.uptodate.com/contents/idiopathic-hypersomnia?search=idiopathic+hypersomnia&source=search_result&selectedTitle=1~17&usage_type=default&display_rank=1#references.

Number	Reference
10	Sodium Oxybate solution prescribing information. Hikma Pharmaceuticals, Inc. April 2023.
11	Lumryz prescribing information. Avadel CNS Pharmaceuticals, LLC. May 2023

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of narcolepsy with cataplexy OR narcolepsy with excessive daytime sleepiness AND ONE of the following: 1. The patient has tried and had an inadequate response to modafinil OR armodafinil **OR** 2. The patient has an intolerance or hypersensitivity to modafinil OR armodafinil **OR** 3. The patient has an FDA labeled contraindication to BOTH modafinil AND armodafinil **OR** B. The patient has a diagnosis of idiopathic hypersomnia AND ALL of the following: 1. The requested agent is Xywav **AND** 2. The patient has completed a sleep study **AND** 3. All other causes of hypersomnia have been ruled out **AND** 4. ONE of the following: A. The patient has tried and had an inadequate response to modafinil **OR** B. The patient has an intolerance or hypersensitivity to modafinil **OR** C. The patient has an FDA labeled contraindication to modafinil **OR** C. The patient has another FDA approved indication for the requested agent and route of administration **AND** 2. If the patient has an FDA approved indication, ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 3. If the request is for brand Xyrem, then ONE of the following: A. The patient has an intolerance or hypersensitivity to authorized generic Sodium Oxybate that is not expected to occur with the requested agent **OR**

Module	Clinical Criteria for Approval
	B. The patient has an FDA labeled contraindication to authorized generic Sodium Oxybate that is not expected to occur with the requested agent **OR** C. The prescriber has provided information to support the use of the requested agent over authorized generic Sodium Oxybate **AND** 4. The patient will NOT be using the requested agent in combination with another oxybate agent, Sunosi, OR Wakix for the requested indication **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., sleep specialist, neurologist, psychiatrist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **Length of Approval:** 12 months

Pain Medications (Combination products)

Quantity Limit

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND BOTH of the following: A. ONE of the following: 1. BOTH of the following: A. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** B. Information has been provided to support therapy with a higher dose for the requested indication **OR** 2. BOTH of the following: A. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** B. Information has been provided to support why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. BOTH of the following: A. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** B. Information has been provided to support therapy with a higher dose for the requested indication **AND** B. If the requested agent contains acetaminophen, the daily dose of acetaminophen does NOT exceed over 4 grams per 24 hours **Length of Approval**: Approval duration is 1 month for dose titration requests and up to 6 months for all other requests

Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) Inhibitors

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Praluent® (alirocumab) Subcutaneous injection	To reduce the risk of myocardial infarction, stroke, and unstable angina requiring hospitalization in adults with established cardiovascular disease Adjunct to diet, alone or in combination with other low density lipoprotein cholesterol (LDL-C)- lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C Adjunct to other LDL-C-lowering therapies in adult patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C		1
Repatha® (evolocumab) Subcutaneous injection	In adults with established cardiovascular disease (CVD) to reduce the risk of myocardial infarction, stroke, and coronary revascularization Adjunct to diet, alone or in combination with other LDL-C-lowering therapies in adults with primary hyperlipidemia, including HeFH, to reduce LDL-C Adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, to reduce LDL-C Adjunct to other LDL-C-lowering therapies in adults and pediatric patients aged 10 years and older with HoFH, to reduce LDL-C		2

CLINICAL RATIONALE

HeFH	Criteria have been developed to aid in diagnosing heterozygous familial hypercholesterolemia (HeFH). These include the Simon Broome Register criteria and Dutch Lipid Clinic Network criteria.(5)
	
	A definite diagnosis of HeFH according to Simon Broome diagnostic criteria requires one of the following:(3,5)
	
	• Total cholesterol >6.7 mmol/L or low-density lipoprotein cholesterol (LDL-C) >4.0 mmol/L in a child/young person, or >7.5 mmol/L or LDL-C >4.9 mmol/L in an adult (levels either pre-treatment or highest on treatment) and tendon xanthomas, or evidence of these signs in a first-degree relative (parent, sibling, child) or second-degree relative (e.g., grandparent, uncle, aunt) OR
	• DNA-based evidence of an LDL-receptor mutation, familial defective Apo B-100, or a PCSK9 mutation
	
	A possible diagnosis of HeFH according to Simon Broome diagnostic criteria requires the following:(3,5)
	
	• Total cholesterol >6.7 mmol/L or low-density lipoprotein cholesterol (LDL-C) >4.0 mmol/L in a child/young person, or >7.5 mmol/L or LDL-C >4.9 mmol/L in an adult (levels either pre-treatment or highest on treatment) AND at least one of the following:
	  ○ Family history of myocardial infarction: aged younger than 50 years in second-degree relative or aged younger than 60 years in first-degree relative OR
	  ○ Family history of raised total cholesterol: >7.5 mmol/L in adult first- or second-degree relative or >6.7 mmol/L in child, brother, or sister aged younger than 16 years
	
	The Dutch Lipid Clinic Network criteria (World Health Organization, 1999) assign points based on personal and family medical history, clinical signs, LDL-C concentration and DNA testing. A score is attributed to each component; the higher the score, the higher the likelihood of the person having HeFH. A definitive diagnosis of HeFH can be made in patients with greater than 8 points. A probable diagnosis can be made in patients with 6-8 points. Although the Simon Broome Register criteria consider a molecular diagnosis as evidence for definite

FH, the Dutch Lipid Clinic Network requires that at least one other criterion be met in addition to molecular diagnosis.(5,6)

Dutch Lipid Clinic Network criteria for diagnosis of HeFH:(6)

Family history	Points
• First-degree relative with known premature (men <55 years, women <60 years) coronary artery disease (CAD), OR • First-degree relative with known LDL-C >95th percentile	1
and/or	
• First-degree relative with tendon xanthomata and/or arcus cornealis, OR • Children <18 years with LDL-C >95th percentile	2
Clinical history	
• Patient has premature (men <55 years, women <60 years) CAD • Patient has premature (men <55 years, women <60 years) cerebral or peripheral vascular disease	2 1
Physical examination	
• Tendinous xanthomata • Arcus cornealis before age 45 years	6 4
Cholesterol levels mg/dL (mmol/liter)	

<table>
<tr><td></td><td>
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<tr><td>• LDL-C >330 mg/dL (>8.5)
• LDL-C 250-329 mg/dL (6.5-8.4)
• LDL-C 190-249 mg/dL (5.0-6.4)
• LDL-C 155-189 mg/dL (4.0-4.9)</td><td>8
5
3
1</td></tr>
<tr><td>DNA analysis</td><td></td></tr>
<tr><td>• Functional mutation in the LDLR, Apo-B, or PCSK9 gene</td><td>8</td></tr>
<tr><td>Diagnosis (based on the total number of points obtained)</td><td></td></tr>
<tr><td>Definitive FH diagnosis: >8 points
Probable FH diagnosis: 6-8 points
Possible FH diagnosis: 3-5 points
Unlikely FH diagnosis: 0 to 2 points</td><td></td></tr>
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</td></tr>
<tr><td>HoFH</td><td>Homozygous familial hypercholesterolemia (HoFH) is a rare autosomal semi-dominant disease affecting males and females equally, characterized by markedly elevated levels of low-density lipoprotein cholesterol (LDL-C) from conception and accelerated atherosclerotic cardiovascular disease (ASCVD), often resulting in early death. Recent estimates indicate that about 30,000 people worldwide have HoFH but less than 5% are identified. Estimated global prevalence of HoFH by United Nations world region, based on 2020 population data and estimates of HoFH prevalence ranging from 1:250,000 to 1:360,000. Inadequate awareness and a disconnect between clinical diagnosis and interpretation of genetic results by health providers and payers contribute to underdiagnosis and undertreatment of HoFH. To address this, the European Atherosclerosis Society (EAS) has recently updated clinical guidance for HoFH care to improve education, early diagnosis, and improve cardiovascular health for patients with HoFH worldwide.(4)

In 2014, the EAS statement on HoFH focused attention on this rare life-threatening disease which at the time had limited therapeutic options. The last decade has shown great progress in understanding the genetic complexity of HoFH, with new highly efficacious LDL-C-lowering therapies leading to improved</td></tr>
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	survival and quality of life. The 2023 EAS consensus statement includes updated criteria for the clinical diagnosis of HoFH and the recommendation to prioritize phenotypic (clinically suspected in the absence of genetic data) features over genotype.(4) The EAS notes plasma LDL-C is the critical discriminator for clinical diagnosis of HoFH. The updated 2023 clinical criteria recommends an untreated LDL-C of >10 mmol/L (>400 mg/dL) is suggestive of HoFH requiring further investigation to confirm the diagnosis (including a detailed medical and family history and/or genetic testing). Additional criteria includes cutaneous or tendon xanthomas before age of 10 years and/or untreated elevated LDL-C levels consistent with HeFH in both parents (or in digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH). Due to the large variety of lipid-lowering treatments that these patients typically receive, the historic cut-offs for a treated LDL-C are likely now obsolete.(4) However, LDL-C criteria are not the sole guide to diagnosis, given the genetic complexity of HoFH and variability in LDL-C levels and clinical phenotype. The updated 2023 genetic criteria is genetic confirmation of bi-allelic pathogenic/likely pathogenic variants on different chromosomes at the LDLR, ApoB, PCSK9, or LDLRAP1 genes or greater than or equal to 2 such variants at different loci. The benefits outweigh the limitations of genetic testing in HoFH with increased certainty of diagnosis and access to, use of, and compliance with appropriate treatment. A significant limitation of genetic testing has and continues to be accessibility and cost. Additionally, predicting individual phenotype and clinical response from genotype is not straightforward, and pathogenicity for many detected DNA variants cannot be definitively established. Some patients with phenotypic HoFH have only one or even no pathogenic variant detected, and some patients with bi-allelic pathogenic variants express HeFH but not HoFH phenotypically.(4) The LDL-C level (i.e., the phenotype) and not the presence of a genetic diagnosis drives therapeutic decisions. Combination lipid-lowering therapy, both pharmacologic intervention and lipoprotein apheresis (LA), is foundational, together with lifestyle measures (diet and smoking cessation). Patients should start on a high-intensity statin and ezetimibe rather than statin monotherapy, but most will require additional therapies to attain goal. Within 8 weeks PCSK9-directed therapy should be considered where available. Response to these treatments is dependent on LDL receptor (LDL-R) activity. If patients show >15% additional LDL-C reduction, PCSK9-directed therapy may be continued, but if response is poor, clinicians should consider stopping this

	therapy. While PCSK9 therapy is likely to reduce the risk of ASCVD events, LDL-C levels will remain substantially above recommended goals for most patients. Other options include LDL receptor–independent therapies (such as evinacumab or lomitapide) and/or LA. Lomitapide is noted to provide better control of LDL-C than LA. Preliminary findings from the Pan-European Project in HoFH including 75 patients with HoFH showed that lomitapide treatment for up to 9 years (median 19 months) resulted in more than half attaining at least 50% reduction from baseline in LDL-C at last visit, with less need for apheresis in a substantial proportion of patients. If LA, evinacumab, or lomitapide are not available, liver transplantation can be considered.(4) The National Organization for Rare Disorders (NORD) states that patients with HoFH should be initially started on statins with preference given to higher potency statins (atorvastatin or rosuvastatin) used at the maximal dose noting that statins can be relatively ineffective in HoFH. This is because the mechanism of action of statins normally "triggers" the liver to express additional LDL-Rs. In the most severe cases of HoFH, the LDL-R are completely inactive which makes this response futile. Statins can be effective in individuals with HoFH if there is some residual LDL-R activity, or if they have causal DNA variants in the APOB or PCSK9 genes. Patients with HoFH often require additional treatment strategies including lomitapide and evinacumab-dgnb (Evkeeza). Additional treatment options include LA or liver transplantation.(7) The American Heart Association (AHA) last released a scientific statement in 2015 for familial hypercholesterolemia that recommended lomitapide may be considered as step 4 in HoFH patients as part of a four-drug combination along with LA. Progression through each drug therapy step happens if the patient's LDL-C is above goal after 3 months of adherent treatment. Initial drug monotherapy is with a high-intensity statin (rosuvastatin or atorvastatin). Step 2 is combination therapy with ezetimibe, which progresses to a three-drug regimen that adds one of the following: PCSK9 inhibitors, colesevelam or other bile acid sequestrant, or niacin.(8)
ASCVD	The most recent 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of Blood Cholesterol states that clinical atherosclerotic cardiovascular disease (ASCVD) includes the following, all of atherosclerotic origin:(9) • Acute coronary syndrome (ACS) • History of myocardial infarction (MI) • Stable or unstable angina

	• Coronary or other arterial revascularization • Stroke • Transient ischemic attack (TIA) • Peripheral artery disease (PAD) including aortic aneurysm
Management	The 2022 American College of Cardiology (ACC) Consensus Decision Pathway was designed to address current gaps in care for LDL-C lowering to reducing ASCVD risk. This effort relies extensively on the evidence established by the 2013 ACC/AHA and 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol, and provides further recommendations regarding the use of newer non-statin therapies. The key updates that the 2022 ACC Consensus Pathway recommends for patients with ASCVD on maximally tolerated statin therapy are a recommendation for a lower LDL-C threshold of 55 mg/dL(or non-HDL-C of 85 mg/dL) for adults with ASCVD at very high risk, and an LDL-C threshold of 70mg/dL (or non-HDL-C of 100 mg/dL) for adults with ASCVD not at very high risk when considering the addition of a non-statin therapy. If adults with clinical ASCVD at very high risk on a statin therapy for secondary prevention require >25% additional lowering of LDL-C, a PCSK9 inhibitor may be preferred as the initial non-statin therapy.(13) The 2022 ACC Consensus Panel also released updated Expert Consensus Decision Pathways (ECDPs) to encourage clinicians to consider a range of important factors as they define treatment plans for their patients. Whenever appropriate, ECDPs seek to provide unified articulation of clinical practice guidelines, appropriate use criteria, and other related ACC clinical policy including when to consult a lipid specialist. Referral is recommended for patients with ASCVD and baseline LDL-C ≥190 mg/dL who did not achieve a reduction of LDL-C ≥50% and LDL-C <70 mg/dL (or non–HDL-C <100 mg/dL) on maximally tolerated statin therapy in combination with non-statin therapy (ezetimibe, PCSK9 inhibitors, bempedoic acid, and/or inclisiran).(13) The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol categorizes high intensity statin therapy as atorvastatin 40-80mg and rosuvastatin 20-40mg which provides an LDL-C lowering of greater than or equal to 50%.(9) The 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA

	Guideline on the Management of Blood Cholesterol states the following regarding PCSK9 therapy:(9)
	
	• Primary severe hypercholesterolemia (LDL-C greater than or equal to 190 mg/dL [greater than or equal to 4.9 mmol/L])
	  ○ In patients 30-75 years of age with HeFH and with an LDL-C level of 100 mg/dL or higher (greater than or equal to 2.6 mmol/L) while taking maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered
	  ○ In patients 40-75 years of age with an untreated LDL-C level of 220 mg/dL or higher (greater than or equal to 5.7 mmol/L) or an LDL-C that is greater than or equal to 130 mg/dL while receiving maximally tolerated statin and ezetimibe therapy, the addition of a PCSK9 inhibitor may be considered
	• Secondary atherosclerotic cardiovascular disease (ASCVD) prevention
	  ○ In patients with clinical ASCVD who are judged to be very high risk and considered for PCSK9 inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe
	
	The National Lipid Association (NLA) 2019 consensus statement identifies the following patients, who are already on maximally tolerated statin therapy, as most likely to benefit from PCSK9 therapy.(10)
	
	• Extreme high-risk (greater than or equal to 40% 10-year ASCVD risk on maximally tolerated statin therapy) with LDL-C greater than or equal to 70 mg/dL and either of the following:
	  ○ Extensive or active burden of ASCVD (i.e., polyvascular ASCVD, which affects all 3 vascular beds—coronary, cerebrovascular, and peripheral arterial; clinical peripheral arterial disease in addition to coronary and/or cerebrovascular disease; a clinical ASCVD event with multivessel coronary artery disease defined as greater than or equal to 40% stenosis in greater than or equal to 2 large vessels; or recurrent myocardial infarction within 2 years of the initial event) in the presence of adverse or poorly controlled cardiometabolic risk factors
	  ○ Extremely high-risk elevations in cardiometabolic factors with less-extensive ASCVD (i.e., HeFH, diabetes, LDL-C greater than or equal to 100 mg/dL, less than high–intensity statin therapy, chronic kidney disease, poorly controlled hypertension, high-sensitivity C-reactive protein greater than 3 mg/L, or metabolic

	syndrome, usually occurring with other extremely high–risk or very-high-risk characteristics), usually with other adverse or poorly controlled cardiometabolic risk factors present. Patients with ASCVD and HeFH or severe hyperlipidemia (SH) LDL-C greater than or equal to 220 mg/dL are an additional group of extremely high–risk patients, with greater than or equal to 45% 10- year ASCVD risk despite statin therapy. Statin-treated HeFH patients with coronary artery calcium (CAC) score greater than 100 Agatston units also have about a 45% 10-year ASCVD risk despite statin therapy • Very high-risk (30-39% 10-year ASCVD risk on maximally tolerated statin therapy) with LDL-C greater than or equal to 100 mg/dL and the following: o Less-extensive clinical ASCVD (i.e., no polyvascular ASCVD, no clinical peripheral arterial disease, a prior ASCVD event greater than or equal to 2 years prior, and no coronary artery bypass grafting) o Adverse or poorly controlled cardiometabolic risk factor(s) including age greater than or equal to 65 years, current smoking, chronic kidney disease, lipoprotein(a) greater than or equal to 37 nmol/L, high-sensitivity C-reactive protein 1–3 mg/L, metabolic syndrome with a history of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease, usually in the presence of other adverse or poorly controlled cardiometabolic risk factors • High-risk (20-29% 10-year ASCVD risk on maximally tolerated statin therapy) with LDL-C greater than or equal to 130 mg/dL and either of the following: o High-risk patients with ASCVD who have the following: ▪ Less-extensive ASCVD ▪ Well-controlled cardiometabolic risk factors (i.e., no diabetes, nonsmoker, on high-intensity statin with LDL-C less than 100 mg/dL, blood pressure less than 140/90 mm Hg, and C-reactive protein less than 1 mg/dL) o Primary prevention patients with HeFH or SH LDL-C greater than or equal to 220 mg/dL and have the following: ▪ No clinical ASCVD or CAC less than 100 Agatston units ▪ Poorly controlled cardiometabolic risk factor CAC Agatston score in non-contrast CT can be used for patient risk classification for coronary heart disease:(11,12)

	• 0 CAC = no CAC, very low risk, • 1-99 CAC = mild CAC, mildly increased risk • 100 - 299 CAC = moderate CAC, moderately increased risk • greater than or equal to 300 CAC = moderate to severely increased risk
Safety	Praluent is contraindicated in patients with a history of a serious hypersensitivity reaction to alirocumab or any of the excipients in Praluent. Hypersensitivity vasculitis, angioedema, and hypersensitivity reactions requiring hospitalization have occurred.(1) Repatha is contraindicated in patients with a history of a serious hypersensitivity reaction to evolocumab or any of the excipients in Repatha. Serious hypersensitivity reactions including angioedema have occurred.(2)

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	

Preferred Target Agent(s)	Non-Preferred Target Agent(s)
Repatha (evolocumab)	Praluent (alirocumab)

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   - A. The patient has a diagnosis of homozygous familial hypercholesterolemia (HoFH) and ALL of the following:
     1. The patient has a diagnosis of HoFH confirmed by ONE of the following:
        - A. Genetic confirmation of bi-allelic pathogenic/likely pathogenic variants on different chromosomes at the *LDLR, Apo-B, PCSK9,* or *LDLRAP1* genes, or greater than or equal to 2 such variants at different loci **OR**
        - B. History of untreated LDL-C greater than 400 mg/dL (greater than 10 mmol/L) and ONE of the following:
          1. The patient had cutaneous or tendon xanthomas before age of 10 years **OR**
          2. Untreated elevated LDL-C levels consistent with heterozygous FH in both parents, (or in digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH) **AND**
     2. ONE of the following:
        - A. The patient has tried a high-intensity statin (e.g., atorvastatin 40-80 mg, rosuvastatin 20-40 mg daily) for 2 months and had an inadequate response **OR**
        - B. The patient has an intolerance or hypersensitivity to ALL high-intensity statins **OR**
        - C. The patient has an FDA labeled contraindication to ALL high-intensity statins **AND**
     3. The patient will use other lipid-lowering therapy (e.g., statin, ezetimibe, lipoprotein apheresis, lomitapide, evinacumab) **OR**
   - B. BOTH of the following:
     1. ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient has a diagnosis of heterozygous familial hypercholesterolemia (HeFH) **AND** ONE of the following: 1. Genetic confirmation of one mutant allele at the *LDLR, Apo-B, PCSK9*, or *1/LDLRAP1* gene **OR** 2. Pre-treatment LDL-C greater than 190 mg/dL (greater than 4.9 mmol/L) **OR** 3. The patient has clinical manifestations of HeFH (e.g., cutaneous xanthomas, tendon xanthomas, corneal arcus) **OR** 4. The patient has "definite" or "possible" familial hypercholesterolemia as defined by the Simon Broome criteria **OR** 5. The Patient has a Dutch Lipid Clinic Network Criteria score of greater than 5 **OR** 6. The patient has a treated LDL-C level greater than or equal to 100 mg/dL after statin treatment with or without ezetimibe **OR** B. The patient has a diagnosis of clinical atherosclerotic cardiovascular disease (ASCVD) AND has ONE of the following: 1. Acute coronary syndrome 2. History of myocardial infarction 3. Stable or unstable angina 4. Coronary or other arterial revascularization 5. Stroke 6. Transient ischemic attack 7. Peripheral arterial disease, including aortic aneurysm, presumed to be of atherosclerotic origin **OR** C. The patient has a diagnosis of primary hyperlipidemia AND ONE of the following: 1. The patient has a coronary artery calcium or calcification (CAC) score greater than or equal to 300 Agatston units **OR** 2. The patient has a pre-treatment LDL-C level greater than or equal to 190 mg/dL (greater than or equal to 4.9 mmol/L) **OR** D. The patient has at least a 20% 10-year ASCVD risk AND ONE of the following: 1. The patient has greater than or equal to 40% 10-year ASCVD risk AND BOTH of the following: A. LDL-C greater than or equal to 70 mg/dL while on maximally tolerated statin therapy **AND** B. ONE of the following:

Module	Clinical Criteria for Approval
	1. The patient has extensive or active burden of ASCVD (i.e., polyvascular ASCVD, which affects all 3 vascular beds—coronary, cerebrovascular, and peripheral arterial; clinical peripheral arterial disease in addition to coronary and/or cerebrovascular disease; a clinical ASCVD event with multivessel coronary artery disease defined as greater than or equal to 40% stenosis in greater than or equal to 2 large vessels; or recurrent myocardial infarction within 2 years of the initial event) in the presence of adverse or poorly controlled cardiometabolic risk factors **OR** 2. Extremely high-risk elevations in cardiometabolic factors with less-extensive ASCVD (i.e., diabetes, LDL-C greater than or equal to 100 mg/dL, less than high–intensity statin therapy, chronic kidney disease, poorly controlled hypertension, high-sensitivity C-reactive protein greater than 3 mg/L, or metabolic syndrome, usually occurring with other extremely high–risk or very-high-risk characteristics), usually with other adverse or poorly controlled cardiometabolic risk factors present. **OR** 3. Patients with ASCVD and LDL-C greater than or equal to 220 mg/dL with greater than or equal to 45% 10- year ASCVD risk despite statin therapy **OR** 2. The patient has 30-39% 10-year ASCVD risk AND ALL of the following: A. LDL-C greater than or equal to 100 mg/dL while on maximally tolerated statin therapy **AND** B. Less-extensive clinical ASCVD (i.e., no polyvascular ASCVD, no clinical peripheral arterial disease, a prior ASCVD event greater than or equal to 2 years prior, and no coronary artery bypass grafting) **AND** C. Adverse or poorly controlled cardiometabolic risk factor(s) including age 65 years or older, current smoking, chronic kidney disease, lipoprotein(a) greater than or equal to 37 nmol/L, high-sensitivity C-reactive

Module	Clinical Criteria for Approval
	protein 1–3 mg/L, metabolic syndrome with a history of myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease, usually in the presence of other adverse or poorly controlled cardiometabolic risk factors **OR** 3. The patient has 20-29% 10-year ASCVD risk AND BOTH of the following: A. LDL-C greater than or equal to 130 mg/dL while on maximally tolerated statins **AND** B. ONE of the following: 1. The patient has less extensive ASCVD and well-controlled cardiometabolic risk factors (i.e., no diabetes, nonsmoker, on high-intensity statin with LDL-C less than 100 mg/dL, blood pressure less than 140/90 mm Hg, and C-reactive protein less than 1 mg/dL) **OR** 2. The use is for primary prevention with LDL-C greater than or equal to 220 mg/dL AND BOTH of the following: A. No clinical ASCVD or CAC less than 100 Agatston units **AND** B. Poorly controlled cardiometabolic risk factor **AND** 2. ONE of the following: A. The patient has been adherent to high-intensity statin therapy (i.e., atorvastatin 40-80mg, rosuvastatin 20-40 mg daily) for at least 8 consecutive weeks AND ONE of the following: 1. The patient's LDL-C level after this statin therapy remains greater than or equal to 70 mg/dL **OR** 2. The patient has not achieved a 50% reduction in LDL-C from this statin therapy **OR** 3. If the patient has ASCVD at very high risk, ONE of the following: A. The patient's LDL-C level after this statin therapy remains greater than or equal to 55 mg/dL **OR** B. The patient's non HDL-C level after this statin therapy remains greater than or equal to 85 mg/dL **OR** B. The patient has been determined to be statin intolerant by meeting ONE of the following: 1. The patient experienced statin-related rhabdomyolysis **OR**

Module	Clinical Criteria for Approval
	2. The patient experienced skeletal-related muscle symptoms (e.g., myopathy, myalgia) and BOTH of the following: A. The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin AND rosuvastatin **AND** B. When receiving separate trials of both atorvastatin and rosuvastatin, the skeletal-related muscle symptoms resolved upon discontinuation of each statin **OR** 3. The patient experienced elevations in hepatic transaminase while receiving separate trials of both atorvastatin and rosuvastatin **OR** C. The patient has a hypersensitivity to atorvastatin AND rosuvastatin **OR** D. The patient has an FDA labeled contraindication to atorvastatin AND rosuvastatin **OR** C. The patient has another FDA labeled indication for the requested agent and route of administration **OR** D. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The patient will NOT be using the requested agent in combination with another PCSK9 agent for the requested indication **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. If the client has preferred agent(s), then ONE of the following: A. The requested agent is a preferred agent **OR** B. The patient has tried and had an inadequate response to the preferred agent **OR** C. The patient has an intolerance or hypersensitivity to the preferred agent **OR** D. The patient has an FDA labeled contraindication to ALL preferred agents **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation**

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The patient has been previously approved for therapy for PCSK9 inhibitors through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. If the client has preferred agent(s), then ONE of the following: A. The requested agent is a preferred agent **OR** B. The patient has tried and had an inadequate response to the preferred agent **OR** C. The patient has an intolerance or hypersensitivity to the preferred agent **OR** D. The patient has an FDA labeled contraindication to ALL preferred agents **AND** 3. The patient has shown clinical benefit with a PCSK9 inhibitor **AND** 4. The patient is currently adherent to therapy with a PCSK9 inhibitor **AND** 5. If the patient has a diagnosis of HoFH, they will continue to use other lipid-lowering therapy (e.g., statin, ezetimibe, lipoprotein apheresis, lomitapide, evinacumab) **AND** 6. If the patient has ASCVD, HeFH, or hyperlipidemia, then ONE of the following: A. The patient is currently adherent to high-intensity statin therapy (i.e., atorvastatin 40-80mg, rosuvastatin 20-40 mg daily) **OR** B. The patient has been determined to be statin intolerant by meeting ONE of the following criteria: 1. The patient experienced statin-related rhabdomyolysis **OR** 2. The patient experienced skeletal-related muscle symptoms (e.g., myopathy, myalgia) and BOTH of the following: A. The skeletal-related muscle symptoms occurred while receiving separate trials of both atorvastatin AND rosuvastatin **AND** B. When receiving separate trials of both atorvastatin and rosuvastatin the skeletal-related muscle symptoms resolved upon discontinuation of each statin **OR** 3. The patient experienced elevations in hepatic transaminase while receiving separate trials of both atorvastatin and rosuvastatin **OR** C. The patient has a hypersensitivity to atorvastatin AND rosuvastatin **OR** D. The patient has an FDA labeled contraindication to atorvastatin AND rosuvastatin **AND** 7. The patient will NOT be using the requested agent in combination with another PCSK9 agent for the requested indication **AND** 8. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months

Peanut Allergy

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Palforzia® (Peanut [Arachis hypogaea] Allergen Powder-dnfp) Powder for oral administration	Mitigation of allergic reactions, including anaphylaxis, that may occur with accidental exposure to peanut. Palforzia is approved for use in patients with a confirmed diagnosis of peanut allergy. Initial dose escalation may be administered to patients aged 1 through 17 years. Up-dosing and maintenance may be continued in patients 1 year of age and older. Palforzia is to be used in conjunction with a peanut-avoidant diet. Limitation of use: not indicated for the emergency treatment of allergic reactions, including anaphylaxis.		1

CLINICAL RATIONALE

Peanut Allergy	Palforzia administration occurs in three sequential phases: initial dose escalation, up-dosing, and maintenance. Initial dose escalation is administered on a single day under the supervision of a health care professional in a health care setting with the ability to manage potentially severe allergic reactions, including anaphylaxis. The initial dose escalation is administered in sequential order on a single day beginning at level A. The dose configurations for each phase of dosing are provided below:(1) Discontinue Palforzia if symptoms requiring medical intervention (e.g., use of epinephrine) occur with any dose during initial dose escalation. Patients 1 through 3 years of age who tolerate all doses (Level A – D) of Palforzia during Initial Dose Escalation must return to the health care setting for initiation of Up-

Dosing. Patients 4 through 17 years of age who tolerate at least the 3 mg single dose (Level D) of Palforzia during Initial Dose Escalation must return to the health care setting for initiation of Up-Dosing. If possible, begin up-dosing the day after initial dose escalation. Repeat initial dose escalation in a health care setting if the patient is unable to begin up-dosing within 4 days.(1)

Dosing Configuration for Initial Dose Escalation Ages 1 through 3 years (Single Day Dose Escalation):(1)

Dose Level	Total Dose	Dose Configuration
A	0.5 mg	One 0.5 mg capsule
B	1 mg	One 1 mg capsule
C	1.5 mg	One 0.5 mg capsule; One 1 mg capsule
D	3 mg	Three 1 mg capsules

Dosing Configuration for Initial Dose Escalation Ages 4 through 17 years (Single Day Dose Escalation):(1)

Dose Level	Total Dose	Dose Configuration
A	0.5 mg	One 0.5 mg capsule
B	1 mg	One 1 mg capsule
C	1.5 mg	One 0.5 mg capsule; One 1 mg capsule
D	3 mg	Three 1 mg capsules
E	6 mg	Six 1 mg capsules

Complete Initial Dose Escalation before starting Up-Dosing. Patients 1 through 3 years of age: Up-Dosing consists of 12 dose levels and is initiated at a 1 mg dose (Level 0) and up-dosed to Level 11. Patients 4 through 17 years of age: Up-

Dosing consists of 11 dose levels and is initiated at a 3 mg dose (Level 1) and up-dosed to Level 11. The first dose of each new up-dosing level is administered under the supervision of a health care professional in a health care setting with the ability to manage potentially severe allergic reactions, including anaphylaxis. Observe patients after administering the first dose of a new Up-Dosing level for at least 60 minutes until suitable for discharge. If the patient tolerates the first dose of the increase dose level, the patient may continue that dose level at home. All dose levels in the up-dosing schedule should be administered in sequential order at 2-week intervals if tolerated. No more than 1 dose should be consumed per day. Consider dose modification or discontinuation for patients who do not tolerate up-dosing as scheduled in label.(1)

Daily Dosing Configuration for Up-Dosing:(1)

Dose Level	Total Daily Dose	Daily Dose Configuration	Dose Duration (weeks)	Patient age (years)
0	1 mg	One 1 mg capsule	2	1-3
1	3 mg	Three 1 mg capsules	2	1-17
2	6 mg	Six 1 mg capsules	2	1-17
3	12 mg	Two 1 mg capsules; One 10 mg capsule	2	1-17
4	20 mg	One 20 mg capsule	2	1-17
5	40 mg	Two 20 mg capsules	2	1-17
6	80 mg	Four 20 mg capsules	2	1-17

7	120 mg	One 20 mg capsule; One 100 mg capsule	2	1-17
8	160 mg	Three 20 mg capsules; One 100 mg capsule	2	1-17
9	200 mg	Two 100 mg capsules	2	1-17
10	240 mg	Two 20 mg capsules; Two 100 mg capsules	2	1-17
11	300 mg	One 300 mg sachet	2	1-17

All dose levels of the up-dosing must be completed before starting maintenance. The maintenance dose of Palforzia is 300 mg daily. Daily maintenance is required to maintain the effect of Palforzia. During maintenance, patients should be contacted and assessed at regular intervals for adverse reactions to Palforzia.(1)

Temporary dose modification may be required for patients who experience allergic reactions during up-dosing or maintenance, for patients who miss doses, or for practical reasons of patient management. Allergic reactions, including gastrointestinal reactions, that are severe, recurrent, bothersome, or last longer than 90 minutes during up-dosing or maintenance should be actively managed with dose modifications. Use clinical judgment to determine the best course of action, which can include maintaining the dose level for longer than 2 weeks, reducing, withholding, or discontinuing Palforzia doses. Following 1 to 2 consecutive days of missed doses, patients may resume Palforzia at the same dose level. Data are insufficient to inform resumption of Palforzia following 3 or more consecutive days of missed doses. Patients who miss 3 or more consecutive days of Palforzia should consult their healthcare providers; resumption of Palforzia should be done under medical supervision.(1)

	Discontinue Palforzia for:(1) • Patients 1 through 3 years of age who are unable to tolerate any dose during the Initial Dose Escalation. • Patients 4 through 17 years of age who are unable to tolerate doses up to and including the 3 mg dose during the Initial Dose Escalation. • Patients with suspected eosinophilic esophagitis. • Patients unable to comply with the daily dosing requirements. • Patients with recurrent asthma exacerbations or persistent loss of asthma control. It should be verified prior to initiation and during therapy with Palforzia that the patient has injectable epinephrine and has been instructed on its use.(1)
Efficacy	Peanut oral immunotherapy was studied in a phase 3 trial (NCT02635776) with patients 4 to 55 years of age with peanut allergy for allergic dose-limiting symptoms at a challenge dose of 100 mg or less of peanut protein (approximately one third of a peanut kernel) in a double-blind, placebo-controlled food challenge.(2) Subjects were required to have serum IgE to peanut greater than or equal to 0.35 kUA/L within 12 months before study entry and/or a mean wheal diameter on skin prick test to peanut greater than or equal to 3 mm greater than the negative control. At study entry, subjects reacted at 100 mg or less of peanut protein in a double-blind, placebo-controlled food challenge (DBPCFC).(1) Participants with an allergic response were randomly assigned, in a 3:1 ratio, to receive AR101 (a peanut-derived investigational biologic oral immunotherapy drug) or placebo in an escalating-dose program. Participants who completed the regimen (i.e., received 300 mg per day of the maintenance regimen for approximately 24 weeks) underwent a double-blind, placebo-controlled food challenge at trial exit. The primary efficacy end point was the proportion of participants 4 to 17 years of age who could ingest a challenge dose of 600 mg or more, without dose limiting symptoms.(2) Of the 551 participants who received AR101 or placebo, 496 were 4 to 17 years of age; of these, 250 of 372 participants (67.2%) who received active treatment, as compared with 5 of 124 participants (4.0%) who received placebo, were able to ingest a dose of 600 mg or more of peanut protein, without dose-limiting symptoms, at the exit food challenge (difference, 63.2 percentage points; 95% confidence interval, 53.0 to 73.3; P <0.001). During the exit food challenge, the maximum severity of symptoms was moderate in 25% of the participants in the active-drug group and 59% of those in the placebo group and severe in 5% and 11%, respectively. Adverse events during the intervention period affected more

	than 95% of the participants 4 to 17 years of age. A total of 34.7% of the participants in the active-drug group had mild events, as compared with 50.0% of those in the placebo group; 59.7% and 44.4% of the participants, respectively, had events that were graded as moderate, and 4.3% and 0.8%, respectively, had events that were graded as severe. Efficacy was not shown in the participants 18 years of age or older.(2)
Safety	Palforzia has a boxed warning for anaphylaxis:(1) • Palforzia can cause anaphylaxis, which may be life-threatening and can occur at any time during Palforzia therapy. • Prescribe injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. • Do not administer Palforzia to patients with uncontrolled asthma. • Dose modifications may be necessary following an anaphylactic reaction. • Observe patients during and after administration of the Initial Dose Escalation and the first dose of each new Up-Dosing level, for at least 60 minutes. • Palforzia is available only through a restricted program called the Palforzia REMS. Palforzia is contraindicated in the following:(1) • Patients with uncontrolled asthma. • Patients with a history of eosinophilic esophagitis or other eosinophilic gastrointestinal disease.

REFERENCES

Number	Reference
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2	AR101 oral immunotherapy for peanut allergy. *New England Journal of Medicine*. 2018;379(21):1991-2001. doi:10.1056/nejmoa1812856

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has been treated with the requested agent within the past 30 days **OR** B. The prescriber states the patient has been treated with the requested agent within the past 30 days AND is at risk if therapy is changed **OR** C. BOTH of the following: 1. The patient has a diagnosed peanut allergy confirmed by ONE of the following: A. A serum peanut-specific IgE level greater than or equal to 0.35 kUA/L **OR** B. A positive skin-prick test determined by a mean wheal diameter that is at least 3mm larger than the negative control upon skin-prick testing for peanut **OR** C. The patient has a positive result to an oral peanut food challenge **AND** 2. The patient was 1-17 years of age at the time of initiating therapy **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient has injectable epinephrine on hand **AND** 4. The requested agent is to be used in conjunction with a peanut-avoidance diet **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months

Peginterferon

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Pegasys®* (peginterferon alfa-2a) Injection for subcutaneous use	**Chronic hepatitis C:** • Adult patients: In combination with other hepatitis C virus (HCV) drugs for adults with compensated liver disease. Pegasys monotherapy is indicated only if patient has contraindication or significant intolerance to other HCV drugs • Pediatric patients: In combination with ribavirin for pediatric patients 5 years of age and older with compensated liver disease Limitations of Use: Pegasys alone or in combination with ribavirin without additional HCV antiviral drugs is not recommended for treatment of patients with chronic hepatitis C who previously failed therapy with an interferon-alfa Pegasys is not recommended for treatment of patients with chronic hepatitis C who have had solid organ transplantation **Chronic hepatitis B:** Adult patients: Treatment of adults with HBeAg positive and HBeAg negative chronic hepatitis B (CHB) infection who have compensated liver disease and evidence of viral replication and liver inflammation Pediatric patients: Treatment of non-cirrhotic, HBeAg-positive patients 3 years of age and older with HBeAg	* For peg-interferons for Multiple sclerosis (e.g. Plegridy), refer to the Multiple Sclerosis PA/QL program	1

Agent(s)	FDA Indication(s)	Notes	Ref#
	positive CHB and evidence of viral replication and elevations in serum alanine aminotransferase (ALT)		

CLINICAL RATIONALE

Hepatitis B	Hepatitis B is an infection of the liver caused by the Hepatitis B virus (HBV). The prevalence of chronic HBV infection is estimated at 240 million persons globally and 704,000 persons in the United States. Deaths due to cirrhosis and cancer secondary to chronic HBV infection are estimated at 310,000 and 340,000 per year respectively. The goal of treatment of chronic HBV infection is to decrease morbidity and mortality.(5) The presence of hepatitis B surface antigen (HBsAg) establishes the diagnosis of hepatitis B. Chronic infection is defined by the presence of HBsAg for at least 6 months. HBV is transmitted by perinatal, percutaneous, and sexual exposure and by close person-to-person contact (presumably by open cuts and sores, especially among children in hyper pandemic areas). HBsAg and antibody to hepatitis B surface antigen (anti-HBs) should be used for screening and indication for immunization. Alternatively, antibody to hepatitis B core antigen (anti-HBc) can be utilized for screening as long as those who test positive are further tested for both HBsAg and anti-HBs to differentiate current infection from previous infection. HBC vaccination does not lead to anti-HBc positivity.(5) There are several agents currently indicated for treatment of chronic HBV. They include adefovir, entecavir, lamivudine, peg-interferon-α-2a, peg-interferon-α-2b, telbivudine, tenofovir alafenamide, and tenofovir dipovoxil fumarate. AASLD prefers entecavir, peg-interferon-α-2a (in adults), peg-interferon-α-2b (in children), tenofovir alafenamide, and tenofovir dipovoxil fumarate as initial therapy for adults HBV infection.(5)
Hepatitis C	Hepatitis C is an infection of the liver caused by the Hepatitis C virus (HCV), a blood-borne virus. Today, most people become infected with HCV by sharing needles or other equipment to inject drugs. Hepatitis C infection can either be acute or chronic. Acute HCV infection is defined as presenting within 6 months following exposure to the virus. In 2018, the reported acute hepatitis C case count in the United States corresponded to a rate of 1.2 cases per 100,000 population, an over 71% increase from the reported incidence rate in 2014. The infection is defined as chronic if the virus is present beyond 6 months following exposure. More than 50% of people who become infected with HCV develop

	chronic infection. Chronic hepatitis C is a serious disease that can result in cirrhosis, liver cancer, and death.(3,4) The American Association for the Study of Liver diseases (AASLD) along with the Infectious Diseases society of America (IDSA) recommend the following:(9) ○ One-time, routine, opt out HCV testing is recommended for all individuals aged 18 years and older ○ One-time HCV testing should be performed for all persons less than 18 years old with activities, exposures, or conditions or circumstances associated with an increased risk of HCV infection ○ Prenatal HCV testing as part of routine prenatal care is recommended with each pregnancy ○ Periodic repeat HCV testing should be offered to all persons with activities, exposures, or conditions or circumstances associated with an increased risk of HCV exposure ○ Annual HCV testing is recommended for all persons who inject drugs, for HIV-infected men who have unprotected sex with men, and men who have sex with men taking pre-exposure prophylaxis (PrEP)= • Risk activities: ○ Injection drug use (current or ever, including those who injected only once) ○ Intranasal illicit drug use ○ Use of glass crack pipes ○ Male engagement in sex with men ○ Engagement in chem sex (defined as the intentional combining of sex with the use of particular nonprescription [illicit] drugs in order to facilitate or enhance the sexual encounter) • Risk exposures: ○ Persons on long-term hemodialysis (ever) ○ Persons with percutaneous/parenteral exposures in an unregulated setting ○ Healthcare, emergency medical, and public safety workers after needlestick, sharps, or mucosal exposure to HCV-infected blood ○ Children born to HCV-infected women ○ Recipients of a prior transfusion or organ transplant, including persons who: ▪ Were notified that they received blood from a donor who later tested positive for HCV ▪ Received a transfusion of blood or blood components, or underwent an organ transplant before July 1992

	▪ Received clotting factor concentrates produced before 1987 ○ Persons who were ever incarcerated • Other conditions and circumstances: ○ HIV infection or HBV infection ○ Sexually active persons about to start pre-exposure prophylaxis (PrEP) for HIV ○ Chronic liver disease and/or chronic hepatitis, including unexplained elevated alanine aminotransferase (ALT) levels ○ Solid organ donors (living and deceased) and solid organ transplant recipients
AASLD/IDSA guidelines on when and in whom to treat	The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response (SVR) (defined as the continued absence of detectable HCV RNA for at least 12 weeks after completion of therapy). According to the AASLD/IDSA guidelines, treatment is recommended for all patients with acute or chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Treatment should be initiated early because delaying therapy may decrease the benefits of SVR and increase the rates of liver-related mortality.(3)
National Comprehensive Cancer Network supported indications	The National Comprehensive Cancer Network (NCCN) lists peginterferon as Category 2A treatment in the following indications (treatment lengths are from the studies NCCN used to support this level of evidence): • Chronic myeloid leukemia(6) ○ Therapy should be continued until progression to accelerated phase, blast crisis or death, or the development of intolerance to treatment whichever occurs first(7) • Hairy cell leukemia(8) ○ Therapy should be continued long-term (up to 164 months studied)(9) ○ Erdheim-Chester disease (ECD)(10) ○ The optimal duration of treatment is unclear but long-term (up to 3 years) treatment with peginterferon alfa (180 mcg/week) was found to have greater efficacy in high-risk ECD with stabilization or improvement in 64% of CNS disease and 79% cardiac disease(11) • Myelofibrosis(12)

	○ In a phase III study, the mean time on peginterferon- alfa 2a therapy was 20.6 months (range 6-56)(13) ○ Polycythemia Vera(12) ○ In a phase II trial, patients were taken off study if they had not reached complete response after 6 months or at any time if they did not tolerate side effects(14) ○ Essential thrombocythemia(12) ○ In a phase II trial, patients were taken off study if they had not reached complete response after 6 months or at any time if they did not tolerate side effects(14) • Primary cutaneous CD30+ T-cell lymphoproliferative disorders(15) ○ Tumor regression should be experienced within 20 weeks(16) • Mycosis fungoides/Sezary Syndrome(15) ○ Real world data suggests complete response should be reached within 12 weeks(17) • Systemic mastocytosis(18) ○ Time to best response may be a year or longer(19) • Adult T-Cell leukemia/lymphoma(20) ○ Treatment was continued for at least four weeks after the onset of complete remission or for up to one year in the absence of such a remission(21)
Safety	Pegasys contains a boxed warning about fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders.(1) Pegasys (peginterferon alfa-2a) is contraindicated in:(1) • Known hypersensitivity reactions such as urticaria, angioedema, bronchoconstriction, anaphylaxis, or Stevens-Johnson syndrome to alpha interferons, including Pegasys, or any of its components • Autoimmune hepatitis • Hepatic decompensation (Child-Turcotte-Pugh score greater than 6 [class B and C]) in cirrhotic patients before treatment • Hepatic decompensation with Child-Turcotte-Pugh score greater than or equal to 6 in cirrhotic CHC patients coinfected with HIV before treatment • In neonates and infants because it contains benzyl alcohol • When used in combination with other HCV antiviral drugs, the contraindications applicable to those agents are applicable to combination therapies

	• Pegasys combination treatment with ribavirin is contraindicated in women who are pregnant and men whose female partners are pregnant

REFERENCES

Number	Reference
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2	Reference no longer used.
3	AASLD/IDSA HCV Guidance: Recommendations for Testing, Managing, and Testing Hepatitis C. Available at www.hcvguidelines.org.
4	The Center for Disease Control and Prevention. Viral Hepatitis Statistics and Surveillance. Available at https://www.cdc.gov/hepatitis/statistics/index.htm.
5	AASLD Guidelines for Treatment of Chronic Hepatitis B. https://www.aasld.org/practice-guidelines.
6	National Comprehensive Cancer Network (NCCN). NCCN Guidelines Chronic Myeloid Leukemia. Version 2.2024.
7	Hochhaus A, Larson RA, Guilhot F, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. *N Engl J Med*. 2017;376(10):917-927. doi:10.1056/NEJMoa1609324
8	National Comprehensive Cancer Network (NCCN). NCCN Guidelines Hairy Cell Leukemia. Version 1.2024.
9	Bohn JP, Gastl G, Steurer M. Long-term treatment of hairy cell leukemia with interferon-α: still a viable therapeutic option. Memo. 2016;9:63-65. doi: 10.1007/s12254-016-0269-1. Epub 2016 Jun 17. PMID: 27429657; PMCID: PMC4923076.
10	National Comprehensive Cancer Network (NCCN). NCCN Guidelines Histiocytic Neoplasms. Version 1.2024.
11	Diamond EL, Dagna L, Hyman DM, et al. Consensus guidelines for the diagnosis and clinical management of Erdheim-Chester disease. Blood. 2014;124(4):483-492. doi:10.1182/blood-2014-03-561381.

Number	Reference
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14	Samuelsson J, Hasselbalch H, Bruserud O, Temerinac S, Brandberg Y, Merup M, Linder O, Bjorkholm M, Pahl HL, Birgegard G; Nordic Study Group for Myeloproliferative Disorders. A phase II trial of pegylated interferon alpha-2b therapy for polycythemia vera and essential thrombocythemia: feasibility, clinical and biologic effects, and impact on quality of life. Cancer. 2006 Jun 1;106(11):2397-405. doi: 10.1002/cncr.21900. PMID: 16639737.
15	National Comprehensive Cancer Network (NCCN), NCCN Guidelines Primary Cutaneous Lymphomas. Version 1.2024.
16	Antonio Cozzio, Werner Kempf, Regula Schmid-Meyer, Michel Gilliet, Sonja Michaelis, Leo Schärer, Günter Burg & Reinhard Dummer (2006) Intra-lesional low-dose interferon α2a therapy for primary cutaneous marginal zone B-cell lymphoma, Leukemia & Lymphoma, 47:5, 865-869, DOI: 10.1080/10428190500399698.
17	Zhang SY, Liu ZR, Yang L, Wang T, Liu J, Liu YH, Fang K. Real-world data on the effectiveness and safety of interferon-alpha-2a intralesional injection for the treatment of focally recalcitrant mycosis fungoides. Ann Transl Med. 2020 Aug;8(15):920. doi: 10.21037/atm-20-1458. PMID: 32953720; PMCID: PMC7475424.
18	National Comprehensive Cancer Network (NCCN). NCCN Guidelines Systemic Mastocytosis. Version 2.2024.
19	Pardanani A. Systemic mastocytosis in adults: 2019 update on diagnosis, risk stratification and management. Am J Hematol. 2019 Mar;94(3):363-377. doi: 10.1002/ajh.25371. Epub 2019 Jan 2. PMID: 30536695.
20	National Comprehensive Cancer Network (NCCN). NCCN Guidelines T-Cell Lymphomas. Version 2.2024.

Number	Reference
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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of chronic hepatitis B AND BOTH of the following: 1. The chronic hepatitis B infection has been confirmed by serological markers **AND** 2. The patient has not been administered peg-interferon for 48 weeks or longer for treatment of chronic hepatitis B **OR** B. The patient has a diagnosis of chronic hepatitis C genotype 1, 2, 3, or 4 AND the requested agent will be used in a treatment regimen AND length of therapy recommended for the patient's genotype as noted in Table 1, 2, or 3 (FDA labeling) **OR** C. The patient has a diagnosis of polycythemia vera **OR** D. The patient has a diagnosis of essential thrombocythemia **OR** E. The patient has a diagnosis of mycosis fungoides/Sezary syndrome **OR** F. The patient has another FDA labeled indication for the requested agent and route of administration **OR** G. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The requested quantity (dose) does not exceed the maximum FDA labeled or compendia supported dose for the requested indication **AND**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
4. The patient does NOT have any FDA labeled contraindications to the requested agent

Compendia Allowed: NCCN 1 or 2a recommended use

Length of approval:

Hepatitis B: Up to 48 weeks total length of treatment
Hepatitis C: Up to the duration as determined in Table 1, 2, or 3
Polycythemia vera or essential thrombocythemia: 6 months
Mycosis fungoides/Sezary syndrome: 12 weeks
All other indications: 12 months or for duration supported in FDA label or compendia whichever is shorter

Table 1: Sovaldi + PEG + RBV Treatment Recommendations based on FDA labeling

<table>
<tr><th>Genotype*</th><th>FDA labeled regimen</th><th>Duration of therapy</th></tr>
<tr><td>1a or 1 b</td><td>Sofosbuvir + PEG-IFN +RBV</td><td>12 weeks</td></tr>
<tr><td>4</td><td>Sofosbuvir + PEG-IFN + RBV</td><td>12 weeks</td></tr>
</table>

*Includes patients with HCV/HIV co-infection

Table 2: Pegasys + RBV Treatment Recommendations based on FDA labeling

<table>
<tr><th>Genotype</th><th>FDA labeled regimen</th><th>Duration of therapy</th></tr>
<tr><td>1 or 4</td><td>Pegasys + RBV</td><td>48 weeks</td></tr>
<tr><td>2 or 3</td><td>Pegasys + RBV</td><td>24 weeks</td></tr>
<tr><td>5 or 6</td><td>There is insufficient data for dosage and duration</td><td></td></tr>
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Module	Clinical Criteria for Approval
	Renewal Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. ONE of the following: A. The patient has a diagnosis of chronic hepatitis B AND the patient has NOT been administered peg-interferon for 48 weeks or longer for treatment of chronic hepatitis B **OR** B. The patient has a diagnosis of chronic hepatitis C genotype 1, 2, 3, or 4 AND the patient did not complete the duration of therapy for the treatment regimen recommended for the patient's genotype as noted in tables 1, 2, or 3 **OR** C. The patient has another diagnosis AND has shown clinical benefit with the requested agent **AND** 3. The requested quantity (dose) does not exceed the maximum FDA labeled or compendia supported dose for the requested indication **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** NCCN 1 or 2a recommended use **Length of approval:** • **Hepatitis B:** Up to duration to complete 48 weeks total length of treatment • **Hepatitis C:** Up to the duration to complete the regimen as determined in Table 1, 2, or 3 • **All other indications:** 12 months or for duration supported in FDA label or compendia whichever is shorter **Table 1: Sovaldi + PEG-IFN + RBV Treatment Recommendations based on FDA labeling**

Genotype*	FDA labeled regimen	Duration of therapy
1a or 1b	Sofosbuvir + PEG-IFN + RBV	12 weeks
4	Sofosbuvir + PEG-IFN + RBV	12 weeks

Module	Clinical Criteria for Approval
	*Includes patients with HCV/HIV co-infection **Table 2: Pegasys + RBV Treatment Recommendations based on FDA labeling**

Genotype	FDA labeled regimen	Duration of therapy
1 or 4	Pegasys + RBV	48 weeks
2 or 3	Pegasys + RBV	24 weeks
5 or 6	There is insufficient data for dosage and duration	

Phenylketonuria

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Kuvan® (sapropterin)* Tablet Oral solution	Reduce blood phenylalanine (Phe) levels in adult and pediatric patients one month of age and older with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4-) responsive phenylketonuria (PKU). To be used in conjunction with a Phe-restricted diet.	* generic available	1
Palynziq® (pegvaliase-pqpz) Subcutaneous injection	To reduce blood phenylalanine concentrations in adult patients with phenylketonuria (PKU) who have uncontrolled blood phenylalanine concentrations greater than 600 micromol/L on existing management. Existing management options include prior or current restriction of dietary phenylalanine and protein intake, and/or prior treatment with sapropterin dihydrochloride.		2

CLINICAL RATIONALE

Phenylketonuria	Phenylketonuria (PKU), also known as phenylalanine hydroxylase (PAH) deficiency, is a rare autosomal recessive error of phenylalanine (Phe) metabolism caused by variants in the gene encoding PAH. PAH deficiency leads to accumulation of Phe in the blood and brain. Untreated, PKU is characterized by irreversible intellectual disability, microcephaly, motor deficits, eczematous rash, autism, seizures, developmental problems, aberrant behavior, and psychiatric symptoms. Since the initiation of newborn screening, almost all cases of PAH deficiency are diagnosed following a positive newborn screening test.(3,4,5) Treatment is recommended to be taken as early as possible, preferably within the first week of life with a goal of having blood Phe in the treatment range within the first 2 weeks of life.(4,5) Dietary therapy, involving dietary Phe restriction and supplementation with reduced or Phe-free amino acid mixtures (medical foods,

	formulas), is the mainstay of therapy and effective in preventing severe mental retardation association with untreated classical PAH deficiency.(3,4,5) There is not clear consensus regarding clinical outcomes in treating patients with Phe blood concentrations between 360 and 600 micromol/L, however given the risk for neurocognitive consequences many treatment centers initiate treatment at a Phe level of 360 micromol/L or higher in patients during the first 12 years of life.(3,4) Guidelines recommend patients less than 12 years of age should have target blood Phe between 120 and 360 micromol/L. Patients age 12 or greater with untreated Phe blood concentration greater than 600 micromol/L should be treated. For patients 12 years of age and older, target Phe levels should be 120 to 600 micromol/L.(3) Pregnancy presents a problem in women with PAH deficiency, as high levels of Phe are toxic to the brain of the developing fetus and along with other teratogenic effects, results in a defined maternal PKU syndrome. Treatment should be considered for women prior to conception with blood Phe greater than 360 micromol/L due to risks of maternal PKU.(3,4,5) Treatment for life is recommended, even though it is acknowledged that dietary management is associated with significant patient burden.(3,4,5) Over time, subtle intellectual and neuropsychiatric issues may manifest even with treatment.(4) In addition, patients treated from the early weeks of life with initial good metabolic control, but who lose control later in childhood or adult life, may experience both reversible and irreversible neuropsychiatric consequences. Even severely intellectually disabled adults with late-diagnosed PAH deficiency show improvements in challenging behavior with lowering of blood Phe levels.(3,4) Sapropterin is a synthetic form of naturally occurring cofactor, tetrahydrobiopterin. Some patients with PAH deficiency who have some residual enzyme activity respond to administration of sapropterin with an increase in the metabolism of Phe to tyrosine.(3) Approximately 25-50% of patients with PAH deficiency are sapropterin responsive. A significant decline in blood Phe is expected in responders with the assumption that diet remains stable with sapropterin therapy. Most sapropterin-responsive patients have a rapid decline in blood Phe level, but occasionally a delay of 2-4 weeks is seen.(4) Clinical judgment is required to determine what constitutes as a significant or beneficial blood Phe decline in an individual patient, but 30% is often cited as evidence of effective Phe reduction since clinical trials for sapropterin identified responders as greater than or equal to 30% decrease in blood Phe from baseline.(1,4) Pegvaliase-pqpz is a phenylalanine-metabolizing enzyme. Patients should discontinue pegvaliase-pqpz if they have not achieved an adequate response (i.e., blood phenylalanine concentration less than or equal to 600 micromol/L)

	after 16 weeks of continuous treatment with the maximum dosage of 60 mg once daily.(2)
Safety	Kuvan (sapropterin) does not have any contraindications.(1) Palynziq (pegvaliase-pqpz) does not have any contraindications but does carry a boxed warning. Anaphylaxis has been reported after administration of pegvaliase-pqpz and may occur at any time during treatment. Auto-injectable epinephrine is prescribed to all patients treated with pegvaliase-pqpz, and the patient (and observer, if applicable) are instructed in recognizing signs and symptoms of anaphylaxis. Due to this, pegvaliase-pqpz is available only through a restricted program called Palynziq REMS.(2)

REFERENCES

Number	Reference
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2	Palynziq prescribing information. BioMarin Pharmaceutical Inc. November 2020.
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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of phenylketonuria (PKU) **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. ONE of the following: A. BOTH of the following: 1. Phenylalanine levels cannot be maintained within the recommended maintenance range with dietary intervention (phenylalanine-restriction) despite strict compliance **AND** 2. The Phe-restricted diet will continue while being treated with the requested agent **OR** B. If the requested agent is Palynziq, the patient's current phenylalanine level is less than 360 micromol/L (6 mg/dL) **AND** 4. If the requested agent is Kuvan or sapropterin, then ONE of the following: A. The patient is less than 12 years of age AND has a baseline (prior to therapy for the requested indication) blood Phe level greater than 360 micromol/L (6 mg/dL) **OR** B. The patient is 12 years of age or over AND has a baseline (prior to therapy for the requested indication) blood Phe level greater than 600 micromol/L (10 mg/dL) **OR** C. The patient is planning on becoming pregnant OR is currently pregnant AND has a baseline (prior to therapy for the requested indication) Phe level greater than 360 micromol/L (6 mg/dL) **AND** 5. If the requested agent is Palynziq, the patient has a baseline (prior to therapy for the requested indication) blood Phe level greater than 600 micromol/L (10 mg/dL) **AND** 6. If the request is for a brand agent, then ONE of the following: A. The patient has tried and had an inadequate response to generic sapropterin despite monitored adherence to treatment **OR** B. The patient has an intolerance or hypersensitivity to generic sapropterin that is not expected to occur with the brand agent **OR** C. The patient has an FDA labeled contraindication to generic sapropterin that is not expected to occur with the brand agent **OR** D. There is support for use of the requested brand agent over generic sapropterin (e.g., presence of two null mutations in trans) **AND**

Module	Clinical Criteria for Approval
	7. The prescriber is a specialist in the area of the patient's diagnosis (e.g., metabolic disorders) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 8. The patient will NOT be using the requested agent in combination with another targeted agent included in this program **AND** 9. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 10. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** **Kuvan (sapropterin):** Approve for 2 months if initial dose is 5 mg/kg/day to less than 20 mg/kg/day, and for 1 month if initial dose is 20 mg/kg/day **Palynziq (pegvaliase-pqpz):** 9 months **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following: A. If the requested agent is Kuvan or sapropterin, then ONE of the following: 1. The patient's blood Phe levels are being maintained within the acceptable range [less than 12 years of age and for females currently pregnant or planning on becoming pregnant: 120-360 micromol/L (2-6 mg/dL); greater than or equal to 12 years of age: 120-600 micromol/L (2-10 mg/dL)] **OR** 2. The patient has had at least a 30% decrease in blood Phe level from baseline (prior to therapy for the requested indication) **OR** B. If the requested agent is Palynziq, then ONE of the following: 1. The patient's blood Phe level is less than or equal to 600 micromol/L (10 mg/dL) **OR** 2. The patient has had at least a 20% decrease in blood Phe level from baseline (prior to therapy for the requested indication) **OR** 3. The patient has NOT received 16 weeks of therapy at the maximum recommended dose in approved labeling AND the prescriber will evaluate for a dose escalation to induce clinical response **AND**

Module	Clinical Criteria for Approval
	3. ONE of the following: A. The patient is currently on a phenylalanine (Phe) restricted diet and will continue while being treated with the requested agent **OR** B. If the requested agent is Palynziq, the patient's phenylalanine level is less than 360 micromol/L (6 mg/dL) **AND** 4. If the request is for a brand agent, then ONE of the following: A. The patient has tried and had an inadequate response to generic sapropterin despite monitored adherence to treatment **OR** B. The patient has an intolerance or hypersensitivity to generic sapropterin that is not expected to occur with the brand agent **OR** C. The patient has an FDA labeled contraindication to generic sapropterin that is not expected to occur with the brand agent **OR** D. There is support for use of the requested brand agent over generic sapropterin (e.g., presence of two null mutations in trans) **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., metabolic disorders) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 6. The patient will NOT be using the requested agent in combination with another targeted agent included in this program **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 8. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months

Proton Pump Inhibitors (PPIs)

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Aciphex® Sprinkle™, Rabeprazole Sprinkle Capsule	• Treatment of GERD in pediatric patients 1 to 11 years of age for up to 12 weeks		2
Aciphex® (rabeprazole)* Tablet	• Healing of erosive or ulcerative gastroesophageal reflux disease (GERD) in adults • Maintenance of healing of erosive or ulcerative GERD in adults • Treatment of symptomatic GERD in adults and adolescents 12 years of age and older • Healing of duodenal ulcers in adults • *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence in adults • Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome in adults	* generic available	1
Dexilant® (dexlansoprazole)* Capsule	• Healing of erosive esophagitis in patients 12 years of age and older • Maintenance of healed erosive esophagitis and relief of heartburn in patients 12 years of age and older • Treatment of symptomatic non-erosive GERD in patients 12 years of age and older	* generic available	3
Konvomep®	• Treatment of active benign gastric ulcer		16

Agent(s)	FDA Indication(s)	Notes	Ref#
(omeprazole/sodium bicarbonate) Oral suspension	• Reduction of risk of upper gastrointestinal (GI) bleeding in critically ill patients		
Nexium® (esomeprazole magnesium) Capsule* Suspension packet	• Treatment of GERD • Risk reduction of NSAID-associated gastric ulcer • *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence • Pathological hypersecretory conditions, including Zollinger-Ellison syndrome	* generic available	5
Prevacid®, Prevacid® SoluTab™ (lansoprazole)* Capsule Orally disintegrating tablet (ODT)	• Short-term treatment of active duodenal ulcer in adults • *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence in adults • Maintenance of healed duodenal ulcers in adults • Short-term treatment of active benign gastric ulcer in adults • Healing of non-steroidal anti-inflammatory drug (NSAID)-associated gastric ulcer • Risk reduction of NSAID-associated gastric ulcer in adults • Treatment of symptomatic GERD • Treatment of erosive esophagitis • Maintenance of healing of erosive esophagitis in adults • Pathological hypersecretory conditions including Zollinger-Ellison syndrome in adults	* generic available	6
Prilosec® (omeprazole)	• Treatment of active duodenal ulcer in adults	* generic available	7

Agent(s)	FDA Indication(s)	Notes	Ref#
Capsule* Suspension packet	• Eradication of *Helicobacter pylori* to reduce the risk of duodenal ulcer recurrence in adults • Treatment of active benign gastric ulcer in adults • Treatment of symptomatic GERD in patients 1 year of age and older • Treatment of erosive esophagitis due to acid-mediated GERD in patients 1 month of age and older • Maintenance of healing of erosive esophagitis due to acid-mediated GERD in patients 1 year of age and older • Pathological hypersecretory conditions in adults		
Protonix® (pantoprazole) Tablet* Suspension packet	• Short-term treatment of erosive esophagitis associated with GERD in patients 5 years of age and older • Maintenance of healing of erosive esophagitis and reduction in relapse rates of daytime and nighttime heartburn symptoms in adult patients with GERD • Pathological hypersecretory conditions including Zollinger-Ellison syndrome in adults	* generic available	8
Voquezna® (vonoprazan) Tablet	• Healing of erosive esophagitis • Maintenance of healed erosive esophagitis • Treatment of *H. pylori* infection		18
Zegerid® (omeprazole/sodium bicarbonate)	• Short-term treatment of active duodenal ulcer in adults • Short-term treatment of active benign gastric ulcer in adults	* generic available	9

Agent(s)	FDA Indication(s)	Notes	Ref#
Capsule* Suspension packet	• Treatment of heartburn and other symptoms associated with GERD in adults • Treatment of erosive esophagitis due to acid-mediated GERD which has been diagnosed by endoscopy in adults • Maintenance of healing of erosive esophagitis due to acid-mediated GERD in adults • Reduction of risk of upper GI bleeding in critically ill adult patients (oral suspension only)		

CLINICAL RATIONALE

Overview	Current guidelines recognize the proton pump inhibitors (PPIs) as first-line therapy for the management of dyspepsia, gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), eradication of Helicobacter pylori (H. pylori), and Zollinger Ellison syndrome (ZES).(10-15,17) In studies comparing PPIs to one another, while some differences have been reported, the magnitude of differences (safety/efficacy) has been small and of uncertain clinical importance. The degree to which any differences would justify the selection of one vs. another PPI, particularly when considering cost-effectiveness, is unclear. Data suggests the similar efficacy of PPIs that has been observed in controlled clinical trials may not necessarily translate into equivalent effectiveness when these drugs are substituted for one another. Differences in dosage formulations and drug interactions may occasionally influence choice of PPI in individual cases.(10-13)
Safety	Aciphex is contraindicated in the following:(1) • Patients with known hypersensitivity to rabeprazole, substituted benzimidazoles, or to any component of the formulation • Patients receiving rilpivirine-containing products Dexilant is contraindicated in the following:(3)

	• Patients with known hypersensitivity to any component of the formulation • Patients receiving rilpivirine-containing products Konvomep is contraindicated in the following:(16) • Known hypersensitivity to any components of the formulation • Patients receiving rilpivirine-containing products Nexium is contraindicated in the following:(5) • Patients with known hypersensitivity to substituted benzimidazoles or any component of the formulation • Patients receiving rilpivirine-containing products Prevacid is contraindicated in the following:(6) • Patients with known severe hypersensitivity to any component of the formulation • Patients receiving rilpivirine-containing products Prilosec is contraindicated in the following:(7) • Patients with known hypersensitivity to substituted benzimidazoles or any component of the formulation • Patients receiving rilpivirine-containing products Protonix is contraindicated in the following:(8) • Patients with known hypersensitivity to substituted benzimidazoles or to any component of the formulation • Patients receiving rilpivirine-containing products Voquezna is contraindicated in the following:(18) • Known hypersensitivity to vonoprazan or any component of Voquezna • Rilpivirine-containing products Zegerid is contraindicated in the following:(9) • Patients with known hypersensitivity to substituted benzimidazoles or to any components of the formulation

	• Patients receiving rilpivirine-containing products

REFERENCES

Number	Reference
1	Aciphex prescribing information. Woodward Pharm Services LLC. July 2023.
2	~~Aciphex Sprinkle prescribing information. Aytu Therapeutics, LLC. December 2020.~~ Reference no longer used.
3	Dexilant prescribing information. Takeda Pharmaceuticals America, Inc. July 2023.
4	~~Esomeprazole strontium prescribing information. Amneal Pharmaceuticals LLC. March 2022.~~ Reference no longer used.
5	Nexium prescribing information. AstraZeneca Pharmaceuticals LP. July 2023.
6	Prevacid prescribing information. Takeda Pharmaceuticals America, Inc. August 2023.
7	Prilosec delayed-release suspension prescribing information. Covis Pharma. July 2023.
8	Protonix prescribing information. Wyeth Pharmaceuticals LLC. July 2023.
9	Zegerid prescribing information. Santarus Inc. July 2023.
10	Katz PO, Dunbar KB, Schnoll-Sussman FH, et al. ACG Clinical Guideline for the Diagnosis and Management of Gastroesophageal Reflux Disease. The American Journal of Gastroenterology. 2022;117(1):27-56.
11	Drugs for GERD and peptic ulcer disease. Medical Letter Treatment Guidelines. 2022;64(1647):49-56.
12	Laine L, Barkun A, Saltzman J, et al. ACG Clinical Guideline: Upper Gastrointestinal and Ulcer Bleeding The American Journal of Gastroenterology 116(5):p 899-917, May 2021.
13	Shaheen N, Falk G, Iyer P, et al. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. American Journal of Gastroenterology 111(1):p 30-50, January 2016.

Number	Reference
14	The Zollinger-Ellison syndrome: dangers and consequences of interrupting antisecretory treatment. Clinical Gastroenterology and Hepatology. 2012 Feb;10(2):199-202.
15	Zollinger-Ellison syndrome: classical considerations and current controversies. The Oncologist. 2014 Jan;19(1):44-50.
16	Konvomep prescribing information. Azuirty Pharmaceuticals, Inc. December 2022.
17	Chey W, Leontiadis G, Howden CW & Moss, S. F. Correction: ACG Clinical Guideline: Treatment of Helicobacter pylori Infection. *The American Journal of Gastroenterology*, *113*(7), 1102, 2018 https://doi.org/10.1038/s41395-018-0132-6
18	Voquezna prescribing information. Phathom Pharmaceuticals, Inc. November 2023

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The patient has ONE of the following: A. A diagnosis of a hypersecretory disease (i.e., Zollinger-Ellison Syndrome, Barrett's esophagitis, or esophageal stricture) **OR** B. Inadequate response to FDA labeled dosing with the requested agent **OR** C. A diagnosis of H pylori **OR** 3. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months • Hypersecretory disease (i.e., Zollinger-Ellison Syndrome, Barrett's esophagitis, or esophageal stricture) - up to 12 months • Inadequate response to FDA labeled dosing - up to 12 months • H. pylori treatment - one time

Primary Biliary Cholangitis

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Iqirvo® (elafibranor) Tablet	Treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. This indication is approved under accelerated approval based on reduction of alkaline phosphatase (ALP). Improvement in survival or prevention of liver decompensation events have not been demonstrated. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). Limitations of Use: Use of Iqirvo is not recommended in patients who have or develop decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy).		8
Livdelzi® (seladelpar) Capsule	Treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. This indication is approved under accelerated approval based on a reduction of alkaline phosphatase (ALP). Improvement in survival or prevention of liver decompensation events have not been demonstrated. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). Limitations of Use: Use of Livdelzi is not recommended in patients who have or develop decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy)		

Agent(s)	FDA Indication(s)	Notes	Ref#
Ocaliva® (obeticholic acid) Tablet	For the treatment of adult patients with primary biliary cholangitis (PBC) • without cirrhosis or • with compensated cirrhosis who do not have evidence of portal hypertension, either in combination with ursodeoxycholic acid (UDCA) with an inadequate response to UDCA or as monotherapy in patients unable to tolerate UDCA		1

CLINICAL RATIONALE

Primary Biliary Cholangitis	Primary biliary cholangitis (PBC), formerly known as primary biliary cirrhosis, is an autoimmune chronic progressive cholestatic liver disease that predominantly affects women. PBC is characterized by a T-lymphocyte-mediated attack on small intralobular bile ducts eventually leading to their gradual destruction and disappearance, ultimately leading to cirrhosis and liver failure. Patients with PBC may be asymptomatic, or they may present with symptoms such as fatigue, pruritus, jaundice, cholestatic liver enzymes, and signs and symptoms of cirrhosis. Common laboratory test abnormalities in patients with PBC include elevated alkaline phosphatase (ALP), antimitochondrial antibodies (AMA), antinuclear antibodies (ANA), and hyperlipidemia.(2-5) AMA is found in 95% of PBC patients. In approximately 5% to 10% of the patients, AMA is absent or present only in low titer (≤1/80), when immunofluorescent techniques are used. The presence or absence of AMA, rather than the magnitude of antibody level, is most important in diagnosis. In some patients, antinuclear antibodies, particularly anti-glycoprotein 210 (anti-gp210) and/or anti-sp100, are present and may correlate with prognosis; in some other AMA-negative patients, antibodies against the major M2 components (PDC-E2 and 2-oxoglutaric acid dehydrogenase complex), are present using enzyme-linked immunosorbent assay or Western blotting techniques. In addition, nearly all AMA-negative PBC patients have PBC-specific antinuclear antibodies, including sp100 and gp210, which are present in over 30% of PBC patients negative for AMA by indirect immunofluorescence.(2)

According to the American Association for the Study of Liver Diseases (AASLD) 2018 Practice Guidance on Primary Biliary Cholangitis, the diagnosis of PBC is generally based on the presence of at least two of the following criteria:(2)

1. Biochemical evidence of cholestasis based on alkaline phosphatase (ALP) elevation
2. Presence of AMA, or other PBC-specific autoantibodies, including sp100 or gp210, if AMA is negative.
3. Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts

Management of PBC includes treatment of symptoms and complications that result from chronic cholestasis and suppression of the underlying pathogenic process (destruction of small intralobular hepatic bile ducts). Ursodeoxycholic acid (ursodiol, UDCA) is first-line therapy for PBC. UDCA improves biochemical indices and delays histologic progression, ultimately enhancing survival. UDCA has minimal side effects and is generally well tolerated.(2,3)

Biochemical response should be assessed after 1 year of treatment with UDCA using one of many published criteria:(2,5)

Source	Response Criteria
Rochester	ALP x ULN (upper level of normal
Barcelona	Reduction in ALP 40% from baseline or normalization of ALP
Paris	ALP 3× ULN; AST 2× ULN; and TB 1 mg/dL
Rotterdam	TB <1× ULN and albumin >1× LLN (lower level of normal)
Toronto	ALP 1.67 x ULN
Paris II	ALP 1.5× ULN; AST 1.5× ULN; and TB 1 mg/dL
Rochester II and Global	ALP 2× ULN

	In patients with an inadequate response to UDCA, obeticholic acid can be used in combination with UDCA or it can be used as monotherapy in patients who are unable to tolerate UDCA. When one of these binary definitions for response to UDCA is used, up to 40% of PBC patients will have an inadequate response to treatment. In addition, scoring systems based on continuous variables have been specifically developed to assess prognosis after initiation of therapy with UDCA. These scores identify patients who are at increased risk for progression to death or liver transplantation and who may benefit from adjuvant therapy. Transient elastography can also be used to risk-stratify patients with PBC: in one study, those with a liver stiffness greater than 9.6 kPa were 5 times more likely to progress with clinical decompensation, death, or transplant.(2) Fibrates can be considered as an off-label alternative for patients with PBC and an inadequate response to UDCA, but are discouraged in patients with decompensated liver disease.(7) Treatment response is monitored using liver biochemical tests. The bilirubin level is the best predictor of survival and is the most important component in all mathematical models of prognosis in PBC. Serum ALP less than twice the upper limit of normal with treatment is a reliable predictor of treatment response. Transient elastography is emerging as a technique to assess prognosis and treatment response as well. Improvement is typically observed within a few weeks, and 90% of the improvement usually occurs by 6-9 months; about 20% of patients achieve normalization of liver biochemistries after two years.(2,3)
Efficacy	Ocaliva (obeticholic acid) is a farnesoid X receptor (FXR) agonist. FXR is a nuclear receptor expressed in the liver and intestine. FXR is a key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways. FXR activation decreases the intracellular hepatocyte concentrations of bile acids by suppressing *de novo* synthesis from cholesterol as well as by increased transport of bile acids out of hepatocytes. These mechanisms limit the overall size of the circulating bile acid pool while promoting choleresis, thus reducing hepatic exposure to bile acids.(1) Obeticholic acid was approved based on a randomized, double-blind, placebo controlled, 12-month trial in patients with PBC (POISE – NCT01473524). Inclusion criteria included an intolerance to UDCA or a suboptimal biochemical response to UDCA after 12 months of UDCA. Suboptimal biochemical response (treatment failure) was defined as ALP 1.67 times the upper limit of normal (ULN) or greater, and/or total bilirubin greater than the ULN but less than 2 times ULN.(1,6) Of note, the suboptimal biochemical response, defined for the study inclusion, was based on a modification of the Toronto criteria.(5,6) Primary

	endpoints for responders were defined as 3 criteria: ALP less than 1.67 times the ULN, total bilirubin less than or equal to ULN, and an ALP decrease of at least 15%.(1) Iqirvo (elafibranor) and its main active metabolite GFT1007 are peroxisome proliferator-activated receptor (PPAR) agonists, both of which activate PPAR-alpha, PPAR-gamma, and PPAR-delta in vitro. However, the mechanism by which elafibranor exerts its therapeutic effects in patients with PBC is not well understood. Pharmacological activity that is potentially relevant to therapeutic effects includes inhibition of bile acid synthesis through activation of PPAR-alpha and PPAR-delta. The signaling pathway for PPAR-delta was reported to include Fibroblast Growth Factor 21 (FGF21)-dependent downregulation of CYP7A1, the key enzyme for the synthesis of bile acids from cholesterol.(8) The efficacy of Iqirvo was evaluated in a 12 month, randomized, double-blind, placebo-controlled study (NCT04526665) in patients with PBC with an inadequate response or intolerance to UDCA and when applicable continued UDCA. Most patients (95%) received study treatment (Iqirvo or placebo) in combination with UDCA or as monotherapy if unable to tolerate UDCA. Patients were included in the study if their ALP was greater than or equal to 1.67-times the ULN and total bilirubin (TB) was less than or equal to 2-times the ULN. Patients were excluded if they had other liver disease or in case of decompensated cirrhosis. The primary endpoint was at Week 52, where biochemical response was defined as achieving ALP less than 1.67-times ULN (defined as 129 U/L for males and 104 U/L for females), TB less than or equal to ULN (1.20 mg/dL), and ALP decrease greater than or equal to 15% from baseline. ALP normalization (i.e., ALP less than or equal to ULN) at Week 52 was a key secondary endpoint. A reduction in mean alkaline phosphatase (ALP) from baseline was observed as early as 4 weeks after treatment compared to the placebo group and lower ALP was generally maintained through week 52. Overall, Iqirvo demonstrated greater improvement in biochemical response and ALP normalization at Week 52 compared to placebo and 96% of patients had a baseline TB concentration less than or equal to ULN.(8)
Safety	Ocaliva has the following boxed warning:(1) Hepatic decompensation and failure, sometimes fatal or resulting in liver transplant, have been reported with Ocaliva treatment in primary biliary cholangitis (PBC) patients with either compensated or decompensated cirrhosis. Ocaliva is contraindicated in PBC patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension. Permanently discontinue Ocaliva in patients who develop

	laboratory or clinical evidence of hepatic decompensation, have compensated cirrhosis and develop evidence of portal hypertension, or experience clinically significant hepatic adverse reactions while on treatment. Ocaliva is contraindicated in patients with the following:(1) • decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event • compensated cirrhosis with evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) • complete biliary obstruction Iqirvo and Livdelzi do not have any contraindications. However, use of these agents are not recommended in patients who have or develop decompensated cirrhosis (e.g., ascites, variceal bleeding, hepatic encephalopathy).(8,9)

REFERENCES

Number	Reference
1	Ocaliva prescribing information. Intercept Pharmaceuticals, Inc. May 2022.
2	Lindor KD, Bowlus CL, Boyer J, et al. Primary Biliary Cholangitis: 2018 Practice Guidance from the American Association for the Study of Liver Diseases. Hepatology 69(1):p 394-419, January 2019. | DOI: 10.1002/hep.30145.
3	Laschtowitz A, de Veer RC, Van der Meer AJ, Schramm C. Diagnosis and treatment of primary biliary cholangitis. United European Gastroenterol J. 2020 Jul;8(6):667-674. doi: 10.1177/2050640620919585. Epub 2020 Apr 16. PMID: 32299307; PMCID: PMC7437077.
4	Tanaka A. Current understanding of primary biliary cholangitis. Clin Mol Hepatol. 2021 Jan;27(1):1-21. doi: 10.3350/cmh.2020.0028. Epub 2020 Dec 3. PMID: 33264835; PMCID: PMC7820210.
5	European Association for the Study of the Liver (EASL) 2017 Clinical Practice Guidelines: The Diagnosis and Management of Patients with Primary Biliary Cholangitis.
6	Corpechot C, Poupon R, Chazouilleres O. New Treatments/Targets for Primary Biliary Cholangitis. J Hepatol Reports. 2019;1(3):203-213.

Number	Reference
7	Lindor KD, Bowlus CL, Boyer J, et al. Primary Biliary Cholangitis: 2021 Practice Guidance Update from the American Association for the Study of Liver Diseases (AASLD).
8	Iqirvo prescribing information. Ipsen Biopharmaceuticals, Inc. June 2024.
9	Livedelzi prescribing information. Gilead Sciences, Inc. August 2024.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of primary biliary cholangitis (PBC) AND ALL of the following: 1. Diagnosis has been confirmed by at least TWO of the following: A. There is biochemical evidence of cholestasis with an alkaline phosphatase (ALP) elevation B. ONE of the following: 1. Positive presence of antimitochondrial antibody (AMA) **OR** 2. Positive presence of other PBC-specific autoantibodies (e.g., sp100, gp210) if AMA is negative C. Histologic evidence of nonsuppurative destruction cholangitis and destruction of interlobular bile ducts **AND** 2. The prescriber has measured the patient's baseline alkaline phosphatase (ALP) level and total bilirubin level (prior to therapy with the requested agent) **AND** 3. ONE of the following: A. BOTH of the following: 1. The patient has tried and had an inadequate response after at least 1 year of therapy with ursodeoxycholic acid (UDCA) (inadequate response defined as ALP greater than the upper limit of normal [ULN], and/or total bilirubin greater than ULN but less than 2x ULN, after 1 year of treatment with UDCA) **AND** 2. The patient will continue treatment with ursodeoxycholic acid (UDCA) in combination with the requested agent **OR**

Module	Clinical Criteria for Approval
	B. The patient has an intolerance or hypersensitivity to therapy with ursodeoxycholic acid (UDCA) **OR** C. The patient has an FDA labeled contraindication to ursodeoxycholic acid (UDCA) **OR** B. The patient has another FDA labeled indication for the requested agent **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, hepatologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval**: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. ONE of the following: A. The patient has a diagnosis of primary biliary cholangitis (PBC) AND ALL of the following: 1. ONE of the following: A. The requested agent will be used in combination with ursodeoxycholic acid (UDCA) **OR** B. The patient has an intolerance, hypersensitivity, or an FDA labeled contraindication to therapy with ursodeoxycholic acid (UDCA) **OR** 2. The patient has had an alkaline phosphatase (ALP) decrease of greater than or equal to 15% from baseline (prior to therapy with the requested agent) AND ALP is less than the upper limit of normal (ULN) **AND** 3. The patient's total bilirubin is less than or equal to the upper limit of normal (ULN) **OR** B. The patient has another FDA labeled indication for the requested agent **AND**

Module	Clinical Criteria for Approval
	3. The patient has had clinical benefit with the requested agent **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, hepatologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval**: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Ops Set Up	Validation Options	Other Explanation
PA	Validation: Apply Baseline and go to Validation Options	Age Verification;Contraind., intolerance, or hypersensitivity to prereq.;Diagnosis;Other (see Other explanation field);Required Concomitant Therapy	-The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ursodeoxycholic acid (UDCA) (Initial and Renewal)

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Procysbi (cysteamine bitartrate)

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Procysbi® (cysteamine bitartrate delayed release) Oral capsule Oral granules	Treatment of nephropathic cystinosis in adults and pediatric patients 1 year of age and older		1

CLINICAL RATIONALE

Cystinosis	Cystinosis is a rare autosomal recessive lysosomal storage disorder in which cystine accumulates in lysosomes of cells. It is a systemic disease wherein cystine crystals accumulate in all body cells and tissues. Cystinosis has three major clinical presentations depending on the severity of mutations affecting the CTNS gene: the infantile nephropathic form, the juvenile nephropathic form, and the adult (non-nephropathic ocular) form. The infantile nephropathic form is the most common and severe form, occurring in over 95% of patients, with consecutively progressive loss of glomerular function leading to end-stage renal disease (ESRD). ESRD usually develops by the end of the first or second decade of life. Nearly all nephropathic cystinosis patients will develop major extra-renal symptoms including retinal, endocrine, and neuromuscular complications by 30 years of age if cystine depletion therapy is not initiated early.(2) Cysteamine, in combination with symptomatic care, is the standard of care for patients with cystinosis. Cysteamine can deplete the intralysosomal cystine through the reduction of cystine, and the formation of cysteine and a cysteamine-cysteine mixed disulfide which exits the lysosome via the cationic amino acid transporter PQLC2, thus bypassing the original genetic and biochemical defects of the disease. Treatment with cysteamine improves overall prognosis by delaying progression to ESRD, preventing hypothyroidism and extra-renal

	complications, and improves growth in affected children. Therefore, cysteamine treatment should be started as soon as possible and needs to be continued lifelong.(2)
Efficacy	A multicenter, open-label, randomized clinical trial was completed comparing Procysbi to immediate-release cysteamine bitartrate (Cystagon). All patients were required to be on a stable dose of immediate-release cysteamine bitartrate prior to randomization. The study demonstrated that Procysbi administered every 12 hours was non-inferior to immediate-release cysteamine bitartrate dosed every 6 hours.(1)
Safety	Procysbi is contraindicated in patients with a serious hypersensitivity reaction, including anaphylaxis, to penicillamine or cysteamine.(1)

REFERENCES

Number	Reference
1	Procysbi prescribing information. Horizon Therapeutics USA, Inc. February 2022.
2	Elmonem MA, Veys KR, Soliman NA, Van Dyck M, Van Den Heuvel LP, Levtchenko E. Cystinosis: a review. *Orphanet Journal of Rare Diseases*. 2016;11(1). doi:10.1186/s13023-016-0426-y

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of nephropathic cystinosis **OR** B. The patient has another FDA labeled indication for the requested agent and route of administration **OR** C. The patient has an indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient has tried and had an inadequate response to Cystagon (immediate release cysteamine) **OR** B. The patient has an intolerance or hypersensitivity to Cystagon that is not expected to occur with the requested agent **OR** C. The patient has an FDA labeled contraindication to Cystagon that is not expected to occur with the requested agent **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., nephrologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months

Progesterones

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Crinone® 4% (progesterone) Vaginal gel	Secondary amenorrhea		1
Crinone® 8% (progesterone) Vaginal gel	Progesterone supplementation or replacement as part of an Assisted Reproductive Technology (“ART”) treatment for infertile women with progesterone deficiency Secondary amenorrhea in women who have failed to respond to treatment with Crinone 4%		1
Endometrin® (progesterone) Vaginal insert	Support of embryo implantation and early pregnancy by supplementation of corpus luteal function as part of an Assisted Reproductive Technology (ART) treatment program for infertile women		2

CLINICAL RATIONALE

Secondary amenorrhea	Amenorrhea is the absence or abnormal cessation of the menses. Primary and secondary amenorrhea describe the occurrence of amenorrhea before and after menarche, respectively. In women with regular menstrual cycles, a delay of menses for as little as one week may require the exclusion of pregnancy. Secondary amenorrhea is defined as the absence of menses for greater than 3 months in women that previously had regular menstrual cycles or 6 months in women who had irregular menstrual cycles.(3) The prevalence of amenorrhea not due to pregnancy, lactation or menopause is approximately 3-4%. The list of potential causes of amenorrhea is long, the majority of cases are caused by six conditions: polycystic ovary syndrome (PCOS), hyperprolactinemia, thyroid dysfunction, hypo- and hypergonadotropic

	hypogonadism, and anatomic abnormalities. The most common cause of secondary amenorrhea is pregnancy. After pregnancy is ruled out, the initial work-up should be based on patient history and physical examination. In addition to a history and physical, an estimation of follicle stimulating hormone (FSH) and estradiol will identify the most common causes of secondary amenorrhea. Patients presenting with amenorrhea should also have measurements of thyroid-stimulating hormone (TSH) and prolactin.(3)
Assisted Reproductive Technology	The modulating effects of progesterone on endometrial structure and function are essential to the success of human reproduction. After ovulation, progesterone produced by the corpus luteum (CL) induces “secretory” maturation of the endometrium, involving a cascade of molecular events that ultimately renders the endometrium receptive to implantation of the embryo. Considering the important role that progesterone plays in human reproduction, it is not surprising that exogenous supplemental progesterone is a common element of treatment regimens in infertility, particularly those relating to the assisted reproductive technologies (ART). To optimize endometrial receptivity, it is common practice to administer a progesterone supplement during the luteal phase. Progesterone supplementation is generally initiated on the day of oocyte retrieval or at the time of embryo transfer.(4) Treatment may be continued until placental autonomy is achieved, up to 10 weeks for Endometrin and up to 10 to 12 weeks for Crinone.(1,2) Progesterone is a naturally occurring steroid that is secreted by the ovary, placenta, and adrenal gland. In the presence of adequate estrogen, progesterone transforms a proliferative endometrium into a secretory endometrium. Progesterone is essential for the development of decidual tissue and the effect of progesterone on the differentiation of glandular epithelia and stroma has been extensively studied.(1,2) Progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy.(2)
Efficacy	Crinone is a bioadhesive vaginal gel containing micronized progesterone in an emulsion system, which is contained in single use, polypropylene vaginal applicators.(1) Endometrin (progesterone) vaginal insert contains micronized progesterone. Endometrin is supplied with polyethylene vaginal applicators.(2)
Safety	Crinone is contraindicated in individuals with any of the following conditions:(1)

	• Known sensitivity to Crinone (progesterone or any of the other ingredients) • Undiagnosed vaginal bleeding • Liver dysfunction or disease • Known or suspected malignancy of the breast or genital organs • Missed abortions • Active thrombophlebitis or thromboembolic disorders, or a history of hormone-associated thrombophlebitis or thromboembolic disorders Endometrin is contraindicated in individuals with any of the following conditions:(2) • Previous allergic reactions to progesterone or any of the ingredients of Endometrin Vaginal Insert • Undiagnosed vaginal bleeding • Known missed abortion or ectopic pregnancy • Liver disease • Known or suspected malignancy of the breast or genital organs • Active arterial or venous thromboembolism or severe thrombophlebitis, or a history of these events

REFERENCES

Number	Reference
1	Crinone Prescribing Information. Allergan, Inc. June 2017.
2	Endometrin Prescribing Information. Ferring Pharmaceuticals Inc. January 2018.
3	Current evaluation of amenorrhea. The practice Committee of the American Society for Reproductive medicine. Birmingham Alabama. Fertility and sterility Vol. 90, Suppl 3 November 2008.
4	Progesterone supplementation during the luteal phase and in early pregnancy in the treatment of infertility: an educational bulletin. The Practice Committee of the American Society for Reproductive Medicine. American Society for Reproductive Medicine, Birmingham Alabama Fertility and Sterility Vol 89, No 4, April 2008.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Parathyroid Hormone Analog for Osteoporosis

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
FORTEO® (teriparatide [recombinant])* Injection solution	Treatment of postmenopausal women with osteoporosis at high risk for fracture (defined herein as having a history of osteoporotic fracture or multiple risk factors for fracture) or who have failed or are intolerant to other available osteoporosis therapy Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy (daily dosage equivalent to 5 mg or greater of prednisone) at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy Use of FORTEO for more than 2 years during a patient's lifetime should only be considered if a patient remains at or has returned to having a high risk of fracture.	*generic available	1
Teriparatide Injection solution	Treatment of postmenopausal women with osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy Increase of bone mass in men with primary or hypogonadal osteoporosis at high risk for fracture, defined as a history of osteoporotic fracture, multiple risk factors for fracture, or patients who have failed or are intolerant to other available osteoporosis therapy Treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy (daily dosage		3

Agent(s)	FDA Indication(s)	Notes	Ref#
	equivalent to 5 mg or greater of prednisone) at high risk for fracture or patients who have failed or are intolerant to other available osteoporosis therapy Use of Teriparatide for more than 2 years during a patient's lifetime should only be considered if a patient remains at or has returned to having a high risk of fracture.		
TYMLOS® (abaloparatide) Injection solution	Treatment of postmenopausal women with osteoporosis at high risk for fracture (defined as a history of osteoporotic fracture or multiple risk factors for fracture), or patients who have failed or are intolerant to other available osteoporosis therapy To increase bone density in men with osteoporosis at high risk for fracture (defined as a history of osteoporotic fracture or multiple risk factors for fracture), or patients who have failed or are intolerant to other available osteoporosis therapy.		2

CLINICAL RATIONALE

Postmenopausal Osteoporosis	The American Association of Clinical Endocrinologists/American College of Endocrinology joint guidelines for postmenopausal osteoporosis state that there are several pathways to diagnose osteoporosis:(6) • T-score -2.5 or below in the lumbar spine, femoral neck, total proximal femur or distal 1/3 of the radius • Low-trauma spine or hip fracture (regardless of bone mineral density) • T-score between -1.0 and -2.5 and a fragility fracture of proximal humerus, pelvis, or distal forearm • T-score between -1.0 and -2.5 and high FRAX (Fracture Risk Assessment Tool) (or if available, TBS [trabecular bone score]-adjusted FRAX) fracture based on country-specific thresholds The World Health Organization (WHO) has defined T-score criteria as follows:(6) • Normal: T-score -1.0 or above • Osteopenia: T-score between -1.0 and -2.5 • Osteoporosis: T-score at or below -2.5

	• Severe or established osteoporosis: -2.5 or below with fragility fracture
Very High-Risk Postmenopausal Women	The 2020 American Association of Clinical Endocrinology (AACE) Guidelines created a 'very high-risk' category for post-menopausal women with osteoporosis. The following patients are considered to be at very high fracture risk:(6) • Patients with a recent fracture (within the past 12 months) • Patients with fractures while on approved osteoporosis therapy • Patients with multiple fractures • Patients with fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids) • Patients with a very low T-score (less than -3.0) • Patients with a high risk for falls or history of injurious falls • Patients with very high fracture probability by FRAX (e.g., major osteoporosis fracture greater than 30%, hip fracture greater than 4.5%) or other validated fracture risk algorithm Patients who have been diagnosed with osteoporosis but do not meet the above definition of very high fracture risk are considered to be at high risk.(6) The AACE recommends alendronate, denosumab, risedronate, and zoledronate as appropriate initial therapy for most osteoporotic patients with high fracture risk. Abaloparatide, denosumab, romosozumab, teriparatide, and zoledronate should be considered for patients unable to use oral therapy and as initial therapy for patients at very high fracture risk.(6)
Men over the age of 50	The Endocrine Society recommends pharmacological treatment for men aged 50 or older at high risk of fracture including, but not limited to:(10) • Men who have had a hip or vertebral fracture without major trauma • Men who have not experienced a spine or hip fracture, but whose Bone Mineral Density (BMD) of the spine, femoral neck, and/or total hip is 2.5 standard deviations below the mean of normal young white males • In the US, men who have a T-score between -1.0 and -2.5 in the spine, femoral neck, or total hip plus a 10-year risk of hip fracture greater than or equal to 3% using FRAX. For men outside the US, region-specific guidelines should be considered • Men who are receiving long-term glucocorticoid therapy in pharmacological doses

	Men at high risk of fracture can be treated with medication approved by regulatory agencies such as the US FDA or the European Medicines Agency (EMA). At the time of this writing of the 2012 Endocrine Society clinical practice guideline for Osteoporosis in Men, alendronate, risedronate, zoledronic acid, and teriparatide were recommended. Denosumab can also be used for men receiving androgen deprivation therapy (ADT) for prostate cancer. The selection of therapeutic agent should be individualized based on factors including fracture history, severity of osteoporosis (T-scores), the risk for hip fracture, patterns of BMD, comorbid conditions, cost, and other factors.(10) The American College of Physicians (ACP) recommends bisphosphonates to reduce the risk for vertebral fracture in men who have clinically recognized osteoporosis.(11)
Treatment	According to the The Bone Health and Osteoporosis Foundation, postmenopausal women and men age 50 and older presenting with the following should be considered for treatment:(4) • A hip or vertebral fracture • A fracture of the pelvis, proximal humerus, or distal forearm in a person with low bone mass or osteopenia • T-score of -2.5 or lower at the femoral neck, total hip, lumbar spine, or 33% radius • T-score between -1 and -2.5 at the femoral neck or total hip and a 10-year probability of a hip fracture greater than or equal to 3% or a 10-year probability of a major osteoporosis-related fracture greater than or equal to 20% based on the US-adapted FRAX algorithm The Endocrine Society also agrees with these treatment thresholds for men with increased fracture risk.(10) In their 2020 Postmenopausal Osteoporosis Guidelines, the AACE stated that osteoporosis can be diagnosed if there is a fragility fracture in the absence of other metabolic bone disease, independent of the T-score. Thus, patients with a T-score indicating osteopenia, but who have had a fragility fracture of the spine, hip, proximal humerus, pelvis, or distal forearm should be diagnosed with osteoporosis and considered for pharmacologic therapy.(6)
Glucocorticoid-Induced Osteoporosis	The 2022 ACR guideline recommends that all adults starting or continuing therapy with glucocorticoids for greater than 3 months should be assessed for fracture risk. Patients who are at moderate, high, or very high risk of fractures should receive osteoporosis therapy. The guideline categorizes the following risk levels:(12)

	• For adults who are 40 years of age or older:
	  ○ Very high risk
	  ▪ Prior osteoporotic fractures OR
	  ▪ T-score less than or equal to -3.5 OR
	  ▪ FRAX 10-year risk of major osteoporotic fracture greater than or equal to 30%, or hip fracture greater than or equal to 4.5% OR
	  ▪ Glucocorticoid use equivalent to greater than or equal to 30 mg/day of prednisone for greater than 30 days OR
	  ▪ Cumulative glucocorticoid doses equivalent to greater than or equal to 5 g/year of prednisone
	  ○ High risk
	  ▪ T-score less than or equal to -2.5 but greater than -3.5 OR
	  ▪ FRAX 10-year risk of major osteoporotic fracture greater than or equal to 20% and less than 30%, or hip fracture greater than or equal to 3% and less than 4.5%
	  ○ Moderate risk
	  ▪ T-score between -1.0 and -2.4 OR
	  ▪ FRAX 10-year risk of major osteoporotic fracture greater than or equal to 10% and less than 20%, or hip fracture greater than 1% and less than 3% OR
	  ○ Low risk
	  ▪ T-score greater than -1.0 OR
	  ▪ FRAX 10-year risk of major osteoporotic fracture less than 10%, or hip fracture less than 1%
	• For adults less than 40 years of age:
	  ○ Very high risk
	  ▪ Prior fractures OR
	  ▪ Glucocorticoid use equivalent to greater than or equal to 30 mg/day of prednisone OR
	  ▪ Cumulative glucocorticoid doses equivalent to greater than or equal to 5 g/year of prednisone
	  ○ Moderate risk
	  ▪ Glucocorticoid treatment equivalent to greater than or equal to 7.5 mg/day of prednisone for greater than or equal to 6 months AND z-score less than -3 OR
	  ▪ Significant BMD loss (more than the least significant change of DXA)
	  ○ Low risk
	  ▪ None of the above risk factors other than glucocorticoid treatment

	Parathyroid hormones/parathyroid hormone related proteins are conditionally recommended over anti-resorptive therapies (bisphosphonate, denosumab) in patients at very high risk of fracture. Denosumab and parathyroid hormones/parathyroid hormone related proteins are conditionally recommended over oral and IV bisphosphonates in high risk patients. There is no preferred ordered of therapies between bisphosphonates, denosumab, or parathyroid hormones/parathyroid hormone related proteins in patients with moderate risk.(12) Until the effect of concomitant use of osteoporosis agents is better understood, the AACE does not recommend concomitant use of agents for osteoporosis.(6)
Safety	FORTEO and Teriparatide is contraindicated in patients with a hypersensitivity to teriparatide or to any of its excipients.(1,3)

REFERENCES

Number	Reference
1	FORTEO prescribing Information. Eli Lilly & Co. April 2021.
2	TYMLOS prescribing information. Radius Health, Inc. November 2023.
3	Teriparatide prescribing information. Almaject, Inc. June 2024.
4	LeBoff MS, Greenspan SL, Insogna KL, et al. The clinician's guide to prevention and treatment of osteoporosis. *Osteoporosis International*. 2022;33(10):2049-2102. doi:10.1007/s00198-021-05900-y
5	Reference no longer used.
6	Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis – 2020 Update. https://www.sciencedirect.com/science/article/pii/S1530891X20428277
7	Reference no longer used.
8	Reference no longer used.

Number	Reference
9	Reference no longer used.
10	Endocrine Society Guideline: Osteoporosis in Men: An Endocrine Society Clinical Practice Guideline 2012. https://academic.oup.com/jcem/article/97/6/1802/2536476
11	Qaseem A, Forciea MA, McLean RM, et. al. Treatment of Low Bone Density or Osteoporosis to Prevent Fractures in Men and Women: A Clinical Practice Guideline Update from the American College of Physicians. Ann Intern Med. 2017;166:818-839. https://annals.org/aim/fullarticle/2625385/treatment-low-bone-density-osteoporosis-prevent-fractures-men-women-clinical
12	Humphrey MB, Russell L, Danila MI, et al. 2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis & Rheumatology*. 2023;75(12):2088-2102. doi:10.1002/art.42646
13	Reference no longer used.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
FORTEO - brand non-preferred, generic preferred	**FORTEO** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is FORTEO generic equivalent AND ONE of the following: 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. The patient has a diagnosis of osteoporosis and ALL of the following: 1. ONE of the following: A. The patient's sex is male and ONE of the following: 1. The patient's age is 50 years or over **OR** 2. The requested agent is medically appropriate for the patient's age and sex **OR** B. The patient's sex is female and ONE of the following: 1. The patient is postmenopausal **OR**

Module	Clinical Criteria for Approval
	2. The requested agent is medically appropriate for the patient's sex and menopause status **AND** 2. The patient's diagnosis was confirmed by ONE of the following: A. A fragility fracture in the hip or spine **OR** B. A T-score of -2.5 or lower **OR** C. A T-score of -1.0 to -2.5 and ONE of the following: 1. A fragility fracture of the proximal humerus, pelvis, or distal forearm **OR** 2. A FRAX 10-year probability for major osteoporotic fracture of greater than or equal to 20% **OR** 3. A FRAX 10-year probability of hip fracture of greater than or equal to 3% **AND** 3. ONE of the following: A. The patient is at a very high fracture risk as defined by ONE of the following: 1. Patient had a recent fracture (within the past 12 months) **OR** 2. Patient had fractures while on FDA labeled osteoporosis therapy **OR** 3. Patient has had multiple fractures **OR** 4. Patient had fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids) **OR** 5. Patient has a very low T-score (less than -3.0) **OR** 6. Patient is at high risk for falls or has a history of injurious falls **OR** 7. Patient has a very high fracture probability by FRAX (e.g., major osteoporosis fracture greater than 30%, hip fracture greater than 4.5%) or by other validated fracture risk algorithm **OR** B. The patient has tried and had an inadequate response to a bisphosphonate (medical records required) **OR** C. The patient has an intolerance or hypersensitivity to a bisphosphonate (medical records required) **OR** D. The patient has an FDA labeled contraindication to ALL bisphosphonates (medical records required) **AND** 4. ONE of the following: A. The requested agent is FORTEO generic equivalent **OR** B. The requested agent is brand FORTEO AND BOTH of the following:

Module	Clinical Criteria for Approval
	1. The patient has an intolerance, hypersensitivity, or has an FDA labeled contraindication to FORTEO generic equivalent that is not expected to occur with the requested agent **AND** 2. The patient has tried and had an inadequate response, has an intolerance, hypersensitivity, or has an FDA labeled contraindication to TYMLOS (abaloparatide) **OR** C. The patient has a diagnosis of glucocorticoid-induced osteoporosis and ALL of the following: 1. The patient is either initiating or currently taking glucocorticoids in a daily dosage equivalent to 5 mg or higher of prednisone **AND** 2. The patient's expected current course of therapy of glucocorticoids is for a period of at least 3 months **AND** 3. ONE of the following: A. The patient is less than 40 years of age AND has ONE of the following: 1. A prior fracture **OR** 2. Either initiating or currently taking glucocorticoids that is equivalent to a prednisone dose that is greater than or equal to 30 mg/day **OR** 3. Either initiating or currently taking glucocorticoids that is equivalent to a cumulative prednisone dose of greater than or equal to 5 g/year **OR** B. The patient is 40 years of age or greater AND has one of the following: 1. A prior osteoporotic fracture **OR** 2. A T-score of less than or equal to -2.5 **OR** 3. A FRAX 10-year probability for major osteoporotic fracture of greater than or equal to 20% **OR** 4. A FRAX 10-year risk probability for hip fracture of greater than or equal to 3% **OR** 5. Either initiating or currently taking glucocorticoids that is equivalent to a prednisone dose that is greater than or equal to 30 mg/day for greater than 30 days **OR** 6. Either initiating or currently taking glucocorticoids that is equivalent to a cumulative prednisone dose of greater than or equal to 5 g/year **OR** C. The patient has tried and had an inadequate response to a bisphosphonate (medical records required) **OR**

Module	Clinical Criteria for Approval
	D. The patient has an intolerance or hypersensitivity to a bisphosphonate (medical records required) **OR** E. The patient has an FDA labeled contraindication to ALL bisphosphonates (medical records required) **AND** 4. ONE of the following: A. The requested agent is FORTEO generic equivalent **OR** B. The requested agent is brand FORTEO and the patient has an intolerance, hypersensitivity, or has an FDA labeled contraindication to FORTEO generic equivalent that is not expected to occur with the requested agent **AND** 2. The patient will NOT be using the requested agent in combination with a bisphosphonate, denosumab (e.g., Prolia, Xgeva), romosozumab-aqqg or another parathyroid hormone analog for osteoporosis (e.g., abaloparatide) **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 4. ONE of the following: A. The total duration of treatment with parathyroid hormone analog(s) for osteoporosis has NOT exceeded 2 years in a lifetime **OR** B. The total duration of treatment with parathyroid hormone analog(s) for osteoporosis has exceeded 2 years in a lifetime AND the patient is at high risk of fracture (e.g., shown by T-score, FRAX score, continued use of glucocorticoids at a daily equivalent of 5 mg of prednisone or higher) **Length of approval:** For those who have not yet received a total of 2 years of treatment in their lifetime between FORTEO (teriparatide), Teriparatide, and TYMLOS (abaloparatide), approve for up to the remainder of that 2-year therapy which has not yet been received. For those who have already received a total of 2 years of treatment in their lifetime between FORTEO (teriparatide) or Teriparatide AND is at high risk of fracture, approve for up to 1 year. NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
Teriparatide - non-preferred	**Teriparatide** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of osteoporosis and ALL of the following: 1. ONE of the following: A. The patient's sex is male and ONE of the following: 1. The patient's age is 50 years or over **OR**

Module	Clinical Criteria for Approval
	2. The requested agent is medically appropriate for the patient's age and sex **OR** B. The patient's sex is female and ONE of the following: 1. The patient is postmenopausal **OR** 2. The requested agent is medically appropriate for the patient's sex and menopause status **AND** 2. The patient's diagnosis was confirmed by ONE of the following: A. A fragility fracture in the hip or spine **OR** B. A T-score of -2.5 or lower **OR** C. A T-score of -1.0 to -2.5 and ONE of the following: 1. A fragility fracture of the proximal humerus, pelvis, or distal forearm **OR** 2. A FRAX 10-year probability for major osteoporotic fracture of greater than or equal to 20% **OR** 3. A FRAX 10-year probability of hip fracture of greater than or equal to 3% **AND** 3. ONE of the following: A. The patient is at a very high fracture risk as defined by ONE of the following: 1. Patient had a recent fracture (within the past 12 months) **OR** 2. Patient had fractures while on FDA labeled osteoporosis therapy **OR** 3. Patient has had multiple fractures **OR** 4. Patient had fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids) **OR** 5. Patient has a very low T-score (less than -3.0) **OR** 6. Patient is at high risk for falls or has a history of injurious falls **OR** 7. Patient has a very high fracture probability by FRAX (e.g., major osteoporosis fracture greater than 30%, hip fracture greater than 4.5%) or by other validated fracture risk algorithm **OR** B. The patient has tried and had an inadequate response to a bisphosphonate (medical records required) **OR** C. The patient has an intolerance or hypersensitivity to a bisphosphonate (medical records required) **OR** D. The patient has an FDA labeled contraindication to ALL bisphosphonates (medical records required) 4. BOTH of the following:

Module	Clinical Criteria for Approval
	A. The patient has tried and had an inadequate response, has an intolerance, hypersensitivity, or has an FDA labeled contraindication to FORTEO generic equivalent that is not expected to occur with the requested agent **AND** B. The patient has tried and had an inadequate response, has an intolerance, hypersensitivity, or has an FDA labeled contraindication to TYMLOS (abaloparatide) **OR** B. The patient has a diagnosis of glucocorticoid-induced osteoporosis and ALL of the following: 1. The patient is either initiating or currently taking glucocorticoids in a daily dosage equivalent to 5 mg or higher of prednisone **AND** 2. The patient's expected current course of therapy of glucocorticoids is for a period of at least 3 months **AND** 3. ONE of the following: A. The patient is less than 40 years of age AND has ONE of the following: 1. A prior fracture **OR** 2. Either initiating or currently taking glucocorticoids that is equivalent to a prednisone dose that is greater than or equal to 30 mg/day **OR** 3. Either initiating or currently taking glucocorticoids that is equivalent to a cumulative prednisone dose of greater than or equal to 5 g/year **OR** B. The patient is 40 years of age or greater AND has one of the following: 1. A prior osteoporotic fracture **OR** 2. A T-score of less than or equal to -2.5 **OR** 3. A FRAX 10-year probability for major osteoporotic fracture of greater than or equal to 20% **OR** 4. A FRAX 10-year risk probability for hip fracture of greater than or equal to 3% **OR** 5. Either initiating or currently taking glucocorticoids that is equivalent to a prednisone dose that is greater than or equal to 30 mg/day for greater than 30 days **OR** 6. Either initiating or currently taking glucocorticoids that is equivalent to a cumulative prednisone dose of greater than or equal to 5 g/year **OR** C. The patient has tried and had an inadequate response to a bisphosphonate (medical records required) **OR**

Module	Clinical Criteria for Approval
	D. The patient has an intolerance or hypersensitivity to a bisphosphonate (medical records required) **OR** E. The patient has an FDA labeled contraindication to ALL bisphosphonates (medical records required) **AND** 4. The patient has tried and had an inadequate response, has an intolerance, hypersensitivity, or has an FDA labeled contraindication to FORTEO generic equivalent that is not expected to occur with the requested agent **AND** 2. The patient will NOT be using the requested agent in combination with a bisphosphonate, denosumab (e.g., Prolia, Xgeva), romosozumab-aqqg or another parathyroid hormone analog for osteoporosis (e.g., abaloparatide) **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 4. ONE of the following: A. The total duration of treatment with parathyroid hormone analog(s) for osteoporosis has NOT exceeded 2 years in a lifetime **OR** B. The total duration of treatment with parathyroid hormone analog(s) for osteoporosis has exceeded 2 years in a lifetime AND the patient is at high risk of fracture (e.g., shown by T-score, FRAX score, continued use of glucocorticoids at a daily equivalent of 5 mg of prednisone or higher) **Length of approval:** For those who have not yet received a total of 2 years of treatment in their lifetime between FORTEO (teriparatide), Teriparatide, and TYMLOS (abaloparatide), approve for up to the remainder of that 2 year therapy which has not yet been received. For those who have already received a total of 2 years of treatment in their lifetime between FORTEO (teriparatide) or Teriparatide AND is at high risk of fracture, approve for up to 1 year. NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
Tymlos - preferred	**TYMLOS** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** B. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** C. The patient has a diagnosis of osteoporosis AND ALL of the following: 1. ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient's sex is male and ONE of the following: 1. The patient's age is 50 years or over **OR** 2. The requested agent is medically appropriate for the patient's age and sex **OR** B. The patient's sex is female and ONE of the following: 1. The patient is postmenopausal **OR** 2. The requested agent is medically appropriate for the patient's sex and menopause status **AND** 2. The patient's diagnosis was confirmed by ONE of the following: A. A fragility fracture in the hip or spine **OR** B. A T-score of -2.5 or lower **OR** C. A T-score of -1.0 to -2.5 and ONE of the following: 1. A fragility fracture of the proximal humerus, pelvis, or distal forearm **OR** 2. A FRAX 10-year probability for major osteoporotic fracture of greater than or equal to 20% **OR** 3. A FRAX 10-year probability of hip fracture of greater than or equal to 3% **AND** 3. ONE of the following: A. The patient is at a very high fracture risk as defined by ONE of the following: 1. Patient had a recent fracture (within the past 12 months) **OR** 2. Patient had fractures while on FDA labeled osteoporosis therapy **OR** 3. Patient has had multiple fractures **OR** 4. Patient had fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids) **OR** 5. Patient has a very low T-score (less than -3.0) **OR** 6. Patient is at high risk for falls or has a history of injurious falls **OR** 7. Patient has a very high fracture probability by FRAX (e.g., major osteoporosis fracture greater than 30%, hip fracture greater than 4.5%) or by other validated fracture risk algorithm **OR** B. The patient has tried and had an inadequate response to a bisphosphonate (medical records required) **OR** C. The patient has an intolerance or hypersensitivity to a bisphosphonate (medical records required) **OR**

Module	Clinical Criteria for Approval
	D. The patient has an FDA labeled contraindication to ALL bisphosphonates (medical records required) **AND** 2. The patient will NOT be using the requested agent in combination with a bisphosphonate, denosumab (e.g., Prolia, Xgeva), romosozumab-aqqg, or another parathyroid hormone analog for osteoporosis (e.g., teriparatide) **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 4. The total duration of treatment with FORTEO (teriparatide), Teriparatide, and TYMLOS (abaloparatide) has NOT exceeded 2 years in a lifetime **Length of approval:** up to the remainder of a total of 2 years of treatment in a lifetime between FORTEO (teriparatide), Teriparatide, and TYMLOS (abaloparatide). NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Ops Set Up	Validation Options	Other Explanation
FORTEO - brand non-preferred, generic preferred	Documentation: Requirements as noted within the policy;Validation: Apply Baseline and go to Validation Options	Continuation of Therapy;Contraind., intolerance, or hypersensitivity to prereq.;Other (see Other explanation field)	*The requested agent is medically appropriate for the patient's sex, age, and/or menopause status *The total duration of treatment with FORTEO (teriparatide), Teriparatide, and TYMLOS (abaloparatide) has NOT exceeded 2 years in a lifetime (Validate claims information and review provider information.) *If the patient has received 2 years of FORTEO (teriparatide) or Teriparatide treatment in a lifetime, there support for using the requested agent for more than two years because the patient is at high risk of fracture
Teriparatide - non-preferred	Documentation: Requirements as noted	Continuation of Therapy;Contraind.,	*There is support that the requested agent is medically

Module	Ops Set Up	Validation Options	Other Explanation
	within the policy;Validation: Apply Baseline and go to Validation Options	intolerance, or hypersensitivity to prereq.;Other (see Other explanation field);Prerequisites	appropriate for the patient's sex, age, and/or menopause status *The total duration of treatment with FORTEO [or its generic equivalent], Teriparatide, and TYMLOS (abaloparatide) has NOT exceeded 2 years in a lifetime OR *If the patient has received 2 years of FORTEO [or its generic equivalent] or Teriparatide treatment in a lifetime, there is for support for using the requested agent for more than two years because the patient has continued to be or has returned to being at high risk for fracture.
Tymlos - preferred	Documentation: Requirements as noted within the policy;Validation: Apply Baseline and go to Validation Options	Continuation of Therapy;Contraind., intolerance, or hypersensitivity to prereq.;Other (see Other explanation field)	*The requested agent is medically appropriate for the patient's sex, age, and/or menopause status *The total duration of treatment with FORTEO (teriparatide), Teriparatide, and TYMLOS (abaloparatide) has NOT exceeded 2 years in a lifetime (Validate claims information and review provider information.)

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval

Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met:
	
	1. The requested quantity (dose) does NOT exceed the program quantity limit **OR**
	2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following:
	  1. BOTH of the following:
	  1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND**
	  2. There is support for therapy with a higher dose for the requested indication **OR**
	  2. BOTH of the following:
	  1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND**
	  2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit
	
	Length of Approval: up to 2 years

Pulmonary Arterial Hypertension

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Adcirca® (tadalafil) Tablets^	Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%)	* – WHO = World Health Organization ^- generic available	1
Adempas® (riociguat) Tablets	Treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (*WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class Treatment of adults with pulmonary arterial hypertension (PAH), (*WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening. Efficacy was shown in patients on monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II-III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%)	* – WHO = World Health Organization	2
Letairis® (ambrisentan) Tablets^	Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1): • To improve exercise ability and delay clinical worsening. • In combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability	* – WHO = World Health Organization ^- generic available	3

Agent(s)	FDA Indication(s)	Notes	Ref#
	Studies establishing effectiveness included predominantly patients with WHO Functional Class II-III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%)		
Liqrev® (sildenafil) Oral suspension	Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) in adults to improve exercise ability and delay clinical worsening.	* – WHO = World Health Organization	24
Opsumit® (macitentan) Tablets	Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) to reduce the risks of disease progression and hospitalization for PAH. Effectiveness was established in a long-term study in PAH patients with predominantly WHO Functional Class II-III symptoms treated for an average of 2 years. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%)	* – WHO = World Health Organization	4
Opsynvi® (macitentan-tadalafil) Tablets	Chronic treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) in adults of WHO functional class (FC) II-III Individually, macitentan reduces the risk of clinical worsening events and hospitalization, and tadalafil improves exercise ability	* – WHO = World Health Organization	28

Agent(s)	FDA Indication(s)	Notes	Ref#
Orenitram® (treprostinil) Tablets	Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) to delay disease progression and to improve exercise capacity. The studies that established effectiveness included predominately patients with WHO functional class II-III symptoms and etiologies of idiopathic or heritable PAH (66%) or PAH associated with connective tissue disease (26%).	* – WHO = World Health Organization	5
Revatio® (sildenafil citrate) Tablets^ Oral solution^ Injection solution	Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) in adults to improve exercise ability and delay clinical worsening. Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) in pediatric patients 1 to 17 years of age to improve exercise ability and, in pediatric patients too young to perform standard exercise testing, pulmonary hemodynamics thought to underly improvements in exercise. Limitation of use: Adding sildenafil to bosentan therapy does not result in any beneficial effect on exercise capacity.	* – WHO = World Health Organization ^- generic available	6
Tadliq® (tadalafil) Oral suspension	Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class II – III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%)	* – WHO = World Health Organization	23
Tracleer® (bosentan) Tablets film coated^ Tablets for suspension	Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1): • In adults to improve exercise ability and to decrease clinical worsening. Studies establishing effectiveness included predominantly patients with WHO Functional Class II-IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH	* – WHO = World Health Organization ^- generic available	7

Agent(s)	FDA Indication(s)	Notes	Ref#
	associated with connective tissue diseases (21%), and PAH associated with congenital heart disease with left-to-right shunts (18%). • In pediatric patients aged 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (PVR), which is expected to result in an improvement in exercise ability.		
Tyvaso®, Tyvaso DPI™ (treprostinil) Inhalation solution Inhalation powder	Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) to improve exercise ability. Studies establishing effectiveness included predominately patients with NYHA Functional Class III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%). While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan (an endothelin receptor antagonist) or sildenafil (a PDE 5 inhibitor). The controlled clinical experience was limited to 12 weeks in duration. Treatment of pulmonary hypertension associated with interstitial lung disease (PH-ILD; WHO group 3) to improve exercise ability. The study establishing effectiveness included patients with etiologies of idiopathic interstitial pneumonia (IIP) inclusive of idiopathic pulmonary fibrosis (IPF), combined pulmonary fibrosis and emphysema (CPFE), and WHO group 3 connective tissue disease.	* – WHO = World Health Organization	8,22
Uptravi® (selexipag) Tablets	Treatment of pulmonary arterial hypertension (PAH, *WHO Group 1) to delay disease progression and reduce the risk of hospitalization for PAH.	* – WHO = World Health Organization	9

Agent(s)	FDA Indication(s)	Notes	Ref#
Powder for injection	Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), PAH associated with congenital heart disease with repaired shunts (10%)		
Ventavis® (iloprost) Inhalation solution	Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration. Studies establishing effectiveness included predominately patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%)	* – WHO = World Health Organization	10
Winrevair™ (sotatercept-csrk) Subcutaneous injection	Treatment of pulmonary arterial hypertension (PAH) (*WHO Group 1) in adults to improve exercise ability, improve WHO functional class (FC) and reduce the risk of clinical worsening events	* – WHO = World Health Organization	27

CLINICAL RATIONALE

Pulmonary Hypertension	The World Health Organization (WHO) has classified pulmonary hypertension (PH) based upon etiology into the following five groups:(15) • Group 1 - Pulmonary arterial hypertension (PAH) • Group 2 – PH due to left heart disease • Group 3 – PH due to chronic lung disease and/or hypoxemia • Group 4 – PH due to chronic thromboembolic pulmonary hypertension • Group 5 – PH due to unclear multifactorial mechanisms Group 1, also known as pulmonary arterial hypertension (PAH), is defined by a pre-capillary pattern in the invasive hemodynamic evaluation, characterized by a mean pulmonary arterial pressure (mPAP) greater than 20 mmHg with a normal pulmonary capillary wedge pressure (i.e., less than or equal to 15 mmHg) and a

	pulmonary vascular resistance greater than or equal to 3 Wood units, in the absence of pulmonary parenchymal or thromboembolic disease. Group 1 can occur in isolation or in association with clinical conditions, as noted in the following subcategories: idiopathic, heritable, drug/toxin induced, association with other diseases (i.e., connective tissue disease, HIV infection, portal hypertension, congenital heart diseases, schistosomiasis), long-term responders to calcium channel blockers, with overt features of venous/capillaries (pulmonary veno-occlusive disease [PVOD]/pulmonary capillary haemangiomatosis [PCH]), and persistent PH of the newborn syndrome.(15) Group 3 is pulmonary hypertension (PH) due to lung disease and/or hypoxia. PH associated with chronic lung disease is linked with reduced functional status and worse outcomes. There are seven subgroups within WHO group 3, one of which is ILD associated PH (WHO group 3.2). Right heart catheterization (RHC) is the gold standard for the diagnosis of PH associated with lung disease. WHO group 3 PH is distinguished from WHO group 1 based on the presence of an FVC less than 70% predicted and extensive parenchymal changes on CT. Prior to starting PAH therapy for the treatment of PH associated with lung disease, the patient's underlying lung disease should be optimally treated according to current guidelines.(21) Group 4 is due to chronic thrombotic and/or embolic disease including chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is characterized pathologically by organized thromboembolic material and altered by vascular remodeling initiated or potentiated by a combination of defective angiogenesis, impaired fibrinolysis and endothelial dysfunction. These changes lead to PH, defined as a mean pulmonary arterial pressure greater than 20 mmHg, pulmonary capillary wedge pressure less than or equal to 15 mmHg, and pulmonary vascular resistance greater than or equal to 3 Woods units. The hemodynamic changes occur in the presence of multiple chronic/organized occlusive thrombi/emboli in the elastic pulmonary arteries (main, lobar, segmental, subsegmental) after at least 3 months of effective anticoagulation. Ventilation/perfusion scan planar images combined with a confirmatory CT pulmonary angiography remain the preferred diagnostic tests for CTEPH despite advances in computed tomography (CT) and magnetic resonance (MR). CT and MR can be used in conjunction with the preferred diagnostic tests to identify complications of the disease but should not be solely relied upon due to concerns of false-positive cases mimicking CTEPH. The 6th World Symposium on Pulmonary Hypertension (WSPH) recommends all patients diagnosed with CTEPH start with lifelong anticoagulation therapy. WSPH notes that antiplatelet therapy is not an alternative to anticoagulation in patients with CTEPH. Pulmonary endarterectomy (PEA) remains the first line treatment option for

	CTEPH. WSPH notes that the best treatment is uncertain for patients that may be technically operable but may not benefit from endarterectomy due to comorbidities. Targeted medical therapy is initiated in those patients that are inoperable or those with persistent/recurrent PH following PEA.(12,17) The diagnosis of PAH requires right heart catheterization (RHC) to demonstrate a mPAP greater than 20 mmHg at rest and a pulmonary vascular resistance greater than or equal to 3 Wood units. Several additional criteria to exclude the remaining categories of PH must also be met:(14,15,19) • Mean pulmonary capillary wedge pressure less than or equal to 15 mmHg (to exclude PH due to left heart disease [i.e., group 2 PH]) • Chronic lung diseases and other causes of hypoxemia are mild or absent (to exclude PH owing to chronic lung disease or hypoxemia [i.e., group 3 PH]) • Venous thromboembolic disease is absent (to exclude chronic thromboembolic PH [i.e., group 4 PH]) • Certain miscellaneous disorders are absent, including systemic disorders (e.g., sarcoidosis), hematologic disorders (e.g., myeloproliferative diseases), and metabolic disorders (e.g., glycogen storage disease). The purpose is to exclude PH with unclear multifactorial mechanisms (group 5 PH). World Health Organization (WHO) Functional Classification of Patients with Pulmonary Hypertension include the following:(20) • Class I: Patients with PH without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea, fatigue, chest pain, or near syncope. • Class II: Patients with PH having slight limitation of physical activity. No discomfort at rest, but ordinary physical activity causes increased dyspnea, fatigue, chest pain, or near syncope. • Class III: Patients with PH having marked limitation of physical activity. No discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or near syncope. • Class IV: Patients with PH unable to carry out any physical activity without symptoms and may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest, with increased discomfort by any physical activity.

<table>
<tr><td></td><td>The 6th symposium on PAH also included recommendations for pediatric patients with PH. The 2019 guidelines and the 2015 American Heart Association and American Thoracic Society guidelines note that the definition of PAH in pediatric patients mirrors the adult definition. The guidelines also recommend the same diagnostic testing and algorithm as adult patients, with the inclusion of a full shunt evaluation during RHC to rule out congenital heart disease.(13,18)</td></tr>
<tr><td>Treatment Guidelines</td><td>Guidelines recommend that patients be referred to a PAH expert center for diagnosis confirmation and management. Current treatment strategies are based on the severity of newly diagnosed patients, assessed by a risk stratification approach. The risk stratification takes clinical, exercise, right ventricular function, and hemodynamic parameters, and combines them to define a low, intermediate, or high-risk status according to patients expected 1-year mortality. The risk stratification includes the following factors:(11,13,14,20)

Initial Assessment Tool:

<table>
<tr><th>Determinates of prognosis (estimated 1-year mortality)</th><th>Low Risk

Less than 5%</th><th>Intermediate Risk

5-20%</th><th>High Risk

Greater than 20%</th></tr>
<tr><td>Clinical signs of right heart failure</td><td>Absent</td><td>Absent</td><td>Present</td></tr>
<tr><td>Progression of symptoms and clinical manifestations</td><td>No</td><td>Slow</td><td>Rapid</td></tr>
<tr><td>Syncope</td><td>No</td><td>Occasional during heavy exercise, or occasional orthostatic in stable patient</td><td>Repeated with little or regular physical activity</td></tr>
<tr><td>WHO functional class</td><td>I-II</td><td>III</td><td>IV</td></tr>
<tr><td>6-minute walking distance</td><td>greater than 440 meters</td><td>165-440 meters</td><td>less than 165 meters</td></tr>
</table>
</td></tr>
</table>

	Cardiopulmonary exercise testing	Peak VO_2 greater than 15 ml/min/kg (greater than 65% pred.) VE/VCO_2 slope less than 36	Peak VO_2 11–15 ml/min/kg (35–65% pred.) VE/VCO_2 slope 36–44	Peak VO_2 less than 11 ml/min/kg (less than 35% pred.) VE/VCO_2 slope greater than 44
	N-terminal pro-brain natriuretic peptide (NT-proBNP) plasma levels	BNP less than 50 ng/l NT-proBNP less than 300 ng/l	BNP 50–800 ng/l NT-proBNP 300–1100 ng/l	BNP greater than 800 ng/l NT-proBNP greater than 1100 ng/l
	Echocardiography	RA area less than 18 cm^2 TAPSE/sPAP greater than 0.32 mm/mmHg No pericardial effusion	RA area 18–26 cm^2 TAPSE/sPAP 0.19–0.32 mm/mmHg minimal pericardial effusion	RA area greater than 26 cm^2 TAPSE/sPAP less than 0.19 mm/mmHg Moderate to large pericardial effusion
	cMRI	RVEF greather than 54% SVI greater than 40 mL/m^2	RVEF 37–54% SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF less than 37% SVI less than 26 mL/m^2 RVESVI greater than 54 mL/m^2

	RVESVI less than 42 mL/m^2		
Hemodynamics	RAP less than 8 mmHg CI greater than or equal to 2.5 L/min/m^2 SVI greater than 38 mL/m^2 SvO_2 greater than 65%	RAP 8–14 mmHg CI 2.0–2.4 L/min/m^2 SVI 31–38 mL/m^2 SvO_2 60–65%	RAP greater than 14 mmHg CI less than 2.0 L/min/m^2 SVI less than 31 mL/m^2 SvO_2 less than 60%

6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; CI, cardiac index; cMRI, cardiac magnetic resonance imaging; CPET, cardiopulmonary exercise testing; HF, heart failure; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; pred., predicted; RA, right atrium; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; SvO2, mixed venous oxygen saturation; RVESVI, right ventricular end-systolic volume index; RVEF, right ventricular ejection fraction; SVI, stroke volume index; TAPSE, tricuspid annular plane systolic excursion; VE/VCO2, ventilatory equivalents for carbon dioxide; VO2, oxygen uptake; WHO-FC, World Health Organization functional class.

Follow-up Assessment Tool:

Determinants of prognosis	Low Risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or IIa	-	III	IV
6MWD, m	Greater than 44	320-440	165-319	Less than 165

BNP or NT-proBNP,a ng/L	Less than 50 Less than 300	50-199 300-649	200-800 650-1100	Greater than 800 Greater than 1100

6MWD, 6-minute walking distance; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-brain natriuretic peptide; WHO-FC, World Health Organization functional class.
Risk is calculated by dividing the sum of all grades by the number of variables and rounding to the next integer.
aWHO-FC I and II are assigned 1 point as both are associated with good long-term survival.

The 6th World Symposium on Pulmonary Hypertension evidence-based treatment algorithm for adults includes the following recommendations:(11,16)

- Treatment Naïve patients:
  - Head-to-head comparisons among different compounds are not available, no evidence-based first line treatment can be proposed for initial monotherapy, if monotherapy is chosen.
  - Vasoreactive patients (only idiopathic PAH, heritable PAH, or drug induced PAH):
    - High dose calcium channel blockers (CCB) that have been progressively titrated
    - Response should be evaluated after 3 to 6 months
    - Adequate treatment response is defined as WHO-FC I/II with sustained hemodynamic improvement after at least 1 year on CCBs alone
    - Patients without an adequate response to high dose CCBs should be treated with approved PAH medications according to non-vasoreactive treatment strategy. In some cases, the combination of CCB with approved PAH is required.
  - Non-vasoreactive patients:
    - Low or intermediate risk: Treat with initial oral combination therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase type-5 (PDE5) inhibitor: ambrisartan plus tadalafil, macitentan plus tadalafil, or other ERA and PDE5 inhibitor

	▪ High risk: Initial combination therapy (an ERA and a PDE5 inhibitor) plus IV prostacyclin with epoprostenol having the strongest recommendation • Response should be evaluated after 3 to 6 months: o Low risk at follow up: continue therapy with structured follow up until risk progression o Intermediate risk: Triple sequential combination therapy or double combination therapy in case initial monotherapy was chosen ▪ Macitentan plus sildenafil, riociguat plus bosentan, selexipag plus ERA and/or PDE5 have the highest levels of recommendations and evidence ▪ Referral for lung transplant should also be considered o High risk: maximal medical therapy including an IV prostacyclin (epoprostenol or treprostinil) is recommended and listing for lung transplant o If still at intermediate or high risk after second treatment step (3 to 6 months after change in therapy), maximal medical therapy (triple therapy including a SC or IV prostacyclin [IV preferred for high risk]) is recommended and listing for lung transplant ▪ Intermediate-risk status on double combination therapy with an ERA and a PDE5 or riociguat, the addition of selexipag should be considered ▪ Triple combination therapy including selexipag who remain in the intermediate-risk group or progress to high risk, substitution with SC or IV prostacyclin should be considered • Transitioning patients from one PAH-specific therapy to another might be considered for a number of reasons, but transitioning patients that have an extraordinary response to therapy and desire to transition to less invasive therapy is not recommended except in rare circumstances and under close expert care The 2022 European Society of Cardiology (ESC) and the European Respiratory Society (ERS) guidelines recommend a risk-based, goal-orientated treatment approach in patients with PAH. Risk stratification at diagnosis is done using a three-strata model and follow-up a four strata model. The recommended treatment algorithm for non-vasoreactive patients or patients unresponsive to CCB is as follows:(11) • Initial treatment:

	○ Patients without cardiopulmonary comorbidities (e.g., obesity, hypertension, diabetes): ▪ Low or intermediate prognosis risk: Treat with oral combination therapy with an endothelin receptor antagonist (ERA) and a phosphodiesterase type-5 (PDE5) inhibitor: ambrisentan plus tadalafil, macitentan plus tadalafil, or other ERA and PDE5 combination ▪ High prognosis risk: Treat with oral combination therapy with an endothelin receptor antagonist (ERA) plus a phosphodiesterase type-5 (PDE5) inhibitor and IV/SC prostacyclin analogue ○ Patients with cardiopulmonary comorbidities (all prognosis risk categories) ▪ Oral monotherapy with PDE5 inhibitors or ERA • Response should be evaluated after 3 to 6 months: ○ Patients without cardiopulmonary comorbidities: ▪ Low risk at follow up: continue therapy ▪ Intermediate to low risk: add prostacyclin receptor agonist (PRA) (selexipag), OR, switch from PDE5 inhibitor to soluble guanylate cyclase stimulator(sGCs) (riociguat) ▪ Intermediate to high or high risk: add IV/SC prostacyclin analogue (epoprostenol or treprostinil) and/or evaluate for lung transplant. If adding IV/SC prostacyclin analogue is unfeasible, adding selexipag or switching from PDE5 inhibitor to riociguat may be considered ○ Patients with cardiopulmonary comorbidities: ▪ Individualized therapy. Patients that present at intermediate or high risk of death while receiving PDE5 inhibitors or ERA monotherapy, treatment based on individual basis The 6th World Symposium on Pulmonary Hypertension pragmatic treatment algorithm in pediatrics includes the following recommendations:(11,18) • Treatment with targeted PAH therapies in children is almost exclusively based on experience and data from adult studies, due to the lack of pediatric clinical trials • Therapeutic strategy is based on risk stratification and treatment response, extrapolated from that in adults, but adapted for age • Patients with a positive vasoreactive response should be initiated on high-dose oral CCBs and continued if there is sustained and improved response.

- Recommend vasoreactive patients remain on CCBs in addition to targeted PAH therapies
- Non-vasoreactive patients or those with failed or non-sustained response should undergo risk stratification to determine therapy. Pediatric risk stratification is as follows:

Determinates of Risk	Low Risk	High Risk
Clinical signs of right heart failure	No	Yes
Progression of symptoms	No	Yes
6-minute walking distance (greater than 6 years of age)	greater than 350 meters	less than 350 meters
Growth	Normal	Failure to thrive
WHO functional class	I, II	III, IV
N-terminal pro-brain natriuretic peptide plasma levels	Minimally elevated	Significantly elevated, Rising level
Echocardiography	NA	RA/RV enlargement Reduced LV size Increased RV/LV ratio Reduced TAPSE Low RV FAC Pericardial effusion
Hemodynamics	Systemic CI greater than 3.0 L/min/m^2 Systemic venous saturation greater than 65%	Systemic CI less than 2.5 L/min/m^2 mRAP greater than 10 mmHg

	Acute vasoreactivity	PVRI greater than 20 WU/m^2 Systemic venous saturation less than 60% PACI less than 0.85 ml/mmHg/m^2

RV: right ventricle; WHO: World Health Organization; RA: right atrium; LV: left ventricle; FAC: fractional area change; TAPSE: tricuspid annular plane systolic excursion; CI: cardiac index; mRAP: mean right atrial pressure; PVRI: pulmonary vascular resistance index; WU: Wood Units; PACI: pulmonary arterial compliance index.

- Low prognosis risk: oral monotherapy with either an ERA (i.e., bosentan, ambrisentan) or a PDE5 inhibitor (i.e., sildenafil, tadalafil) is recommended
  - Early combination therapy should be considered in children that deteriorate on either ERA or PDE5 therapy
  - Remain low risk despite deterioration: addition of inhaled prostacyclin may be beneficial
- High prognosis risk: IV epoprostenol or treprostinil are recommended, with early consideration of lung transplantation in patients with deteriorating high-risk features
- In cases of insufficient response to recommended therapy or when drugs are not available, a Potts shunt, balloon atrial septostomy (BAS) or lung transplant may be considered in patients with severe pulmonary hypertension

The American College of Chest Physicians (CHEST) guideline (2019) states:(20)

- WHO FC II [treatment naïve and not a candidate for or failure to calcium channel blocker (CCB) therapy]:
  - Combination with ambrisentan and tadalafil
  - Patients unable to tolerate or unwilling to take combination therapy: monotherapy with an ERA or PDE5 inhibitor (listed in order of recommendation level and alphabetically)
    - Ambrisentan, sildenafil, bosentan, macitentan, tadalafil, riociguat

	○ Parenteral or inhaled prostanoids should not be used as initial or second line therapy • WHO FC III [treatment naïve, not a candidate for or failure to calcium channel blocker (CCB) therapy, and no evidence of rapid progression of their disease or poor prognosis]: ○ Combination with ambrisentan and tadalafil ○ Patients unable to tolerate or unwilling to take combination therapy: monotherapy with an ERA or PDE5 inhibitor (listed in order of recommendation level and alphabetically) ▪ Ambrisentan, bosentan, sildenafil, macitentan, tadalafil, riociguat • WHO FC III [treatment naïve with evidence of rapid progression of their disease, or other markers of a poor clinical prognosis]: ○ Initial treatment with IV or SC prostanoid ○ There is no recommendation for patients unwilling to manage PAH with IV or SC prostanoid, so may consider addition of inhaled or oral prostanoid • WHO FC III [who have evidence of progression of their disease, and/or markers of poor clinical prognosis despite treatment with one or two classes of oral agents]: addition of a parenteral or inhaled prostanoid ○ Suggest the addition of inhaled prostanoid (i.e., treprostinil, iloprost) in patients that remain symptomatic on stable and appropriate doses of an ERA or PDE5 inhibitor • WHO FC IV [treatment naïve]: monotherapy with a parenteral prostanoid agent • WHO FC IV [treatment naïve and unable/or do not desire parenteral prostanoid therapy]: an inhaled prostanoid in combination with an ERA and PDE5 inhibitor • WHO FC III or IV [with unacceptable or deteriorating clinical status despite established PAH pharmacotherapy]: a second or third class of PAH therapy should be started • Due to insufficient evidence, recommendations cannot be made for or against the use of selexipag • There is no evidence to support the use of oral treprostinil as add-on or combination therapy The AHA/ATS guidelines for the treatment of pediatric pulmonary hypertension state:(13) • Oral therapy in children with lower-risk PAH is recommended and should include either a PDE5 inhibitor or an ERA

	• A goal-targeted therapy approach in which PAH-specific drugs are added progressively to achieve specified therapeutic targets can be useful • Intravenous and subcutaneous prostacyclin or its analogs should be initiated without delay for patients with higher-risk PAH The Chest guideline recognizes that there is still a lack of head-to-head comparisons of pharmacologic agents for the treatment of PAH, and because of their differing burdens and risks to patients, it is recommended that drug therapy be chosen on the basis of a methodical evaluation of disease severity and the risk for further short-term deterioration. The optimal method of evaluation has not been studied. No one agent can be definitively recommended preferentially. Additionally, it notes that adding a second class of PAH therapy for patients whose clinical status remains unacceptable despite established PAH-specific monotherapy requires that the clinician assess whether the patient has received an adequate trial of the initial monotherapy. At present, this assessment combines evaluation of the duration of monotherapy, the expected response to the monotherapy, the observed response to the monotherapy, and the patient's severity of illness and pace of decline. Unacceptable clinical status will vary for individual patients and clinicians, but symptomatic limitation of desired physical activities usually guides these decisions.(20)
Efficacy of Winrevair (sotatercept)	The safety and efficacy of sotatercept was evaluated in the STELLAR trial. This was a multicenter, double-blinded, randomized phase three trial. Eligible adult patients had symptomatic PAH Group 1 confirmed by right heart catheterization (RHC) and classified as WHO FC II or III. Patients were on stable background therapy for at least 90 days. Background PAH therapy refers to combination therapy consisting of drugs from two or more of the following drug classes: an endothelin-receptor antagonist (ERA), a phosphodiesterase 5(PDE5) inhibitor, a soluble guanylate cyclase stimulator, and/or a prostacyclin analogue or receptor agonist. Excluded criteria included: pregnancy or breastfeeding, uncontrolled systemic hypertension of greater than 160/100 mmHg, and baseline systolic blood pressure under 90 mmHg.(25-26) Patients were randomly assigned in a 1:1 ratio to receive subcutaneous sotatercept (starting dose, 0.3 mg per kilogram of body weight; target dose, 0.7 mg per kilogram) or placebo every 3 weeks. The primary end point was the change from baseline at week 24 in the 6-minute walk distance. There were nine secondary end points: multicomponent improvement, change in pulmonary vascular resistance (PVR), change in N-terminal pro–B-type natriuretic peptide (NT-proBNP) level, improvement in WHO FC, time to death or clinical worsening event, French risk score, and changes in the Pulmonary Arterial Hypertension–

	Symptoms and Impact (PAH-SYMPACT), Cardiopulmonary Symptoms, and Cognitive/Emotional Impacts domain scores. All were assessed at week 24 except time to death or clinical worsening, which was assessed when the last patient completed the week 24 visit. (25-26) A total of 163 patients were assigned to receive sotatercept and 160 to receive placebo. The median change from baseline at week 24 in the 6-minute walk distance was 34.4 m (95% confidence interval [CI], 33.0 to 35.5) in the sotatercept group and 1.0 m (95% CI, −0.3 to 3.5) in the placebo group. The first eight secondary end points were significantly improved with sotatercept as compared with placebo, whereas the PAH-SYMPACT Cognitive/Emotional Impacts domain score was not. Adverse events that occurred more frequently with sotatercept than with placebo included epistaxis, dizziness, telangiectasia, increased hemoglobin levels, thrombocytopenia, and increased blood pressure.(25-26)
Safety	**Adcirca(1), Tadliq(23)** Tadalafil has the following contraindications: • Concurrent use (regular or intermittent) of organic nitrates in any form • Do not use Adcirca in patients who are using a Guanylate Cyclase (GC) stimulator, such as riociguat • History of known serious hypersensitivity reaction to tadalafil (Adcirca, Cialis, or Tadliq) **Adempas(2)** Riociguat has the following contraindications: • Pregnancy • Co-administration with nitrates or nitric oxide donors (e.g., amyl nitrite) in any form • Concomitant use with specific phosphodiesterase (PDE) inhibitors (e.g., sildenafil, tadalafil, vardenafil) or nonspecific PDE inhibitors (e.g., dipyridamole, theophylline) • Concomitant use with other soluble guanylate cyclase (sGC) stimulators • Pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP)

	Boxed warnings include: • Do not administer Adempas to a pregnant female because it may cause fetal harm. Adempas was consistently shown to have teratogenic effects when administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. • Females of reproductive potential: exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. To prevent pregnancy, females of reproductive potential must use effective forms of contraception during treatment and for one month after stopping treatment. **Letairis(3)** Ambrisentan has the following contraindications: • Pregnancy • Idiopathic pulmonary fibrosis (including IPF patients with pulmonary hypertension [WHO group 3]) Boxed warnings include: • Do not administer Letairis to a pregnant female because it may cause fetal harm. Letairis is very likely to produce serious birth defects if used by pregnant females, as this effect has been seen consistently when it is administered to animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. • Exclude pregnancy before the initiation of treatment with Letairis. Females of reproductive potential must use acceptable methods of contraception during treatment with Letairis and for one month after treatment. Obtain monthly pregnancy tests during treatment and 1 month after discontinuation of treatment. **Opsumit(4)** Macitentan has the following contraindications: • Pregnancy

	• History of hypersensitivity reaction to macitentan or any component of the product Boxed warnings include: • Do not administer Opsumit to a pregnant female because it may cause fetal harm. Opsumit was consistently shown to have teratogenic effects when administered to animals. If Opsumit is used during pregnancy, advise the patient of the potential risk to a fetus. • Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception. **Opsynvi(28)** Macitentan-tadalafil has the following contraindications: • Pregnancy • History of hypersensitivity reaction to macitentan, tadalafil or any component of the product • Concomitant organic nitrates • Concomitant guanylate cyclase (GC) stimulators Boxed warnings include: • Do not administer Opsynvi to a pregnant female because it may cause fetal harm. Macitenan was consistently shown to have teratogenic effects when administered to animals. If Opsynvi is used during pregnancy, advise the patient of the potential risk to a fetus. • Females of reproductive potential: Exclude pregnancy before the start of treatment, monthly during treatment, and 1 month after stopping treatment. Prevent pregnancy during treatment and for one month after stopping treatment by using acceptable methods of contraception. • For all female patients, Opsynvi is available only through a restricted program called Macitentan-Containing Products Risk Evaluation and Mitigation Strategy (REMS). **Orenitram(5)** Treprostinil tablets have the following contraindication:

	• Severe hepatic impairment (Child-Pugh Class C) **Revatio(6) Liqrev (24)** Sildenafil has the following contraindications: • Concomitant use of organic nitrates in any form, either regularly or intermittently • Concomitant use of riociguat • Known hypersensitivity to sildenafil or any component of the tablet, injection, or oral suspension **Tracleer(7)** Bosentan has the following contraindications: • Pregnancy • Use with cyclosporine A • Use with glyburide • Hypersensitivity to bosentan or any component of the product Boxed warnings include: *Hepatotoxicity* In clinical studies, Tracleer caused at least 3-fold upper limit of normal (ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious hepatotoxicity, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly. In the post marketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (greater than 12 months) therapy with Tracleer in patients with multiple comorbidities and drug therapies. There have also been reports of liver failure. The contribution of Tracleer in these cases could not be excluded. In at least one case, the initial presentation (after greater than 20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by nonspecific symptoms, all of which resolved slowly over time after discontinuation of Tracleer. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm,

	which includes stopping Tracleer with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction. Elevations in aminotransferases require close attention. Tracleer should generally be avoided in patients with elevated aminotransferases (greater than 3 × ULN) at baseline because monitoring for hepatotoxicity may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of hepatotoxicity (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin greater than or equal to 2 × ULN, treatment with Tracleer should be stopped. There is no experience with the reintroduction of Tracleer in these circumstances. *Embryo-Fetal Toxicity* Tracleer is likely to cause major birth defects if used by pregnant females based on animal data. Therefore, pregnancy must be excluded before the start of treatment with Tracleer. Throughout treatment and for one month after stopping Tracleer, females of reproductive potential must use two reliable methods of contraception unless the patient has an intrauterine device (IUD) or tubal sterilization, in which case no other contraception is needed. Hormonal contraceptives, including oral, injectable, transdermal, and implantable contraceptives should not be used as the sole means of contraception because these may not be effective. **Uptravi(9)** Selexipag has the following contraindications: • Hypersensitivity to the active substance or to any of the excipients • Concomitant use of a strong CYP2C8 inhibitor (e.g., gemfibrozil) **Winrevair (27)** Sotatercept-csrk has no contraindications

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Number	Reference
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3	Letairis prescribing information. Gilead. August 2019.
4	Opsumit prescribing information. Actelion Pharmaceuticals, Inc. June 2023.
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6	Revatio prescribing information. Pfizer. January 2023.
7	Tracleer prescribing information. Actelion Pharmaceuticals, Inc. July 2022.
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Number	Reference
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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. BOTH of the following: 1. The requested agent is eligible for continuation of therapy AND ONE of the following: **Target Agents Eligible for Continuation of Therapy** All target agents are eligible for continuation of therapy A. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** B. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **AND** 2. The patient has an FDA labeled indication for the requested agent and route of administration **OR** B. The patient has a diagnosis of chronic thromboembolic pulmonary hypertension (CTEPH), WHO Group 4 and ALL of the following: 1. The requested agent is Adempas **AND** 2. The patient's diagnosis has been confirmed by a ventilation-perfusion scan and a confirmatory selective pulmonary angiography **AND** 3. The patient has a mean pulmonary artery pressure of greater than 20 mmHg **AND** 4. The patient has a pulmonary capillary wedge pressure less than or equal to 15 mmHg **AND** 5. The patient has a pulmonary vascular resistance greater than or equal to 3 Wood units **AND**

Module	Clinical Criteria for Approval
	6. ONE of the following: A. The patient is NOT a candidate for surgery **OR** B. The patient has had a pulmonary endarterectomy AND has persistent or recurrent disease **AND** 7. The patient will NOT be using the requested agent in combination with a PDE5 inhibitor (e.g., tadalafil [Adcirca or Cialis] or sildenafil [Revatio or Viagra]) **OR** C. The patient has a diagnosis of pulmonary arterial hypertension (PAH), WHO Group 1 and ALL of the following: 1. The patient's diagnosis has been confirmed by right heart catheterization (medical records required) **AND** 2. The patient's mean pulmonary arterial pressure is greater than 20 mmHg **AND** 3. The patient has a pulmonary capillary wedge pressure less than or equal to 15 mmHg **AND** 4. The patient has a pulmonary vascular resistance greater than or equal to 3 Wood units **AND** 5. The patient's World Health Organization (WHO) functional class is II or greater **AND** 6. If the requested agent is sotatercept, then BOTH of the following: A. The patient has been stable on background PAH therapy for at least 90 days (Please note: Background therapy refers to combination therapy consisting of drugs from two or more of the following drug classes: ERA, PDE5i, soluble guanylate cyclase stimulator, and/or prostacyclin analogue or receptor agonist) **AND** B. The patient is not pregnant or planning to become pregnant while on therapy with the requested agent **AND** 7. If the requested agent is Adcirca, Adempas, Revatio, sildenafil, or tadalafil, the patient will NOT be using the requested agent in combination with a PDE5 inhibitor (e.g., tadalafil [Adcirca or Cialis] or sildenafil [Revatio or Viagra]) **AND** 8. If the requested agent is NOT sotatercept, then ONE of the following: A. The requested agent will be utilized as monotherapy **OR** B. The requested agent will be utilized as dual therapy that consists of an endothelin receptor antagonist (ERA) plus phosphodiesterase 5 inhibitor (PDE5i) as initial therapy **OR** C. The requested agent will be utilized for add-on therapy to existing monotherapy (dual therapy) [except combo requests for endothelin receptor antagonist (ERA) plus phosphodiesterase 5 inhibitor (PDE5i) for dual therapy], and BOTH of following: 1. The patient has unacceptable or deteriorating clinical status despite established PAH pharmacotherapy **AND**

Module	Clinical Criteria for Approval
	2. The requested agent is in a different therapeutic class **OR** D. The requested agent will be utilized for add-on therapy to existing dual therapy (triple therapy) and ALL of the following: 1. The patient is WHO functional class III or IV **AND** 2. ONE of the following: A. A prostanoid has been started as one of the agents in the triple therapy **OR** B. The patient has an intolerance, FDA labeled contraindication, or hypersensitivity to ALL prostanoids **AND** 3. The patient has unacceptable or deteriorating clinical status despite established PAH pharmacotherapy **AND** 4. All three agents in the triple therapy are from a different therapeutic class **OR** E. The requested agent will be utilized as part of triple therapy in a treatment naive patient AND both of the following: 1. The patient is WHO functional class IV **AND** 2. The 3 agents being utilized consist of: endothelin receptor antagonist (ERA) plus PDE5i plus prostanoid **OR** D. The patient has a diagnosis of pulmonary hypertension associated with interstitial lung disease (PH-ILD, WHO group 3) AND ALL of the following: 1. The requested agent is Tyvaso **AND** 2. The patient's diagnosis has been confirmed by right heart catheterization (medical records required) **AND** 3. The patient's mean pulmonary arterial pressure is greater than 20 mmHg **AND** 4. The patient has a pulmonary capillary wedge pressure less than or equal to 15 mmHg **AND** 5. The patient has a pulmonary vascular resistance greater than or equal to 3 Wood units **AND** 6. The patient has an FVC less than 70% of predicted **AND** 7. The patient has extensive parenchymal changes on computed tomography (CT) **AND** 8. BOTH of the following: A. The patient is currently treated with standard of care therapy for ILD (e.g., Ofev) **AND** B. The patient will continue standard of care therapy for ILD (e.g., Ofev) **OR** E. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following:

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
A. The patient's age is within FDA labeling for the requested indication for the requested agent OR
B. There is support for using the requested agent for the patient's age for the requested indication AND
3. If the request is for ONE of the following brand agents with an available generic equivalent (listed below), then ONE of the following:
<table>
<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Revatio (tablet, oral suspension)</td><td>sildenafil (tablet, oral suspension)</td></tr>
<tr><td>Adcirca</td><td>tadalafil</td></tr>
<tr><td>Tracleer 62.5 mg and 125 mg tablets</td><td>bosentan 62.5 mg and 125 mg tablets</td></tr>
<tr><td>Letairis</td><td>ambrisentan</td></tr>
</table>
A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
C. There is support for the use of the requested brand agent over the generic equivalent AND
4. If the request is for Tadliq, then one of the following:
A. The patient has tried and had an inadequate response to generic tadalafil tablets OR
B. The patient has an in intolerance or hypersensitivity to generic tadalafil tablets that is not expected to occur with the requested agent OR
C. The patient has an FDA labeled contraindication to generic tadalafil tablets that is not expected to occur with the requested agent AND
5. If the request is for Liqrev, then one of the following:
A. The patient has tried and had an inadequate response to generic sildenafil oral suspension OR
B. The patient has an intolerance or hypersensitivity to the generic sildenafil oral suspension that is not expected to occur with the requested agent OR
C. The patient has an FDA labeled contraindication to generic sildenafil oral suspension that is not expected to occur with the requested agent AND
</td></tr>
</table>

Module	Clinical Criteria for Approval
	6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [NOTE: Patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent (e.g., stabilization, decreased disease progression) (medical records required) **AND** 3. If the requested agent is Tyvaso for a diagnosis of pulmonary hypertension associated with interstitial lung disease (PH-ILD, WHO group 3), then the patient will continue standard of care therapy for ILD (e.g., Ofev) **AND** 4. If the requested agent is sotatercept for a diagnosis of pulmonary arterial hypertension (PAH), the patient will continue to use background PAH therapy (Please note: Background therapy refers to combination therapy consisting of drugs from two or more of the following drug classes: ERA, PDE5i, soluble guanylate cyclase stimulator, and/or prostacyclin analogue or receptor agonist) **AND** 5. If the request is for ONE of the following brand agents with an available generic equivalent (listed below), then ONE of the following:

Brand	Generic Equivalent
Revatio (tablet, oral suspension)	sildenafil (tablet, oral suspension)
Adcirca	tadalafil
Tracleer 62.5 mg and 125 mg tablets	bosentan 62.5 mg and 125 mg tablets

Module	Clinical Criteria for Approval
	<table><tr><td>Letairis</td><td>ambrisentan</td></tr></table> A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent **OR** B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent **OR** C. There is support for the use of the requested brand agent over the generic equivalent **AND** 6. If the request is for Tadliq, then one of the following: A. The patient has tried and had an inadequate response to generic tadalafil tablets **OR** B. The patient has an in intolerance or hypersensitivity to generic tadalafil tablets that is not expected to occur with the requested agent **OR** C. The patient had an FDA labeled contraindication to generic tadalafil tablets that is not expected to occur with the requested agent **AND** 7. If the request is for Liqrev, then one of the following: A. The patient has tried and had an inadequate response to generic sildenafil oral suspension **OR** B. The patient has an intolerance or hypersensitivity to the generic sildenafil oral suspension that is not expected to occur with the requested agent **OR** C. The patient has an FDA labeled contraindication to generic sildenafil oral suspension that is not expected to occur with the requested agent **AND** 8. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 9. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support of therapy with a higher dose for the requested indication **Length of Approval**: 12 months

Pyrukynd (mitapivat)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Pyrukynd® (mitapivat) Tablet	Treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency		1

CLINICAL RATIONALE

Pyruvate kinase deficiency	Pyruvate kinase deficiency (PKD) is the most common enzyme-related glycolytic defect that results in red cell hemolysis. PKD is characterized by clinical heterogeneity. Heterogeneity results in a variable degree of hemolysis, causing irreversible cellular disruption. Invariably, PKD results in hereditary non-spherocytic anemia. Manifestations occur from the neonatal period through adult life.(2) Red blood cell (RBC) metabolism hinges on glycolysis. Pyruvate kinase (PK) enzyme is key to this process. PK converts phosphoenolpyruvate to pyruvate. This step yields 50% of RBC ATP. PK modulates NADH production for methemoglobin reduction. These metabolites enable RBCs to function effectively. In PKD, cellular energy efficiency and longevity decrease. Young RBCs are most affected in PKD. PK expression is controlled by the Pyruvate Kinase L/R (PKLR) gene and follows an autosomal recessive inheritance pattern.(2) Cellular integrity of RBCs is maintained by membrane-bound ATPases that exchange sodium for potassium. The sodium and potassium exchange maintains transcellular electrochemical neutrality, cellular fluid balance, and deformability. The absence of the PK enzyme results in a decrease in RBC ATP production, which results in RBC deformability. Intracellular potassium and water loss also occur and results in RBC damage. PKD manifests with enzyme levels of less than 25%. Splenic and hepatic capillaries trap defective RBCs. Extravascular hemolysis occurs, causing hepatosplenomegaly. Intravascular hemolysis may

	also occur, causing hemoglobinuria. Anemia underlies the progressive fatigue in PKD. Increased 2,3-diphosphoglycerate (2.3-DPG) causes oxygen unloading in tissues. This shifts the oxygen dissociation curve rightward. Elevated 2,3-DPG helps compensate for anemia.(2) Testing for PK deficiency can be done by measuring PK activity in RBCs (biochemical testing) and/or by identifying a pathogenic PKLR gene mutation (genetic testing). The most direct evidence of functional PK deficiency is by biochemical testing, unless the patient has had a recent transfusion since the transfused RBCs will have normal activity and can make the patient's results appear normal. The diagnosis of PKD is confirmed in a patient with hemolytic anemia (or compensated hemolysis) who has laboratory evidence of reduced RBC PK enzymatic activity and/or genetic evidence or pathogenic PKLR mutations.(3) It is recommended that for those who have an initial diagnosis determined by pyruvate kinase enzyme activity measurements, a confirmatory diagnosis be obtained through PKLR gene molecular analysis. And for those who have an initial diagnosis assessed by PKLR gene molecular analysis, if the patient does not have two known pathogenic mutations in PKLR, a confirmatory diagnosis should be obtained through pyruvate kinase enzyme activity measurement. (5) The differential diagnoses of PKD include ruling out other causes of hemolytic anemia, e.g., antibody or immune hemolysis, or enzyme deficiencies.(2) Iron overload is a risk in PKD despite transfusion status and can result in complications, e.g., cardiac issues, bone deformities, and fractures. Routine screening with iron studies is necessary as it may reveal the presence of iron toxicity. The presence of hyperferritinemia may indicate the onset of iron overload. Magnetic resonance imaging (MRI) for hemosiderosis is useful in selected patients. Hemosiderosis (the accumulation of iron in the organs) requires iron-chelation therapy with deferoxamine.(2,4) The management of chronic anemia requires supportive treatment. Of concern are states that are associated with increased folate demand, e.g., growth during childhood, pregnancy, and hemolytic crises. In these cases, folic acid supplementation is often warranted. Blood transfusions often help to alleviate anemia, but decisions for transfusion must take into account the risks and benefits.(2) Splenectomy is indicated for massive splenomegaly. This eliminates the risk of traumatic rupture. Severe anemia may also benefit from splenectomy. Total splenectomy is advocated in late childhood.(2)

	Current guidelines for PKD principally focus on supportive, rather than curative treatment of the disease. After a definitive diagnosis is established by qualitative and quantitative reduction in enzyme activity and a positive finding of homozygous or heterozygous gene mutations in the PKLR gene, patients are put into supportive care which constitutes the following framework:(3)
	
	• Folic acid supplementation
	  ○ Daily folic acid supplementation recommended in patients with moderate hemolysis, or with mild hemolysis coupled with a restricted diet to maintain effective erythropoiesis
	• Red cell transfusions
	  ○ These should be specified for each patient after a meticulous assessment of their tolerance regarding anemia, quality of life, and physical activity, rather than a measure of their absolute hemoglobin levels. Further assessment after each transfusion is also required
	• Splenectomy is the definitive treatment in those who are severely anemic or receive regular transfusions and in those at risk of splenic rupture
	  ○ Indicated between the age of 5 year to before adolescence
	
	Pyrukynd is recommended in adult patients with pyruvate kinase deficiency who are anemic, and who don't have two non-missense mutations, regardless of transfusion or splenectomy status.(5) Pyrukynd therapy should be discontinued is the patient who are not receiving a clinical response after 3-6 months, depending on if the patient is receiving transfusions. Patients who do not achieve at least a 33% reduction in transfusion requirement after optimizing Pyrukynd therapy should discontinue therapy unless the patient is achieving marked improvement in other key disease parameters such as iron status, jaundice, and patient reported health outcomes.(5)

Efficacy	The efficacy of Pyrukynd was evaluated in ACTIVATE, a multinational, randomized, double-blind, placebo-controlled clinical study (NCT03548220) of 80 adults with PKD who were not regularly transfused, defined as having had no more than 4 transfusions in the 52-week period prior to treatment and no transfusion in the 3-month period prior to treatment. Patients were included if they had documented presence of at least 2 variant alleles in the pyruvate kinase liver and red blood cell (PKLR) gene, of which at least 1 was a missense variant and Hb less than or equal to 10g/dL. Patients who were homozygous for the c1436G > A (p.R479H) variant or had 2 non-missense variants (without the presence of another missense variant) in the PKLR gene were excluded because these patients did not achieve Hb response (change from baseline in Hb greater

	than or equal to 1.5 g/dL at great than 50% of assessments) in the dose-ranging study.(1) Efficacy was based upon Hb response, defined as a greater than or equal to 1.5 g/dL increase in Hb from baseline sustained at 2 or more scheduled assessments (Weeks 16, 20, and 24) during the fixed dose period without transfusions. In ACTIVATE, the LS Mean change form baseline with Pyrukynd compared to placebo was -0.4 (standard error [SE] 0.1) for jaundice (scale: 0-4), -1.1 (SE 0.4) for tiredness (scale: 0-10), and -0.3 (SE 0.3) for shortness of breath (scale: 0-10), assessed with the daily Pyruvate Kinase Deficiency Diary (PKDD) where lower scores represent less sign/symptom severity.(1) In ACTIVATE, the majority of Pyrukynd-treated patients experienced an increase in Hb, while the majority of patients in the placebo arm experienced a decrease in Hb as measured by average change from baseline at Weeks 16, 20, and 24. 40% of patients in the Pyrukynd arm met the Hb response rate and 0% of patients in the placebo arm met the Hb response rate (p-value less than 0.0001).(1) The efficacy of Pyrukynd in patients with PK deficiency who were regularly transfused was evaluated in ACTIVATE-T, a multinational single-arm clinical trial (NCT03559699) of 27 adults with PK deficiency who had a minimum of 6 transfusion episodes in the 52-week period prior to informed consent. Patients were included if they had documented presence of at least 2 variant alleles in the PKLR gene, of which at least 1 was a missense variant. Patients who were homozygous for the c1436G > A (p.R479H) variant or had 2 non-missense variants (without the presence of another missense variant) in the PKLR gene were excluded.(1) Efficacy was based on transfusion reduction response and was defined as greater than or equal to 33% reduction in the number of red blood cell (RBC) units transfused during the fixed dose period compared with the patient's historical transfusion burden. 33% of patients (95% CI) met the transfusion reduction response endpoint and 22% (95% CI) of patients were transfusion free.(1)
Safety	Pyrukynd (mitapivat) has no known FDA labeled contraindications.(1)

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of hemolytic anemia with pyruvate kinase deficiency (PKD) AND ONE of the following: A. Genetic testing showing a pathogenic PKLR gene mutation **OR** B. The patient does NOT have two known pathogenic mutations in the PKLR gene, AND the patient has a decrease in pyruvate kinase enzyme activity 2. The patient is NOT homozygous for the c.1436G > A (p.R479H) variant **AND** 3. The patient has at least 2 variant alleles in the PKLR gene, of which at least 1 is a missense variant **AND** 4. The patient does NOT have two non-missense mutations **AND**

Module	Clinical Criteria for Approval
	5. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months NOTE: If Quantity Limit applies, please see Quantity Limit Criteria **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent (e.g., hemoglobin has increased or is within normal range, decrease in red blood cell transfusion burden) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please see Quantity Limit Criteria

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months

Radicava (edaravone)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Radicava® (edaravone) Intravenous infusion*	Treatment of amyotrophic lateral sclerosis (ALS)	*generic available	1
Radicava ORS® (edaravone) Oral suspension Oral suspension starter kit	Treatment of amyotrophic lateral sclerosis (ALS)		1

CLINICAL RATIONALE

Amyotrophic Lateral Sclerosis (ALS)	Amyotrophic lateral sclerosis (ALS) is an idiopathic, fatal neurodegenerative disease.(2) It is characterized by loss of motor neurons in the spinal cord, brainstem, and motor cortex.(3) Age of onset is between 58-63 years for sporadic disease and 47-52 years for familial disease, with rapidly decreased incidence after 80 years. The clinical hallmark of ALS is the presence of upper and lower motor neuron (UMN and LMN) features involving the brainstem and multiple spinal cord regions of innervation.(2) ALS is a rapidly progressive disease with 50% of patients dying within 30 months of symptom onset, and about 20% of patients survive between 5 years and 10 years after symptom onset. Older age at symptom onset, early respiratory muscle dysfunction, and bulbar-onset disease are associated with reduced survival, whereas limb-onset disease, younger age at presentation, and longer diagnostic delay are independent predictors of prolonged survival. Dysphagia develops in most patients, with consequent weight loss and malnutrition.

	Respiratory compromise eventually develops in most cases, leading to exertional dyspnea, orthopnea, hypoventilation with resultant hypercapnia, and early morning headaches. Progressive weakening of the respiratory muscles leads to respiratory failure, often precipitated by pneumonia.(2) Respiratory function is a critical predictor of survival in ALS. International guidelines recommend the assessment of respiratory function in ALS patients at first visit and every 3 months thereafter.(7) Forced (FVC) and slow (SVC) vital capacities are non-invasive conventional tests used to estimate respiratory function in ALS. Their results depend on age, gender, height, and ethnicity, in addition to the functional integrity of the inspiratory and expiratory muscles. FVC is sensitive to detect hypoventilation in ALS and can be more sensitive in detecting diaphragmatic weakness when performed in the supine position.(8) However, the patient must expel air quickly and forcefully, which may cause fatigue and induce bronchospasm and result in an underestimation of actual lung capacity. SVC is easier for the patient with ALS to perform even in the presence of orofacial paresis because it involves exhalation of air in a slow, gentle manner after a maximal inspiration. FVC and SVC have been shown to be tightly correlated, can be used interchangeably, and decline similarly in ALS (about 2%/month).(8,9) Symptomatic treatments remain the cornerstone for management of patients with ALS. Disease modifying treatment options for ALS are limited. Riluzole is the only agent shown to have any impact on survival in ALS. The American Academy of Neurology (AAN) has recommended that riluzole be offered to slow disease progression in patients with ALS.(2) While edaravone has been shown to slow the decline of functional and quality of life ratings in patients with ALS, the short duration of trials did not allow for the assessment of an effect on survival.(6) According to CADTH Common Drug Review (CDR) of Radicava, Radicava should be considered for the majority of newly diagnosed ALS patients with preserved respiratory function and with functional independence. Patients with advanced ALS with severe disability, such as ventilator-dependence with very little limb function, are unlikely to benefit from therapy and should not be offered Radicava.(5)
Efficacy	The efficacy of edaravone was evaluated in a post-hoc analysis of a 6-month, phase III randomized, placebo-controlled, double-blind study, in patients aged 20 to 75 years with ALS. All study patients had to meet all of the following criteria at screening:

	1. Functionality retained most activities of daily living (defined as scores of 2 points or better on each individual item of the ALS Functional Rating Scale – Revised [ALSFRS-R]) 2. Normal respiratory function (defined as percent-predicted forced vital capacity [%FVC] values of greater than or equal to 80%) 3. Definite or probable ALS based on the El Escorial revised criteria 4. Disease duration of 2 years or less Patients who met the criteria above (n= 137) were randomized to receive either edaravone 60 mg intravenously (IV) or placebo for 6 cycles (4 weeks per cycle with 2 weeks on, 2 weeks off). 91% of patients in both the edaravone and placebo group were also receiving treatment with riluzole. The primary efficacy endpoint was change in the Revised ALS Functional Rating Scale (ALSFRS-R) score from baseline to 24 weeks or therapy discontinuation (if discontinuation occurred after the third cycle) after randomization. The change in ALSFRS-R score was -5.01 (SE 0.64) and -7.50 (0.66) in the edaravone and placebo group respectively. The trial authors concluded edaravone showed efficacy in a small subset of patients (i.e., those meeting the criteria noted above) and that "there is no indication that edaravone might be effective in a wider population of patients with ALS who do not meet the criteria".(1,4)
Safety	Edaravone is contraindicated in patients with history of hypersensitivity to edaravone or any of its inactive ingredients.(1)

REFERENCES

Number	Reference
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8	Pinto S, de Carvalho M. SVC Is a Marker of Respiratory Decline Function, Similar to FVC, in Patients With ALS. Front Neurol. 2019 Feb 28;10:109. doi: 10.3389/fneur.2019.00109.
9	Andrews JA, Meng L, Kulke SF, et al. Association Between Decline in Slow Vital Capacity and Respiratory Insufficiency, Use of Assisted Ventilation, Tracheostomy, or Death in Patients With Amyotrophic Lateral Sclerosis. JAMA Neurol. 2018;75(1):58–64. doi:10.1001/jamaneurol.2017.3339.

ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
74509030001820	Radicavaors	edaravone oral susp	105 MG/5ML	Starter Kits QL set up at NDC	70510232201		

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
74509030001820	Radicavaors starter kit	edaravone oral susp	105 MG/5ML	Starter Kits QL set up at NDC	70510232101 ; 70510232102		

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** All target agents are eligible for continuation of therapy 1. The patient has been treated with the requested agent within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent within the past 90 days AND is at risk if therapy is changed **OR** B. ALL of the following: 1. The patient has a diagnosis of amyotrophic lateral sclerosis (ALS) **AND** 2. The patient has had the diagnosis of ALS for a duration of 2 years or less **AND** 3. The patient has a baseline percent forced vital capacity (FVC%) or slow vital capacity (SVC) of 80% or greater **AND** 4. The patient is able to perform most activities of daily living, defined as scores of 2 points or better on each individual item of the ALS Functional Rating Scale – Revised [ALSFRS-R] **AND** 5. ONE of the following: A. BOTH of the following: 1. The patient is currently being treated with riluzole **AND**

Module	Clinical Criteria for Approval
	2. The patient will continue riluzole in combination with the requested agent **OR** B. The patient has an intolerance, hypersensitivity, or FDA labeled contraindication to riluzole **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months **NOTE:** For patients initiating therapy, approval will include 28 bags per 28 days (initial dose) for the first month and 20 bags per 28 days for the remainder of the 6 months. For patients initiating therapy with oral suspension, approval will include 70 mL starter kit per 180 days (initial dose) and 50 mL per 28 days for the remainder of the 6 months. NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The patient is NOT dependent on invasive ventilation or tracheostomy **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** Initial: up to 6 months; Renewal: up to 12 months

Rapid to Intermediate Acting Insulin

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Admelog® (insulin lispro) Injection	To improve glycemic control in adult and pediatric patients with diabetes mellitus	Rapid-Acting Insulins	1
Apidra® (insulin glulisine) Injection	To improve glycemic control in adults and pediatric patients with diabetes mellitus	Rapid-Acting Insulins	2
Fiasp® (insulin aspart) Injection	To improve glycemic control in adult and pediatric patients with diabetes mellitus	Rapid-Acting Insulins	3
Humalog®, Humalog Junior®, Insulin Lispro, Insulin Lispro Junior Injection	To improve glycemic control in adults and children with diabetes mellitus	Rapid-Acting Insulins	4
Humalog® Mix 50/50 (50% insulin lispro protamine/50% insulin lispro) Injection	To improve glycemic control in adult and pediatric patients with diabetes mellitus	NPH-Lispro Combinations	14
Humalog® Mix 75/25, Insulin Lispro Protamine/Insulin Lispro (75/25)	To improve glycemic control in adult and pediatric patients with diabetes mellitus	NPH-Lispro Combinations	13

Agent(s)	FDA Indication(s)	Notes	Ref#
Injection			
Humulin® 70/30 (70% human insulin isophane/30% regular human insulin) Injection	To improve glycemic control in adults with diabetes mellitus	NPH-Regular Combinations	11
Humulin® N (human isophane insulin) Injection	To improve glycemic control in adult and pediatric patients with diabetes mellitus	Intermediate-Acting Insulins	9
Humulin® R (regular human insulin) Injection	To improve glycemic control in adult and pediatric patients with diabetes mellitus	Short-Acting Insulins	7
Novolin® 70/30, Insulin aspart protamine/insulin aspart Injection	To improve glycemic control in adults and pediatric patients with diabetes mellitus	NPH-Regular Combinations	12
Lyumjev® (insulin lispro-aabc) Injection	To improve glycemic control in adults with diabetes mellitus	Rapid-Acting Insulins	5
Novolin® N, ReliOn® N (human isophane insulin) Injection	To improve glycemic control in adult and pediatric patients with diabetes mellitus	Intermediate-Acting Insulins	10

Agent(s)	FDA Indication(s)	Notes	Ref#
Novolin® R, ReliOn® R (regular human insulin) Injection	To improve glycemic control in adult and pediatric patients with diabetes mellitus	Short-Acting Insulins	8
NovoLog®, Insulin Aspart Injection	To improve glycemic control in adults and pediatric patients with diabetes mellitus	Rapid-Acting Insulins	6
NovoLog® Mix 70/30, Insulin aspart protamine/insulin aspart Injection	To improve glycemic control in patients with diabetes mellitus	NPH – NovoLog Combination	15

CLINICAL RATIONALE

Overview	The American Diabetes Association Standards of Medical Care in Diabetes recommend the following therapy for type 1 diabetes mellitus:(16) • Most individuals with type 1 diabetes should be treated with multiple daily injections of prandial and basal insulin, or subcutaneous insulin infusion. • Most individuals with type 1 diabetes should use rapid-acting insulin analogs to reduce hypoglycemia risk. • Individuals with type 1 diabetes should receive education on how to match mealtime insulin doses to carbohydrate intake, fat and protein content, and anticipated physical activity. For type 2 diabetes mellitus, the American Diabetes Association recommends the following:(16) • Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals.

	• In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. • Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy. • Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals. • Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. • Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. • The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. • A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. • Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. • In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible. • If insulin is used, combination therapy with a glucagon-like peptide 1 receptor agonist is recommended for greater efficacy, durability of treatment effect, and weight and hypoglycemia benefit. Recommendation for treatment intensification for individuals not meeting treatment goals should not be delayed. • Medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate specific factors that impact choice of treatment.

	• Clinicians should be aware of the potential for overbasalization with insulin therapy. Clinical signals that may prompt evaluation of overbasalization include basal dose more than approximately typ0.5 units/kg/day, high bedtime–morning or postpreprandial glucose differential, hypoglycemia (aware or unaware), and high glycemic variability. Indication of overbasalization should prompt reevaluation to further individualize therapy. The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) 2023 algorithm for type 2 diabetes recommends the overall goal of insulin therapy is to achieve glycemic control after failure of noninsulin antihyperglycemic agents. Glycemic targets should be individualized, although an A1C of 6.5% to 7% for persons on insulin is recommended for most patients. Although A1C is a key measure, insulin titration requires use of multiple glycemic parameters including fasting blood glucose (FBG), premeal or 2-hour postprandial blood glucose, and data from continuous glucose monitoring (CGM), when available. In general, targets for fasting and premeal glucose are <110 mg/dL without hypoglycemia and can be individualized based on a person's comorbidities and clinical status. The use of CGM is recommended for persons treated with insulin to optimize glycemic control while minimizing hypoglycemia.(17) Given that type 2 diabetes is a progressive disease, many individuals will require >1 antihyperglycemic medication to achieve their individualized A1C target over the course of the disease. Clinicians should consider multiple factors when selecting the second agent, including presence of overweight or obesity, hypoglycemia risk, access/cost, and presence of severe hyperglycemia. Patients often present with >1 of these factors, so using a patient-centered, shared decision-making approach is important. The order that medications are listed in the algorithm denotes the suggested preference hierarchy for selection. In those patients with overweight or obesity and the additional goal of weight loss, dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist (GIP/GLP-1 RA), GLP-1 RA, or sodium glucose cotransporter 2 inhibitor (SGLT2i) class are preferred options. Persons with a history of hypoglycemia, at high risk of hypoglycemia, and/or at risk for severe complications from hypoglycemia should preferentially be initiated with an agent associated with low risk for hypoglycemia, including GLP-1 RA, SGLT2i, dual GIP/GLP-1 RA, thiazolidinedione (TZD), or dipeptidyl peptidase-4 inhibitor (DPP-4i).(17) Patients with symptomatic hyperglycemia and/or an A1C >10% suggestive of marked insulin deficiency should start basal insulin to improve glycemia as

	quickly as possible. Basal insulin can be initiated with or without initiation and titration of a GLP-1 RA if the patient is not already on this class of agents. Some patients with severe hyperglycemia may need simultaneous initiation of bolus insulin. Clinicians should be cognizant that combination of incretin-based therapies is not recommended (ie, DPP-4i with GLP-1 RA or dual GIP/GLP-1 RA). Antihyperglycemic medications should be titrated to the maximally tolerated dose to achieve the individualized A1C goal, and additional antihyperglycemic agents should be considered in a timely fashion to avoid therapeutic inertia. If the A1C is >9% or >1.5% above goal, greater than 2 antihyperglycemic agents may need to be initiated at once.(17) Basal with or without prandial insulin treatment may be needed as initial therapy if the A1C is >10% and/or glucose values are >300 mg/dL, combined with catabolic symptoms, such as weight loss. If symptomatic hyperglycemia is present, a GLP-1 RA alone is not recommended as it requires titration and may delay glucose control. The goal of initial intensive insulin therapy for symptomatic hyperglycemia is to reduce glucose levels safely and promptly. After improved glycemic control is achieved with short-term insulin therapy, especially with a new diagnosis of DM, a role for noninsulin antihyperglycemic agents could be considered. For most persons who need intensification of glycemic control and who are already undergoing 3 to 4 oral therapies, a GLP-1 RA or GIP/GLP-1 RA should be the initial choice, if not already in use. If glycemic targets are not achieved with these therapies, basal insulin should be added alone or as a basal insulin/GLP-1 RA combination injection. Stepwise addition of prandial insulin at 1 to 3 meals is recommended if additional glycemic control is required. The dose of basal insulin can be based on A1C levels at the time of initiation. For an A1C <8%, basal insulin can be started at 0.1 to 0.2 U/kg/day and for an A1C >8%, 0.2 to 0.3 U/kg/day can be considered. Analog insulins, including detemir, glargine, or degludec are preferred over human insulins such as neutral protamine Hagedorn (NPH) to reduce hypoglycemia.(17)
Safety	All rapid to intermediate-acting insulin agents have the following contraindications:(1-15) • Do not use during episodes of hypoglycemia. • Do not use in patients with hypersensitivity to the insulin agent or any of the excipients.

REFERENCES

Number	Reference
1	Admelog prescribing information. Sanofi-Aventis US, LLC. August 2023.
2	Apidra (insulin glulisine [rDNA origin] injection) solution for injection. Sanofi-Aventis. November 2022.
3	Fiasp prescribing information. Novo Nordisk Inc. June 2023.
4	Humalog, Humalog Kwikpen, Humalog Junior Kwikpen, Humalog Tempo Pen (insulin lispro injection [rDNA origin] solution for subcutaneous injection). Eli Lilly and Company. July 2023.
5	Lyumjev, Lyumjev Kwikpen, Lyumjev Junior Kwikpen, Lyumjev Kwikpen prescribing information. Eli Lilly and Company. October 2022.
6	NovoLog (insulin aspart [rDNA origin] injection) solution for subcutaneous use. Novo Nordisk, Inc. February 2023.
7	Humulin R (insulin human injection [rDNA origin]) solution for subcutaneous injection. Eli Lilly and Company. June 2022.
8	Novolin R (human insulin injection [rDNA origin]). Novo Nordisk, Inc. November 2022.
9	Humulin N (insulin [rDNA origin] isophane suspension). Eli Lilly and Company. June 2022.
10	Novolin N (human insulin isophane suspension injection) suspension. Novo Nordisk. November 2022.
11	Humulin 70/30 (70% human insulin isophane suspension and 30% human insulin injection (rDNA origin). Eli Lilly and Company. June 2022.
12	Novolin 70/30 (70% NPH, Human Insulin Isophane Suspension and 30% Regular, Human Insulin Injection, [rDNA]). Novo Nordisk. November 2022.
13	Humalog Mix 75/25 (75% insulin lispro protamine suspension and 25% insulin lispro injection (rDNA origin). Eli Lilly and Company. July 2023.
14	Humalog Mix 50/50 (50% insulin lispro protamine suspension and 50% insulin lispro injection [rDNA origin]). Eli Lilly and Company. July 2023.

Number	Reference
15	NovoLog 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection. Novo Nordisk Inc. February 2023.
16	American Diabetes Association, 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2023. Diabetes Care 1 January 2023; 46 (Supplement_1): S140–S157. https://doi.org/10.2337/dc23-S009.
17	Samson, S. L., Vellanki, P., Blonde, L., et. al. (2023). American association of clinical endocrinology consensus statement: Comprehensive type 2 diabetes management algorithm – 2023 update. Endocrine Practice: Official Journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists, 29(5), 305–340. https://doi.org/10.1016/j.eprac.2023.02.001

ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	
27104005	Admelog ; Admelog solostar ; Humalog ; Humalog junior kwikpen ; Humalog kwikpen ; Humalog tempo pen ; Lyumjev ; Lyumjev	insulin lispro inj soln ; insulin lispro soln cartridge ; insulin lispro soln pen-inj w/transmitter port ; insulin lispro soln pen-injector ; insulin lispro-aabc inj ; insulin lispro-aabc soln pen-inj ; insulin lispro-aabc soln pen-inj w/transmit port	100 UNIT/ML ; 200 UNIT/ML	Quantity limit is cumulative at GPI 8 for injectable formulations.			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	
	kwikpen ; Lyumjev tempo pen	; insulin lispro-aabc soln pen-injector					
27104005	Admelog ; Admelog solostar ; Humalog ; Humalog junior kwikpen ; Humalog kwikpen ; Humalog tempo pen ; Lyumjev ; Lyumjev kwikpen ; Lyumjev tempo pen	insulin lispro inj soln ; insulin lispro soln cartridge ; insulin lispro soln pen-inj w/transmitter port ; insulin lispro soln pen-injector ; insulin lispro-aabc inj ; insulin lispro-aabc soln pen-inj ; insulin lispro-aabc soln pen-inj w/transmit port ; insulin lispro-aabc soln pen-injector	100 UNIT/ML ; 200 UNIT/ML	Quantity limit is cumulative at GPI 8 for injectable formulations.			
27104004	Apidra ; Apidra solostar	insulin glulisine inj ; insulin glulisine soln pen-injector inj	100 UNIT/ML	Quantity limit is cumulative at GPI 8 for injectable formulations.			
27104002	Fiasp ; Fiasp flextouch ; Fiasp penfill ; Fiasp pumpcart ; Novolog ; Novolog flexpen ;	insulin aspart (with niacinamide) inj ; insulin aspart (with niacinamide) sol pen-inj ; insulin aspart (with niacinamide) soln cartridge ; insulin aspart inj soln ; insulin	100 UNIT/ML	Quantity limit is cumulative at GPI 8 for injectable formulations.			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	
	Novolog flexpen relion ; Novolog penfill ; Novolog relion	aspart soln cartridge ; insulin aspart soln pen-injector					
27104080	Humalog mix 50/50 ; Humalog mix 50/50 kwikpen ; Humalog mix 75/25 ; Humalog mix 75/25 kwikpen	insulin lispro prot & lispro inj ; insulin lispro prot & lispro sus pen-inj ; insulin lispro protamine & lispro inj	(50-50) 100 UNIT/ML ; (75-25) 100 UNIT/ML	Quantity limit is cumulative at GPI 8 for injectable formulations.			
27104090	Humulin 70/30 ; Humulin 70/30 kwikpen ; Novolin 70/30 ; Novolin 70/30 flexpen ; Novolin 70/30 flexpen rel ; Novolin 70/30 relion	insulin nph & regular susp pen-inj ; insulin nph isophane & regular human inj	(70-30) 100 UNIT/ML	Quantity limit is cumulative at GPI 8 for injectable formulations.			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	
27104020	Humulin n ; Humulin n kwikpen ; Novolin n ; Novolin n flexpen ; Novolin n flexpen relion ; Novolin n relion	insulin nph (human) (isophane) inj ; insulin nph (human) (isophane) susp pen-injector	100 UNIT/ML	Quantity limit is cumulative at GPI 8 for injectable formulations.			
27104010020	Humulin r ; Humulin r u-500 (concentr ; Novolin r ; Novolin r relion	insulin regular (human) inj	100 UNIT/ML ; 500 UNIT/ML	Quantity limit is cumulative at GPI 8 for injectable formulations.			
271040100 0D2	Humulin r u-500 kwikpen ; Novolin r flexpen ; Novolin r flexpen relion	insulin regular (human) soln pen-injector	100 UNIT/ML ; 500 UNIT/ML	Quantity limit is cumulative at GPI 8 for injectable formulations.			
27104070	Novolog mix 70/30 ; Novolog mix 70/30 prefill ; Novolog mix 70/30 relion	insulin aspart prot & aspart (human) inj ; insulin aspart prot & aspart sus pen-inj	(70-30) 100 UNIT/ML	Quantity limit is cumulative at GPI 8 for injectable formulations.			

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Recorlev (levoketoconazole)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Recorlev® (levoketoconazole) Tablet	Treatment of endogenous hypercortisolemia in adult patients with Cushing's syndrome for whom surgery is not an option or has not been curative Limitations of use: Recorlev is not approved for the treatment of fungal infections		

CLINICAL RATIONALE

Cushing's syndrome	Cushing's syndrome is pathologic hypercortisolism caused by excessive adrenocorticotropic hormone (ACTH) production or autonomous adrenal production of cortisol. This potentially lethal disorder is associated with significant comorbidities including hypertension, diabetes, coagulopathy, cardiovascular disease, infections, and fractures. As a result, even after cure of hypercortisolism, mortality rates may be increased. Because of this it is important to make the diagnosis as early in the disease course as possible to prevent additional morbidity and residual disease. Signs and symptoms of Cushing's syndrome are broad and often common among the general population such as obesity, depression, diabetes, hypertension, or menstrual irregularities. Some features are more discriminatory and unique to Cushing's syndrome such as reddish-purple striae, plethora, proximal muscle weakness, bruising with no obvious trauma, and unexplained osteoporosis.(4) Cushing's disease is a form of Cushing syndrome. Cushing's disease occurs when a benign tumor in the pituitary gland causes the pituitary gland to produce too much ACTH. Cushing's disease can also occur with diffuse growth of the pituitary gland (pituitary hyperplasia). Pituitary hyperplasia can lead to the release of too much ACTH which then leads to over-production of cortisol by the adrenal glands.(2)

	Diagnosis of Cushing's syndrome is often delayed for years, partly because of lack of awareness of the insidious progressive disease process and testing complexity. Screening and diagnostic tests for Cushing's syndrome assess cortisol secretory status: abnormal circadian rhythm with late-night salivary cortisol (LNSC), impaired glucocorticoid feedback with overnight 1 mg dexamethasone suppression test (DST) or low-dose 2-day dexamethasone test (LDDT), and increased bioavailable cortisol with 24-hour urinary free cortisol (UFC). The sensitivity of all tests is higher than 90%; the highest sensitivity rates are obtained with DST and LNSC and the lowest with UFC. Specificity is somewhat lower than sensitivity, with LNSC being the most specific and DST and UFC the least specific. LNSC should not be used in patients with disruption of normal day and night cycle, such as night-shift workers.(3)
	
	Clinical considerations and recommendations for Cushing's syndrome diagnosis and monitoring of Cushing's disease recurrence:(3)
	
	• If Cushing's syndrome is suspected:
	  ○ Start with UFC, LNSC or both; DST could be an option if LNSC is not feasible
	  ○ Multiple LNSC might be easier for patient collection
	
	• If confirming Cushing's syndrome:
	  ○ Can use any test
	  ○ UFC (average 2 or 3 collections) above the upper limit of normal – cutoff is assay-specific reference range
	  ○ LNSC (2 or more tests) above the upper limit of normal – cutoff is assay-specific reference range
	  ○ DST useful in night-shift workers, not in women on estrogen containing contraceptives – above cutoff of 1.8 mcg/dL
	  ○ Measuring dexamethasone concentration, with cortisol concentration the morning after 1 mg dexamethasone ingestion improves interpretability
	
	• If Cushing's syndrome due to adrenal tumor is suspected
	  ○ Start with DST as LNSC has lower specificity in these patients
	
	• Monitoring for recurrence:
	  ○ Consider which tests were abnormal at initial diagnoses

	○ LNSC most sensitive and should be done annually – above cutoff of 0.27 mcg/dL ○ DST and UFC usually become abnormal after LNSC (with UFC usually the last to become abnormal) ○ UFC 1.6 X upper limit of normal ○ DST above 1.8 mcg/dL Transsphenoidal surgery is recommended as first-line therapy for patients with Cushing's disease. Remission, typically defined as postoperative serum cortisol concentrations lower than 2 mcg/dL, is seen in approximately 80% of patients with microadenomas and 60% with macroadenomas if the procedure is performed by an experienced surgeon. Patients in remission require glucocorticoid replacement until HPA axis recovery. As remission could be delayed, monitoring until postoperative cortisol nadir can usually identify such cases.(3) Recurrence after successful pituitary surgery is characterized as the reappearance of clinical and biochemical features of hypercortisolism after initial remission. Published recurrence rates vary between 5% and 35% with half of recurrences appearing within the first 5 years after surgery and half after up to 10 years or more. Compared with use in the initial diagnosis of Cushing's syndrome, LNSC, DST, UFC, and desmopressin tests have a lower sensitivity for recurrence, but specificity is high. Repeat transsphenoidal surgery can be considered in patients with biochemical evidence of recurrent Cushing's disease with visible tumor on MRI.(3) Medications used for the treatment of Cushing's disease target adrenal steroidogenesis, somatostatin, and dopamine receptors in the pituitary gland, and glucocorticoid receptors.(3) • Adrenal steroidogenesis inhibitor agents ○ Ketoconazole: European Medicines Agency (EMA) approved, off-label use in USA ○ Osilodrostat: FDA approved ○ Metyrapone: EMA approved, off-label use in USA ○ Mitotane: EMA approved, off label use in USA ○ Etomidate: Off-label use only ○ Levoketoconazole:FDA approved, EMA indicated • Somatostatin receptor ligands

	○ Pasireotide: Widely approved ○ Pasireotide long-acting: Widely approved • Dopamine receptor agonists ○ Cabergoline: Off-label use only • Glucocorticoid receptor blocker ○ Mifepristone: FDA-approved for hyperglycemia associated with Cushing's syndrome. There are several factors helpful in selection of medical therapy:(3) • If there is a need for rapid normalization of cortisol adrenal steroidogenesis inhibitors are recommended. Osilodrostat and metyrapone have the fastest action and etomidate can be used in very severe cases (high quality, strong recommendation) • In mild disease, if residual tumor is present and there is a potential for tumor shrinkage, consider pasireotide or cabergoline (moderate quality, strong recommendation) • If there is a history of bipolar or impulse control disorder, consider avoiding cabergoline (moderate quality, strong recommendation) • If an expert pituitary endocrinologist is not available to monitor treatment response, use mifepristone cautiously (low quality, discretionary recommendation) • In pregnant women or those desiring pregnancy, consider cabergoline or metyrapone (low quality, strong recommendation), although no Cushing's disease medications are approved for use in pregnancy • Drug intolerance or side-effects, as well as concomitant comorbidities such as type 2 diabetes and hypertension should further guide type of medication used (moderate quality, strong recommendation) • Consider cost and estimated therapy duration, especially if definitive treatment (i.e., pituitary or adrenal surgery) is planned or while awaiting effects of radiotherapy (low quality, discretionary recommendation) Adrenal steroidogenesis inhibitors are usually used first given their reliable effectiveness. For patient with mild disease and no visible tumor on MRI, ketoconazole, osilodrostat, or metyrapone are typically preferred. For patients with mild-to-moderate disease and some residual tumor, there might be a preference for cabergoline or pasireotide because of the potential for tumor shrinkage. For patients with severe disease, rapid normalization of cortisol is the

	most important goal. With osilodrostat and metyrapone, response will typically be seen within hours, and with ketoconazole within a few days.(3) Change in treatment should be considered if cortisol levels are persistently elevated after 2-3 months on maximum tolerated doses. If cortisol does not normalize but is reduced or there is some clinical improvement, combination therapy can be considered (low quality, discretionary recommendation). Many experts consider combining ketoconazole with metyrapone or potentially ketoconazole with osilodrostat to maximize adrenal blockade when monotherapy is not effective, or to allow lower doses of both drugs (low quality, discretionary recommendation). Ketoconazole plus cabergoline or pasireotide, and pasireotide plus cabergoline could be rational combinations if there is visible tumor present (low quality, discretionary recommendation). Other combinations that can be used include triplets of cabergoline, pasireotide, plus ketoconazole, and ketoconazole, metyrapone, plus mitotane (low quality, discretionary recommendation).(3) Radiotherapy is primarily used as adjuvant therapy for patients with persistent or recurrent disease after transsphenoidal surgery or for aggressive tumor growth.(3)
Efficacy	Recorlev (levoketoconazole) contains the 2S,4R-enantiomer derived from racemic ketoconazole and is a cortisol synthesis inhibitor.(1) The effectiveness of Recorlev in patients with Cushing's syndrome was evaluated in two studies (labeled Study 1 and Study 2).(1) Study 1 (NCT03277690) consisted of an open-label dose titration and maintenance phase of up to 19 weeks duration, followed by an 8-week double blind, placebo-controlled, randomized withdrawal phase. Persistence or recurrence of Cushing's syndrome was evidenced by the mean of three 24-hour UFC levels greater than or equal to 1.5 X upper limit of normal.(1) The key secondary efficacy endpoint was the proportion of patients with mean UFC normalization, defined as a patient with mean UFC at or below the ULN at the end of the randomized withdrawal phase without meeting a requirement for early rescue during the randomized withdrawal phase.(1) The percent of patients who had normal mean UFC at the end of the randomized withdrawal phase was 52.4% in the Recorlev group and 5.6% in the placebo group, and the treatment difference (CI) was 46.8%.(1)

	Supportive evidence of efficacy was obtained from Study 2 (NCT01838551) which was a multicenter, single-arm, open-label study that consisted of three study phases (dose titration, maintenance, and extended evaluation) for a total of estimated treatment duration of up to 73 weeks. The primary efficacy endpoint of the study was the proportion of patients with normalization of mean UFC at or below the upper limit of normal based on central laboratory result without requiring a dose increase during maintenance phase. At the end of the maintenance phase, 30.9% of patients (95% exact confidence interval) met the primary endpoint.(1)

Safety	• Recorlev contains a boxed warning with the following:(1)
	  ○ Cases of hepatotoxicity with fatal outcome or requiring liver transplantation have been reported with oral ketoconazole. Some patients had no obvious risk factors for liver disease. Recorlev is associated with serious hepatotoxicity. Evaluate liver enzymes prior to and during treatment
	  ○ Recorlev is associated with dose-related QT interval prolongation. Perform ECG prior to and during treatment
	• Recorlev is contraindicated in:(1)
	  ○ Patients with cirrhosis, acute liver disease or poorly controlled chronic liver disease, baseline AST or ALT greater than 3 times the upper limit of normal, recurrent symptomatic cholelithiasis, a prior history of drug induced liver injury due to ketoconazole or any azole antifungal therapy that required discontinuation of treatment, or extensive metastatic liver disease
	  ○ Patients taking drugs that cause QT prolongation associated with ventricular arrhythmias, including torsades de pointes
	  ○ Patients with prolonged QT_cF interval greater than 470 msec at baseline, history of torsades de pointes, ventricular tachycardia, ventricular fibrillation, or prolonged QT syndrome
	  ○ Patients with hypersensitivity to levoketoconazole, ketoconazole or any excipient in Recorlev
	  ○ Patients taking certain that are sensitive substrates of CYP3A4 or CYP3A4 and P-gp

REFERENCES

Number	Reference
1	Recorlev Prescribing Information. Xeris Pharmaceuticals, Inc. June 2023.
2	Endocrine Society. Cushing's disease. Accessed at: https://www.hormone.org/diseases-and-conditions/cushings-disease
3	Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol December 2021;9 847-75.
4	Nieman, Lynnette K. Recent Updates on the Diagnosis and Management of Cushing's Syndrome. Endocrinology and Metabolism. 2018 Jun;33:139-146. doi: 10.3803/EnM.2018.33.2.139.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** All target agents are eligible for continuation of therapy 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. The patient has a diagnosis of Cushing's syndrome **AND** ALL of the following: 1. ONE of the following: A. The patient had an inadequate response to pituitary surgery **OR**

Module	Clinical Criteria for Approval
	B. The patient is NOT a candidate for pituitary surgery **AND** 2. The patient's disease is persistent or recurrent as evidenced by ONE of the following: A. The patient has a mean of three 24-hour urine free cortisol (UFC) greater than 1.5 times the upper limit of normal **OR** B. Morning plasma adrenocorticotropic hormone (ACTH) above the lower limit of normal **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response to at least ONE of the following conventional agents: 1. Mifepristone 2. Signifor/Signifor LAR (pasireotide) 3. Isturisa (osilodrostat) 4. Cabergoline 5. Metyrapone 6. Lysodren (mitotane) **OR** B. The patient has an intolerance or hypersensitivity to mifepristone, pasireotide, or osilodrostat **OR** C. The patient has an FDA labeled contraindication to mifepristone, pasireotide AND osilodrostat **AND** 4. ONE of the following: A. The patient has tried and had an inadequate response to ketoconazole tablets **OR** B. The patient has an intolerance or hypersensitivity to ketoconazole tablets that is NOT expected to occur with the requested agent (medical records required) **OR** C. The patient has an FDA labeled contraindication to ketoconazole tablets that is NOT expected to occur with the requested agent (medical records required) **AND** 5. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient will NOT be using the requested agent in combination with glucocorticoid replacement therapy **AND**

Module	Clinical Criteria for Approval
	4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: Patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with glucocorticoid replacement therapy **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies please see Quantity Limit Criteria

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months

reSET

Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
reSET® (Computerized behavioral therapy device for psychiatric disorders) Digital therapeutic application	Cognitive behavioral therapy, as an adjunct to a contingency management system, for patients 18 years of age and older who are currently enrolled in outpatient treatment under the supervision of a clinician for Substance Use Disorder, who are not currently on opioid replacement therapy, who do not abuse alcohol solely, or who do not abuse opioids as their primary substance of abuse. The intent is to increase abstinence from a patient's substance of abuse during treatment and increase retention in the outpatient treatment program		1

CLINICAL RATIONALE

Efficacy	The therapeutic content of reSET was validated in a pivotal, randomized clinical trial conducted through the National Institute of Drug Abuse (NIDA) Clinical Trials Network (labeled NIDA CTN-044). The reSET smartphone app itself was not tested in this clinical trial; rather, the desktop-based Therapeutic Education System (TES), which has equivalent content to reSET, was tested. The pivotal study enrolled 507 patients seeking treatment for SUD in ten (10) nationwide community treatment programs (CTPs). All study participants either reported illicit drug use within the past 30 days or were discharged from a SUD treatment program within the past 60 days. Patients were randomized to 12-weeks of treatment as usual (TAU) or a reduced TAU condition where 2 hours of face-to-face therapy each week was replaced with use of TES (rTAU + TES). TAU was intensive face-to-face counseling at each CTP. Participants in the rTAU + TES arm of the study could access TES both off site and in clinic (with an opportunity for potential interaction with study staff during onboarding). A significant number

	(39%) of study participants accessed TES offsite (remotely). Study participants included “all-comers”: participants who reported recent use of stimulants, alcohol, cocaine, marijuana, and/or opioids. Although participants reported a primary substance of abuse, ninety-one percent used more than one substance. Given that non-abstinence at study start is a poor prognostic indicator, patients were randomized to study condition based on abstinence versus non-abstinence at study start. (1) All participants in the rTAU + TES group received contingency management (CM) rewards. Patients enrolled in the rTAU + TES group received virtual messages, prizes or vouchers for module completion and abstinence. CM rewards were not available for participants in the TAU group. The rewards for contingency management were small, ranging from $1 to $20 in monetary value, with smaller monetary rewards were more likely than larger rewards. The primary outcome measures of the pivotal study were abstinence from drug and alcohol use and treatment retention. Abstinence was measured twice a week (i.e., for each half-week) by Urine Drug Screen (UDS), Breathalyzer and Time-Line-Follow-Back (TLFB) self-report of substance use. Treatment retention was assessed by the date of the patient’s last-face-to-face contact with the clinician/therapist. The study results demonstrated that TES, when used with outpatient SUD therapy and contingency management, significantly improved abstinence and retention (refer ClinicalTrials.gov Identifier NCT01104805). (1) Abstinence results were divided into three cohorts for analysis, all-comers, cohort that excluded patients whose primary substance of abuse opioids, and a cohort that excluded patients that used any opioids. Patients in the cohort that excluded those whose primary substance of abuse opioids were not on opioid-replacement therapy (ORT), which is typically standard of care. Missing abstinence data was statistically treated as a treatment failure (not abstinent). (1) In the all-comer population analysis, patients who received rTAU + TES exhibited statistically significant improvements in abstinence compared to participants who received TAU alone, 29.7% vs 16.0% (odds ratio=2.22, 95% CI=1.24, 3.99; p= 0.0076). This effect was even more apparent in patients with the worst prognosis, those who were not abstinent at baseline. Among participants who were non-abstinent at baseline, 10.1% of participants who received rTAU + TES were abstinent during weeks 9-12 compared to 3.0% of those who received TAU (odds ratio 3.59, 95% CI=1.36, 9.48; p=0.0099). The subanalysis of participants by primary substance of abuse showed that TES was the most effective for individuals who reported cocaine as their primary substance of abuse and not effective for patients who report opioids as their primary substance of abuse. In

	the analysis of the Excluding Primary Opioids population of patients (excluding those who reported opioids as their primary substance of abuse *and* not on ORT), patients who received rTAU + TES exhibited statistically significant improvements in abstinence compared to participants who received TAU alone, 40.3% vs 17.6% (odds ratio=3.17, 95% CI=1.68, 5.99. p = 0.0004). Like the all-comers analysis, this effect was highly significant in patients with the worst prognosis, those who were not abstinent at baseline. Among participants who were non-abstinent at baseline, 16.1% of participants who received rTAU + TES were abstinent during weeks 9-12 compared to 3.2% of those who received TAU (odds ratio 5.74, 95% CI=1.99, 16.60; p=0.0013). Similar results were observed in the Excluding All Opioids population (excluding those who used any opioids during the study). A significant increase in abstinence rates were observed in the rTAU + TES group, 38.5% compared to 17.5% of participants who received TAU (Odds Ratio=2.95, 95% CI=1.43, 6.09, p=0.0034). A similar trend was observed among participants who were non-abstinent at baseline, 10.4% of participants who received rTAU + TES were abstinent during weeks 9-12 compared to 3.7% of those who received TAU (odds ratio 3.04, 95% CI=0.89, 10.43; p=0.0765). (1) Overall, improved abstinence rates were observed in all three cohorts demonstrating that TES/reSET is a digital therapy, when used as an adjunct to outpatient treatment, improves abstinence in patients with SUD, particularly those with historically poor outcomes and for those who do not report opioids as their primary substance of abuse. (1) Treatment program dropout during the 12-week intervention was reduced in the rTAU + TES group compared to the TAU group. This reduction in treatment dropout was significant. In the All-Comers Cohort, the dropout rate in the rTAU + TES group was 27.8% compared to 36.5% in the TAU group, with a p-value of 0.0316. This increase in treatment retention is important as treatment retention is strongly associated with positive outcomes. High attrition rates represent a significant problem to provisioning care to patients with SUD. The finding that rTAU + TES significantly improved patient retention rates strongly supports the efficacy of reSET. (1)
Safety	reSET has no FDA labeled contraindications for use. (1)

References

Number	Reference
1	reSET prescribing information. Pear Therapeutics, Inc. May 2022.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when BOTH of the following are met: 1. ONE of the following: A. The patient completed the previous 90 days of therapy with the requested agent **OR** B. BOTH of the following: 1. The patient has NOT completed the previous 90 days of therapy with the requested agent **AND** 2. The prescriber has provided information indicating the patient is now capable of completing a full course of therapy **AND** 2. The prescriber has provided information indicating that the patient would benefit from additional time with reSET **Length of Approval:** one additional course (90 day) per 365 days

reSET-O

Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
reSET-O® Digital therapeutic application	Cognitive behavioral therapy, as an adjunct to outpatient treatment that includes transmucosal buprenorphine and a contingency management system, for patients 18 years of age and older who are currently enrolled in outpatient treatment under the supervision of a clinician for Opioid Use Disorder. The intent is to increase retention in the outpatient treatment program		1

CLINICAL RATIONALE

Efficacy(1)	Therapeutic content utilized in reSET-O was validated in a randomized clinical trial (Clinical Trials identifier, NCT00929253). Note that the reSET-O mobile device app itself was not tested in the clinical trial; rather, the Therapeutic Education System (TES), which has equivalent content to reSET-O, was tested via an internet-connected browser delivery method. The study enrolled 170 patients seeking treatment for OUD. All study participants met DSM-IV criteria for opioid dependence and qualified for buprenorphine treatment. Patients were randomized to 12-weeks of treatment as usual (TAU) or TAU plus TES. TAU included three times weekly in-person administration of buprenorphine treatment, three times weekly urine testing, contingency management system, and a face to face visit with a clinician every other week. Patients receiving the TES condition completed web-based topics on the clinic computers at each clinic visit (three times a week) for approximately 30 minutes per visit. All study participants received contingency management (CM) rewards. This general approach has been validated as improving outcomes. Patients enrolled

	in the study received vouchers based on urine drug screen results. The first negative urine drug screen earned a credit worth $2.50 with escalating rewards for consecutive negative samples. Credits could be redeemed when a value of $100 or more was reached. The maximum amount that could be earned over the 12-week treatment was $997.50. The benefit of reSET-O without the use of CM was not demonstrated in this study, therefore it is unclear how the reSET-O device will perform if CM is not offered. The primary outcomes, measured over the course of treatment, were longest continuous abstinence, total abstinence, and days retained in treatment. Abstinence was measured three times a week (third-week) by Urine Drug Screen (UDS). Retention in treatment was assessed by last-face-to-face contact. The study results demonstrated that TES, when used with outpatient treatment, and contingency management, significantly improved retention among patients with previous treatment experience (dropout rate in the TES group was 17.6% compared to 31.6% in the TAU group, with a p-value of 0.0224). The ability of reSET-O to produce abstinence has not been established as clinically significant. Additionally, the addition of TES did not affect treatment retention in patients who were treatment naïve.
Safety(1)	reSET-O does not carry any FDA labeled contraindications for use.

References

Number	Reference
1	reSET-O prescribing information. Pear Therapeutics, Inc. May 2022.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when BOTH of the following are met: 1. ONE of the following: A. The patient completed the previous 84 days of therapy with the requested agent **OR** B. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The patient has NOT completed the previous 84 days of therapy with the requested agent **AND** 2. The prescriber has provided information indicating the patient is now capable of completing a full course of therapy **AND** 2. The prescriber has provided information indicating that the patient would benefit from additional time with reSET-O **Length of Approval:** one additional course (84 days) per 365 days

Retinoids (topical)

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Adapalene Gel* Pads Solution	Topical treatment of acne vulgaris	*generic available	3,12,13
Aklief® (trifarotene) Cream	Topical treatment of acne vulgaris in patients 9 years of age and older		19
Altreno® (tretinoin) Lotion	Topical treatment of acne vulgaris in patients 9 years of age and older		11
Arazlo® (tazarotene) Lotion	Topical treatment of acne vulgaris in patients 9 years of age and older		20
Atralin® (tretinoin) Gel*	Topical treatment of acne vulgaris	*generic available	1
CABTREO™ (adapalene/benzoyl peroxide/clindamycin)	Topical treatment of acne vulgaris in adult and pediatric patients 12 years of age and older		28

Agent(s)	FDA Indication(s)	Notes	Ref#
Gel			
Differin® (adapalene) Cream* Gel* Lotion	Cream (0.1%): Topical treatment of acne vulgaris Gel (0.3%) and Lotion (0.1%): Topical treatment of acne vulgaris in patients 12 years of age and older	*generic available	2,10,15
Epiduo® Forte (adapalene/benzoyl peroxide) Gel*	Topical treatment of acne vulgaris in adults and pediatric patients 12 years of age and older	*generic available	26
Epiduo® (adapalene/benzoyl peroxide) Gel*	Topical treatment of acne vulgaris in patients 9 years of age or older	*generic available	25
Fabior®, Tazarotene Foam	Topical treatment of acne vulgaris in patients 12 years of age or older		14
Retin-A® (tretinoin) Cream* Gel*	Topical application in the treatment of acne vulgaris	*generic available	4
Retin-A Micro® (tretinoin) Gel microsphere*	Topical application in the treatment of acne vulgaris	*generic available	5

Agent(s)	FDA Indication(s)	Notes	Ref#
Tazorac® (tazarotene) Cream* Gel*	Cream (0.1%): Topical treatment of plaque psoriasis Topical treatment of acne vulgaris Gel: • 0.05% and 0.1% gel are indicated for the topical treatment of patients with plaque psoriasis of up to 20% body surface area involvement • 0.1% gel is indicated for the topical treatment of mild to moderate severity facial acne vulgaris Limitations of Use: • The safety of Tazorac Gel use on more than 20% body surface area has not been established	*generic available	8,9
Twyneo® (tretinoin/benzoyl peroxide) Cream	Topical treatment of acne vulgaris in adults and pediatric patients 9 years of age and older		24

CLINICAL RATIONALE

Acne	Acne vulgaris is a common, chronic, inflammatory skin disorder of the pilosebaceous unit. Signs and symptoms include comedones, papules, pustules, or nodules on the face, but may also affect the upper arms, trunk, and back. Acne vulgaris most commonly occurs in adolescents, but it can affect most age groups and can persist into adulthood.(17,18) Topical therapies are the mainstay of acne treatment, and are used alone or in combination with other topical or oral agents. Using a combination of multiple mechanisms of action of topical therapies is recommended as multimodal therapy to optimize efficacy and

	reduce the risk of antibiotic resistance. Systemic oral antibiotics are typically used to treat moderate to severe acne. (17) Topical retinoids are vitamin A derivatives and are strongly recommended for the treatment of acne by the American Academy of Dermatology (AAD). Topical retinoid agents include tretinoin, adapalene, tazarotene, and trifarotene. Only modest differences in activity, tolerability, and efficacy have been noted between the different retinoids, and comparative effectiveness data does not suggest superiority of one topical retinoid against another.(17) BP is strongly recommended by the AAD for the treatment of acne. BP is a topical antimicrobial agent and is available over-the-counter. BP use is limited by concentration and formulation dependent side effects, including burning, stinging, dryness, erythema, and irritation. (17) Topical antibiotics are strongly recommended by the AAD for the treatment of acne and have both antibacterial and anti-inflammatory effects. Treatment options include erythromycin, clindamycin, minocycline, and dapsone. Topical antibiotic monotherapy is not recommended due to the risk of antibiotic resistance, and they should be used in combination with BP and/or a topical retinoid. There is a lack of evidence to suggest superiority of one topical antibiotic against another.(17) Fixed dose combination products of topical antibiotics, topical retinoids, and/or BP are strongly recommended by the AAD. Fixed dose combination products assist in treatment regimen adherence and may be less expensive than their individual components separately. When using a combination topical retinoid/antibiotic agent, it is recommended to use concomitant BP to prevent antibiotic resistance. Insufficient evidence is available to recommend topical BP, retinoids, antibiotics, or their combinations over one another.(17) Clascoterone (Winlevi) is a topical antiandrogen agent. It is conditionally recommended for the treatment of acne by the AAD due to treatment access and cost, despite a high certainty of benefits over risks. Azelaic acid is a topical comedolytic, antibacterial, and anti-inflammatory agent and is also conditionally recommended for the treatment of acne by the AAD. Azelaic acid may be beneficial for patients with sensitive skin or dyspigmentation due to its lightening effects. Insufficient evidence is available to develop a recommendation on the use of topical sodium sulfacetamide for acne even though it is used in practice.(17)
Additional Information	The age limit of 40 years or older as the edit parameter has been based on analysis of National Ambulatory Medical Care Survey (NAMCS) data (1990-

	1994)(21) and (1990-2004).(22) In the initial analysis, acne-related treatment with tretinoin was equal to non-acne conditions around 44 years of age.(21) The second analysis confirmed that there was a “minute probability” of non-acne-related use of topical retinoids in the population aged 40 years and younger.(22) The authors of the NAMCS data evaluations suggest a minimum age of 40 years as a cut-off to determine coverage of retinoid agents for acne.(21,22) These analyses were consistent with a study of the prevalence of acne in adults in the United Kingdom (UK). Data from the UK study indicated the prevalence of acne did not substantially decline between the ages of 24 and 44 years of life but fell significantly after 45 years of age.(23)
Safety	Adapalene is contraindicated for use in individuals who are hypersensitive to adapalene or any of the components in the vehicle.(3,12,13) Aklief has no FDA labeled contraindications for use.(19) Altreno has no FDA labeled contraindications for use.(11) Arazlo is contraindicated in pregnancy.(20) Atralin has no FDA labeled contraindications for use.(1) CABTREO is contraindicated in the following:(28) • Individuals with known hypersensitivity to clindamycin, adapalene, benzoyl peroxide, any components of the formulation, or lincomycin • History of regional enteritis, ulcerative colitis, or antibiotic-associated colitis Differin is contraindicated for use in individuals who have known hypersensitivity to adapalene or any of the components in the vehicle.(2,10,15) Epiduo has no FDA labeled contraindications for use.(25) Epiduo Forte is contraindicated in patients with a history of hypersensitivity reactions to benzoyl peroxide or any components of the formulation in Epiduo Forte.(26) Fabior is contraindicated in pregnancy.(14)

	Retin-A is contraindicated for use in individuals who have hypersensitivity to any of the ingredients.(4) Retin-A Micro has no FDA labeled contraindications for use.(5) Tazorac is contraindicated in the following:(8,9) • Pregnancy • Individuals who have a known hypersensitivity to any of its components Twyneo is contraindicated in patients with a history of hypersensitivity reaction to benzoyl peroxide or any components of Twyneo.(24)

REFERENCES

Number	Reference
1	Atralin prescribing information. Bausch Health US, LLC. February 2024.
2	Differin Gel 0.3% prescribing information. Galderma Laboratories, L.P. December 2023.
3	Adapalene 0.1% gel prescribing information. PruGen, Inc. January 2018.
4	Retin-A prescribing information. Bausch Health US, LLC. May 2024.
5	Retin-A Micro prescribing information. Bausch Health US, LLC. April 2024.
6	Reference no longer used.
7	Reference no longer used.
8	Tazorac Gel prescribing information. Almirall, LLC. February 2020.
9	Tazorac Cream prescribing information. Almirall, LLC. December 2022.
10	Differin Cream prescribing information. Galderma Laboratories, L.P. October 2022.
11	Altreno lotion prescribing information. Bausch Health US, LLC. March 2020.

Number	Reference
12	Adapalene 0.1% solution prescribing information. Rochester Pharmaceuticals. October 2023.
13	Adapalene 0.1% swab prescribing information. Rochester Pharmaceuticals. October 2023.
14	Fabior prescribing information. Mayne Pharma. May 2024.
15	Differin Lotion 0.1% prescribing information. Galderma Laboratories, LP. April 2023.
16	Reference no longer used.
17	Reynolds RV, Yeung H, Cheng CE, et al. Guidelines of care for the management of acne vulgaris. *Journal of the American Academy of Dermatology*. 2024;90(5):1006.e1-1006.e30. doi:10.1016/j.jaad.2023.12.017
18	Sutaria AH, Masood S, Saleh HM, Schlessinger J. Acne vulgaris. StatPearls - NCBI Bookshelf. Published August 17, 2023. https://www.ncbi.nlm.nih.gov/books/NBK459173/
19	Aklief prescribing information. Galderma Laboratories, L.P. October 2023.
20	Arazlo prescribing information. Bausch Health US, Inc. September 2023.
21	McConnel RC, Fleisher AB, Williford PM, Feldman SR. Most topical tretinoin treatment is for acne vulgaris through the age of 44 years: An analysis of the National Ambulatory Medical Care Survey, 1990-1994. *J Am Acad Dermatol.* 1998;38:221-226.
22	Balkrishnan R, Bhosle MJ, Camacho F, Fleischer Jr AB, Feldman SR. Prescribing patterns for topical retinoids: Analyses of 15 years of data from the National Ambulatory Medical Care Survey. *J Dermatol Treat.* 2010;21:193-200.
23	Goulden V, Stables GI, Cunliffe WJ. Prevalence of acne in adults. *J Am Acad Dermatol.* 1999;41(4):577-580.
24	Twyneo prescribing information. Galderma Laboratories L.P. July 2023.
25	Epiduo prescribing information. Galderma Laboratories, L.P. February 2018.
26	Epiduo Forte prescribing information. Galderma Laboratories, L.P. April 2022.

Number	Reference
27	Reference no longer used.
28	CABTREO prescribing information. Bausch Health US, LLC. November 2023.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Brand Retinoids	**Brand Retinoid Agent(s)** will be approved when ALL of the following are met: 1. The patient is 40 years of age or over **AND** 2. The patient is not using the requested agent for treatment of wrinkles, stretch marks, age spots, or skin lightening **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response to a generic topical retinoid **OR** B. The patient has an intolerance or hypersensitivity to a generic topical retinoid **OR** C. The patient has an FDA labeled contraindication to ALL generic topical retinoids **Length of Approval:** 12 months
Generic Retinoids	**Generic Retinoid Agent(s)** will be approved when BOTH of the following are met: 1. The patient is 40 years of age or over **AND** 2. The patient is not using the requested agent for treatment of wrinkles, stretch marks, age spots, or skin lightening **Length of Approval:** 12 months

Rezurock (belumosudil)

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Rezurock® (belumosudil) Tablet	Treatment of adult and pediatric patients 12 years and older with chronic graft-versus-host disease (chronic GVHD) after failure of at least two prior lines of systemic therapy		1

CLINICAL RATIONALE

Graft-Versus-Host-Disease	Chronic graft-versus-host disease (cGVHD) is the leading cause of non-relapse mortality (NRM) after an allogeneic hematopoietic cell transplant (HCT), has a profound impact on quality of life. cGVHD usually develops within the first year after HCT in most patients, but it can also develop many years later. cGVHD affects multiple organ systems and is characterized by fibrosis and variable clinical features resembling autoimmune disorders.(2) Standard of care in the treatment of cGvHD depends on the particular organ(s) or site(s) that is/are affected and adopted treatments can be topical or systemic. About 50%–60% of patients with cGvHD will require a second-line treatment within 2 years.(4,5) Approximately 40% to 50% of patients with acute or chronic GVHD develop steroid-refractory disease, which is associated with high mortality. Currently, ruxolitinib, ibrutinib, and belumosudil are the only FDA-approved agents for treatment of steroid-refractory cGVHD.(2,3)
Efficacy	Study KD025-213 (NCT03640481) was a randomized, open-label, multicenter study of Rezurock for treatment of patients with chronic GVHD who had received 2 to 5 prior lines of systemic therapy and required additional treatment. There were 66 patients treated with Rezurock 200 mg taken orally once daily. Concomitant treatment with supportive care therapies for chronic GVHD was permitted. Concomitant treatment with GVHD prophylaxis and standard care systemic chronic GVHD therapies was permitted as long as the subject has been on a stable dose for at least 2 weeks prior to study. Initiation of new systemic chronic GVHD therapy while on study was not permitted.(1,6)

	The efficacy of Rezurock was based on overall response rate (ORR) through Cycle 7 Day 1 where overall response included complete response or partial response according to the 2014 NIH Response Criteria. The ORR was 75% (95% CI: 63, 85). The median duration of response, calculated from first response to progression, death, or new systemic therapies for chronic GVHD, was 1.9 months (95% CI: 1.2, 2.9). The median time to first response was 1.8 months (95% CI: 1.0, 1.9). In patients who achieved response, no death or new systemic therapy initiation occurred in 62% (95% CI: 46, 74) of patients for at least 12 months since response.(1,6) ORR results were supported by exploratory analyses of patient-reported symptom bother which showed at least a 7-point decrease in the Lee Symptom Scale summary score through Cycle 7 Day 1 in 52% (95% CI: 40, 65) of patients. The median duration of response was 54 weeks; 44% of patients remained on therapy for greater than or equal to one year. Overall median follow-up was 14 months.(1,6)
Safety	Rezurock carries no boxed warnings or contraindications.(1)

REFERENCES

Number	Reference
1	Rezurock prescribing information. Kadmon Pharmaceuticals, LLC. April 2023.
2	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology - Hematopoietic Cell Transplantation (HCT). Version 1.2023.
3	Hamilton BK. Updates in Chronic Graft-Versus-Host Disease. Hematology Am Soc Hematol Educ Program. 2021;1:648–654.
4	Wolff D, Fatobene G, Rocha V, et al. Steroid-Refractory Chronic Graft-Versus-Host Disease: Treatment Options and Patient Managment. Bone Marrow Transplant. 2021 Jul;56:2079-2087.
5	Saidu NEB, Bonini C, Dickinson A, et al. New Approaches for the Treatment of Chronic Graft-Versus-Host Disease: Current and Future Directions. Front Immunol. 2020;11:578314.
6	Cutler C, Lee SJ, Arai S. Belumosudil for Chronic Graft-Versus-Host Disease after Two or More Prior Lines of Therapy: the ROCKstar Study. Blood. 2021 Dec;138(22):2278-2289.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** Rezurock 1. Information has been provided that indicates the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. The patient has chronic graft-versus-host disease (chronic GVHD) **AND** 2. The patient has failed at least two prior lines of systemic therapy **AND** 2. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist, oncologist) or has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to therapy with the requested agent **Length of Approval:** 12 months Note: If Quantity Limit applies, please refer to Quantity Limit criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met:

Module	Clinical Criteria for Approval
	1. The patient has been previously approved for the requested agent through the plan's Prior Authorization Review process **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hematologist, oncologist) or has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months Note: If Quantity Limit applies, please refer to Quantity Limit criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. The prescriber has provided information in support of therapy with a higher dose for the for the requested indication **Length of Approval:** 12 months

Rho Kinase Inhibitor

Quantity Limit

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Risdiplam

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Evrysdi® (risdiplam) Powder for oral solution	Treatment of spinal muscular atrophy (SMA) in pediatric and adult patients		1

CLINICAL RATIONALE

Spinal Muscular Atrophy	Spinal muscular atrophy (SMA) is the second most common autosomal recessive neurodegenerative disorder, caused by bi-allelic loss or dysfunction of the survival motor neuron 1 (SMN1) gene.(2,11) SMA is characterized by dysfunction and then loss of the alpha motor neurons in the spinal cord that causes progressive muscle atrophy and weakness.(10) The SMN1 and SMN2 genes are all located on chromosome 5q13.2, an unstable chromosomal region that is prone to deletion, duplication, and gene conversion. There are two forms of survival motor neuron (SMN), SMN1 and SMN2, that differ by only five nucleotides.(5) SMN1 is the primary gene responsible for functional production of SMN protein. SMN1 produces a full-length transcript that encodes functional SMN protein.(3) SMN1 can be absent because of deletion or SMN1-to-SMN2 conversion.(5) The most common mutation causing SMA is a homozygous deletion of the SMN1 exon 7.(11) SMN2 preferentially excludes exon 7 during splicing and, as a result, produces only a small fraction of functional SMN protein as compared with SMN1.(3) Because SMN2 produces a reduced number of full-length transcripts, the number of SMN2 copies can modify the clinical phenotype and is an essential predictive factor.(3,11) About 94% of SMA patients have a homozygous deletion of SMN1 exon 7. SMA has an incidence of approximately 1 in 10,000 live births and a carrier frequency of approximately 1 in 54.(3) SMA is classified into four subtypes (1-4) based on age of onset of symptoms and motor milestone achievement. This variability in the clinical phenotype is largely a result of the number of copies of the survival motor neuron 2 (SMN2)

gene. The SMA type 1 (SMA1) phenotype is the most severe.(2) The presence of two copies of SMN2 is associated with SMA1. Infants with SMN1 bi-allelic deletions and two copies of SMN2 have a 97% risk of SMA1.(3)

Clinical Classification of SMA(11)

SMA Type	Number of SMN2 Copies	Percent of Cases	Age of Onset	Highest Achieved Motor Function	Natural Age of Death Prior to Disease Modifying Therapy
0	1	Rare, less than 1%	Prenatal, at birth	Non-sitter, no head control	Death within weeks of birth
1	1-2	45%	0-6 months	Non-sitter	Death by age 2
2	3	20%	6-18 month	Sit independently, never stands or ambulates	Most alive at 25 years
3	3-4	30%	3a: 18 months-3 years 3b: 3-30 years	Ambulates independently	Normal lifespan
4	Greater than or equal to 4	Less than 5%	Greater than 30 years	Ambulates independently	Normal lifespan

The onset of symptoms for SMA1 occurs shortly after birth and prior to six months of age with a clinical hallmark of the inability to achieve independent sitting.(2) A historical cohort showed that the median age at symptom onset among infants with the disease was 1.2 months (range, 0 to 4

	months).(3) Infants with SMA1 rapidly lose motor function and ultimately succumb to respiratory complications often within the first year of life. Studies of SMA1 infants with two SMN2 copies offered standard of care showed a median age of death or permanent ventilation (greater than or equal to 16h/day for at least 14 consecutive days) that ranged from 8 to 10.5 months.(2) Patients with SMA1 do not achieve major milestones in function and have a decline in function, as measured on the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scale, which ranges from 0 to 64, with higher scores indicating better motor function. In a historical analysis of 34 patients with SMA1, all but one of the patients did not reach a score of at least 40 after 6 months of age. In another cohort, CHOP-INTEND scores decreased by a mean of 10.7 points from 6 months to 12 months of age.(3) Molecular genetic testing is the standard tool for diagnosis of SMA. Genetic testing for homozygous deletion will confirm the disease in 95% of patients. Essentially all other patients with SMN-related SMA will be compound heterozygotes with a single SMN1 deletion and a mutation in the other SMN1 copy.(4) Guidelines recommend use of age-appropriate testing to advise initiation and follow-up of drug therapy in SMA patients. They acknowledge that the tests vary in availability, physician expertise and preference, and the patient's ability, based on age, to participate. The function assessments that were considered for use in SMA patients were CHOP-INTEND, Hammersmith Infant Neurological Examination (HINE-2), Hammersmith Functional Motor Scale-Expanded (HFMSE), six-minute walk test (6MWT), Revised Upper Limb Module (RULM) test, and Bayley Scales of Infant and Toddler Development (BSID). Risdiplam efficacy trials utilized Bayley Scales of Infant and Toddler development, Third Edition (BSID-III), and Motor Function Measurement score (MFM32).(10) In addition to risdiplam, there are two additional FDA-approved therapies for SMA, Zolgensma and Spinraza. Zolgensma is an SMN1 gene transfer via adenovirus vector dosed once via intravenous infusion.(6,11) Spinraza, a modified antisense oligonucleotide the binds SMN2 mRNA to modify splicing, causing an increase in SMN protein production. Spinraza is administered as an intrathecal injection dosed every four months after completing a loading dose series.(7,11)
Efficacy	Risdiplam modifies pre-mRNA splicing of SMN2, increasing the production of SMN2. Risdiplam's New Drug Application included two clinical trials: FIREFISH (NCT02913482) and SUNFISH (NCT02908685). FIREFISH was an open-label, multi-center clinical study to assess the safety, tolerability, pharmacokinetic, pharmacodynamics, and efficacy of risdiplam in infants with Type 1 SMA. It

	consisted of an exploratory dose finding segment and a confirmatory segment that investigated risdiplam for 24-months. Primary outcome measures were finding the recommended segment 2 dose of risdiplam, and in segment 2, finding the percentage of infants who are sitting without support at 12-months of treatment, assessed by the Gross Motor Scale of the Bayley Scales of Infant and Toddler development, Third Edition (BSID-III). Inclusion criteria included a clinical history of Type 1 SMA with onset after 28 days but prior to three months, a confirmed diagnosis of 5q-autosomal SMA, and having two SMN2 gene copies. Exclusion criteria included concomitant or previous administration of a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier, or gene therapy, patients that were hospitalized for a pulmonary event within the last two months, requiring invasive ventilation or tracheostomy, and patients with unstable GI, renal, hepatic, endocrine, or cardiovascular disease.(8) SUNFISH was a multi-center, double-blind, placebo-controlled, Phase II/III study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in adult and pediatric participants with Type 2 and Type 3 SMA. There were two segments to the study: a 12-week exploratory dose finding segment and a 24-month confirmatory segment. Outcome (motor function) was assessed by the 32-item Motor Function Measure score (MFM32). At one year, risdiplam treatment led to clinically meaningful improvement, with an average increase in MFM36 score of 1.36, compared with an average 0.19 decrease in MFM32 score for the placebo group. The inclusion criteria for segment 2 were patients with Type 2 or 3 SMA (with a confirmed diagnosis of 5q-autosomal recessive SMA) that were non-ambulatory and a negative blood pregnancy test. Exclusion criteria included concomitant or previous administration of a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier, or gene therapy, patients that were hospitalized for a pulmonary event within the last two months, unstable GI, renal, hepatic, endocrine, or cardiovascular disease considered to be clinically significant by the investigator, or requirement of invasive ventilation or tracheostomy.(9)
Safety	Risdiplam has no FDA labeled contraindications for use.(1)

REFERENCES

Number	Reference
1	Evrysdi prescribing information. Genentech, Inc. March 2023.
2	Al-Zaidy S, Pickard AS, Kotha K, et al. Health outcomes in spinal muscular atrophy type 1 following AVXS-101 gene replacement therapy. *Pediatr Pulmonol.* 2019;54(2):179-185.
3	Mendell JR, Al-Zaidy S, Shell R, et al. Single-Dose Gene Replacement Therapy for Spinal Muscular Atrophy. *N Engl J Med* 2017;377:1713-22.
4	Arnold WA, Kassar D, Kissel JT. Spinal Muscular Atrophy: Diagnosis and Management in a New Therapeutic Era. *Muscle Nerve* 2015 Feb;51(2):157-167. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4293319/
5	Fang P, Li L, Zeng J, et al. Molecular Characterization and Copy Number of SMN1, SMN2 and NAIP in Chinese Patients with Spinal Muscular Atrophy and Unrelated Healthy Controls. *BMC Musculoskelet Disord.* 2015;16(1):11.
6	Zolgensma Prescribing Information. Novartis Gene Therapy, Inc. February 2023.
7	Spinraza Prescribing Information. Biogen. February 2023.
8	Investigate Safety, Tolerability, PK, PD and Efficacy of Risdiplam (RO7034067) in Infants With Type 1 Spinal Muscular Atrophy (FIREFISH). https://clinicaltrials.gov/ct2/show/NCT02913482
9	A Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of Risdiplam (RO7034067) in Type 2 and 3 Spinal Muscular Atrophy (SMA) Participants (SUNFISH). https://clinicaltrials.gov/ct2/show/NCT02908685
10	Glascock J, Sampson J, Haidet-Phillips A, et al. Treatment Algorithm for Infants Diagnosed with Spinal Muscular Atrophy through Newborn Screening. *J Neuromuscul Dis*. 2018;5(2):145-158.
11	Keinath MC, Prior DE, Prior TW. (2021). Spinal Muscular Atrophy: Mutations, Testing, and Clinical Relevance. *The application of clinical genetics,* 14, 11-25. https://doi.org/10.2147/TACG.S239603

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of Spinal Muscular Atrophy (SMA) type 1, 2, or 3 **AND** 2. The patient's diagnosis was confirmed by genetic testing confirming the mutation or deletion of genes in chromosome 5q (medical records required) **AND** 3. The patient has had at least ONE of the following baseline (prior to starting therapy with the requested agent) functional assessments based on patient age and motor ability: A. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) B. Hammersmith Infant Neurological Examination (HINE-2) C. Hammersmith Functional Motor Scale-Expanded (HFMSE) D. Six-minute walk test (6MWT) E. Bayley Scales of Infant and Toddler Development (BSID) F. Motor Function Measurement score (MFM32) G. Revised Upper Limb Module (RULM) test **AND** 4. The patient does NOT require invasive ventilation or tracheostomy **AND** 5. The patient has not received gene therapy for the requested indication (e.g., Zolgensma [onasemnogene abeparvovec-xioi]) **AND** 6. If the patient has used Spinraza (nusinersen) in the last four months, they will complete a four-month washout period between the last Spinraza (nusinersen) dose and the initiation of therapy with the requested agent **AND** 7. The patient will NOT be using the requested agent in combination with Spinraza (nusinersen) **AND** 8. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 9. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation**

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. The patient has had improvements or stabilization from baseline (prior to starting therapy with the requested agent) with the requested agent as indicated by one of the following functional assessments based on patient age and motor ability: A. Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) B. Hammersmith Infant Neurological Examination (HINE-2) C. Hammersmith Functional Motor Scale-Expanded (HFMSE) D. Six-minute walk test (6MWT) E. Bayley Scales of Infant and Toddler Development (BSID) F. Motor Function Measurement score (MFM32) G. Revised Upper Limb Module (RULM) test **AND** 3. The patient does NOT require invasive ventilation or tracheostomy **AND** 4. The patient has not received gene therapy for the requested indication (e.g., Zolgensma [onasemnogene abeparvovec-xioi]) **AND** 5. The patient will NOT be using the requested agent in combination with Spinraza (nusinersen) **AND** 6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND**

Module	Clinical Criteria for Approval
	B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** 12 months

Self-Administered Oncology Agents

Prior Authorization with Quantity Limit

CLINICAL RATIONALE

<table>
<tr><td>Indications</td><td>For the purposes of the Self-Administered Oncology Agents criteria, indications deemed appropriate are those within FDA labeling or supported in the allowed compendia (National Comprehensive Cancer Network [NCCN] Drugs & Biologics Compendium with a 1 or 2a recommended use, American Society of Health-System Pharmacists [AHFS], DrugDex level of evidence 1 or 2a).</td></tr>
<tr><td>Safety</td><td>
<table>
<tr><th>Agents</th><th>Boxed Warnings and Contraindications</th></tr>
<tr><td>Afinitor/Afinitor Disperz (everolimus)(3)</td><td>Contraindicated in patients with clinically significant hypersensitivity to everolimus or to other rapamycin derivatives.</td></tr>
<tr><td>Akeega (niraparib and abiraterone)(114)</td><td>None</td></tr>
<tr><td>Alecensa (alectinib)(4)</td><td>None</td></tr>
<tr><td>Alunbrig (brigatinib)(5)</td><td>None</td></tr>
<tr><td>Augtyro (repotrectinib)(118)</td><td>None</td></tr>
<tr><td>Ayvakit (avapritinib)(6)</td><td>None</td></tr>
<tr><td>Balversa (erdafitinib)(7)</td><td>None</td></tr>
<tr><td>BESREMi (ropeginterferon alfa-2b-njft)(8)</td><td>BESREMi has a boxed warning for risk of serious disorders:
Interferon alfa products may cause or aggravate fatal or life-threatening</td></tr>
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</td></tr>
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		neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping therapy. BESREMi is contraindicated in patients with: • Existence of, or history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt. • Hypersensitivity to interferons including interferon alfa-2b or any of the inactive ingredients of BESREMi. • Moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment. • History or presence of active serious or untreated autoimmune disease. • History of transplantation and receiving immunosuppressant agents.
	Bosulif (bosutinib)(9)	Contraindicated in patients with a history of hypersensitivity to bosutinib.

	Braftovi (encorafenib)(10)	None
	Brukinsa (zanubrutinib)(11)	None
	Cabometyx (cabozantinib)(12)	None
	Calquence (acalabrutinib)(13)	None
	Caprelsa (vandetanib)(14)	Caprelsa has a boxed warning for QT prolongation, torsades de pointes, and sudden death: • Caprelsa can prolong the QT interval. Torsades de pointes and sudden death have occurred in patients receiving Caprelsa. Do not use Caprelsa in patients with hypocalcemia, hypokalemia, hypomagnesemia, or long QT syndrome. Correct hypocalcemia, hypokalemia and/or hypomagnesemia prior to Caprelsa administration. Monitor electrolytes periodically. Avoid drugs known to prolong the QT interval. Contraindicated in patients with congenital long QT syndrome.
	Cometriq (cabozantinib)(15)	None
	Copiktra (duvelisib)(16)	Copiktra has a boxed warning for treatment-related mortality and serious toxicities: infections, diarrhea or colitis, cutaneous reactions, and pneumonitis:

		• Treatment-related mortality occurred in 15% of Copiktra-treated patients. • Fatal and/or serious infections occurred in 31% of Copiktra-treated patients. Monitor for signs and symptoms of infection. Withhold Copiktra if infection is suspected. • Fatal and/or serious diarrhea or colitis occurred in 18% of Copiktra-treated patients. Monitor for the development of severe diarrhea or colitis. Withhold Copiktra. • Fatal and/or serious cutaneous reactions occurred in 5% of Copiktra-treated patients. Withhold Copiktra. • Fatal and/or serious pneumonitis occurred in 5% of COPIKTRA-treated patients. Monitor for pulmonary symptoms and interstitial infiltrates. Withhold Copiktra. Copiktra has no contraindications of use.
	Cotellic (cobimetinib)(17)	None
	Daurismo (glasdegib)(18)	Daurismo has a boxed warning for embryo-fetal toxicity: • Daurismo can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Daurismo is embryotoxic, fetotoxic, and teratogenic in animals.

		• Conduct pregnancy testing in females of reproductive potential prior to initiation of Daurismo treatment. Advise females of reproductive potential to use effective contraception during treatment with Daurismo and for at least 30 days after the last dose. • Advise males of the potential risk of Daurismo exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with Daurismo and for at least 30 days after the last dose to avoid potential drug exposure. Daurismo has no contraindications of use.
	Erivedge (vismodegib)(19)	Erivedge has a boxed warning for embryo-fetal toxicity: • Erivedge can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Erivedge is embryotoxic, fetotoxic, and teratogenic in animals. Teratogenic effects included severe midline defects, missing digits, and other irreversible malformations. • Verify the pregnancy status of females of reproductive potential within 7 days prior to initiating Erivedge. Advise

		pregnant women of the potential risks to a fetus. Advise females of reproductive potential to use effective contraception during and after Erivedge. • Advise males of the potential risk of Erivedge exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential. Erivedge has no contraindications of use.
	Erleada (apalutamide)(20)	None
	Fotivda (tivozanib)(23)	None
	Fruzaqla (fruquintinib)(116)	None
	Gavreto (pralsetinib)(24)	None
	Gilotrif (afatinib)(25)	None
	Gleevec (imatinib)(26)	None
	Hycamtin (topotecan)(27)	Hycamtin has a boxed warning for myelosuppression: • Hycamtin can cause severe myelosuppression. Administer first cycle only to patients with baseline neutrophil counts of greater than or equal to 1,500/mm^3 and platelet counts greater than or equal to 100,000/mm^3. Monitor blood cell counts.

		Contraindicated in patients with a history of severe hypersensitivity to topotecan.
	Ibrance (palbociclib)(28)	None
	Iclusig (ponatinib)(29)	Iclusig has a boxed warning for arterial occlusive events, venous thromboembolic events (VTE), heart failure, and hepatotoxicity: • Arterial occlusive events (AOEs), including fatalities, have occurred in Iclusig-treated patients. AOEs included fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures. Patients with and without cardiovascular risk factors, including patients age 50 years or younger, experienced these events. Monitor for evidence of AOEs. Interrupt or discontinue Iclusig based on severity. • VTEs have occurred in Iclusig-treated patients. Monitor for evidence of VTEs. Interrupt or discontinue Iclusig based on severity. • Heart failure, including fatalities, occurred in Iclusig-treated patients. Monitor for heart failure and manage patients as clinically indicated. Interrupt or

		discontinue Iclusig for new or worsening heart failure. • Hepatotoxicity, liver failure and death have occurred in Iclusig-treated patients. Monitor liver function tests. Interrupt or discontinue Iclusig based on severity. Iclusig has no contraindications of use.
	Idhifa (enasidenib)(30)	Idhifa has a boxed warning for differentiation syndrome: • Patients treated with Idhifa have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, lymphadenopathy, bone pain, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution. Idhifa has no contraindications of use.
	Imbruvica (ibrutinib)(31)	None
	Inlyta (axitinib)(32)	None
	Inqovi (decitabine/ cedazuridine)(33)	None

	Inrebic (fedratinib)(34)	Inrebic has a boxed warning for encephalopathy including Wernicke's: • Serious and fatal encephalopathy, including Wernicke's, has occurred in patients treated with Inrebic. Wernicke's encephalopathy is a neurologic emergency. Assess thiamine levels in all patients prior to starting Inrebic, periodically during treatment, and as clinically indicated. Do not start Inrebic in patients with thiamine deficiency; replete thiamine prior to treatment initiation. If encephalopathy is suspected, immediately discontinue Inrebic and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize. Inrebic has no contraindications of use.
	Iressa (gefitinib)(35)	None
	Iwilfin (eflornithine)(120)	None
	Jakafi (ruxolitinib)(36)	None
	Jaypirca (pirtobrutinib)(110)	None
	Kisqali (ribociclib)(38)	None

	Kisqali Femara Pack (ribociclib and letrozole co-packaged)(37)	Contraindicated in patients with known hypersensitivity to letrozole or any excipients of Femara.
	Koselugo (selumetinib)(39)	None
	Krazati (adagrasib)(109)	None
	Lazcluze (lazertinib)(2)	None
	Lenvima (lenvatinib)(40)	None
	Lonsurf (trifluridine/tipiracil)(41)	None
	Lorbrena (lorlatinib)(42)	Contraindicated in concomitant use with a strong CYP3A inducer, due to potential for serious hepatotoxicity.
	Lumakras (sotorasib)(43)	None
	Lynparza (olaparib)(44)	None
	Lysodren (mitotane)(45)	Lysodren has a boxed warning for adrenal crisis in the setting of shock, severe trauma or infection: • Patients treated with Lysodren are at increased risk for developing adrenal crisis in the setting of shock, severe trauma or infection that may lead to death. • If shock, severe trauma or infection occurs or develops, temporarily discontinue Lysodren and administer exogenous steroids. Monitor patients closely for infections and instruct patients to contact their physician immediately if injury,

		infection, or any other concomitant illness occurs. Lysodren has no contraindications of use.
	Lytgobi (futibatinib)(107)	None
	Matulane (procarbazine)(46)	Matulane has a boxed warning that recommends that Matulane be given only by or under the supervision of a physician experienced in the use of potent antineoplastic drugs. Adequate clinical and laboratory facilities should be available to patients for proper monitoring of treatment. Contraindicated in patients with known hypersensitivity to the drug or inadequate marrow reserve as demonstrated by bone marrow aspiration.
	Mekinist (trametinib)(47)	None
	Mektovi (binimetinib)(48)	None
	Nerlynx (neratinib)(49)	None
	Nexavar (sorafenib)(50)	Contraindicated in the following: • Patients with known severe hypersensitivity to sorafenib or any other component of Nexavar. • Combination with carboplatin and paclitaxel in patients with squamous cell lung cancer.
	Ninlaro (ixazomib)(51)	None

	Nubeqa (darolutamide)(52)	None
	Odomzo (sonidegib)(53)	Odomzo has a boxed warning for embryo-fetal toxicity: • Odomzo can cause embryo-fetal death or severe birth defects when administered to a pregnant woman. Odomzo is embryotoxic, fetotoxic, and teratogenic in animals. • Verify the pregnancy status of females of reproductive potential prior to initiating therapy. Advise females of reproductive potential to use effective contraception during treatment with Odomzo and for at least 20 months after the last dose. • Advise males of the potential risk of exposure through semen and to use condoms with a pregnant partner or a female partner of reproductive potential during treatment with Odomzo and for at least 8 months after the last dose. Odomzo has no contraindications of use.
	Ogsiveo (nirogacestat)(119)	None
	Ojemda (tovorafenib)(121)	None
	Ojjaara (momelotinib)(115)	None

	Onureg (azacitidine)(54)	Contraindicated in patients with history of severe hypersensitivity to azacitidine or its components.
	Orgovyx (relugolix)(55)	Contraindicated in patients with known severe hypersensitivity to relugolix or to any of the product components.
	Orserdu (elacestrant)(111)	None
	Pemazyre (pemigatinib)(56)	None
	Piqray (alpelisib)(57)	Contraindicated in patients with a severe hypersensitivity to Piqray or to any of its components.
	Pomalyst (pomalidomide)(58)	Pomalyst has a boxed warning for embryo-fetal toxicity and venous and arterial thromboembolism: • Pomalyst is contraindicated in pregnancy. Pomalyst is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting Pomalyst treatment. • Deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction, and stroke occur in patients with multiple myeloma treated with Pomalyst. Prophylactic antithrombotic measures were employed in clinical trials.

		Thromboprophylaxis is recommended, and the choice of regimen should be based on assessment of the patient's underlying risk factors. Pomalyst is only available through a restricted distribution program called the Pomalyst REMS. Contraindicated in patients who have demonstrated severe hypersensitivity (e.g., angioedema, anaphylaxis) to pomalidomide or any of the excipients.
	Qinlock (ripretinib)(59)	None
	Retevmo (selpercatinib)(60)	None
	Revlimid (lenalidomide)(61)	Revlimid has a boxed warning for embryo-fetal toxicity, hematologic toxicity, and venous and arterial thromboembolism: • Do not use Revlimid during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. • Revlimid can cause significant neutropenia and thrombocytopenia.

		• Revlimid has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE), as well as risk of myocardial infarction and stroke in patients with multiple myeloma who were treated with Revlimid and dexamethasone therapy. Contraindicated in patients with severe hypersensitivity to lenalidomide. Contraindicated in pregnancy and can cause fetal harm when administered to a pregnant female.
	Rezlidhia (olutasidenib)(108)	Rezlidhia has a boxed warning for differentiation syndrome: • Differentiation syndrome, which can be fatal, can occur with Rezlidhia treatment. Symptoms may include dyspnea, pulmonary infiltrates/pleuropericardial effusion, kidney injury, hypotension, fever, and weight gain. • If differentiation syndrome is suspected, withhold Rezlidhia and initiate treatment with corticosteroids and hemodynamic monitoring until symptom resolution. Rezlidhia has no contraindications of use.
	Rozlytrek (entrectinib)(62)	None

	Rubraca (rucaparib)(63)	None
	Rydapt (midostaurin)(64)	Contraindicated in patients with hypersensitivity to midostaurin or any of the excipients.
	Scemblix (asciminib)(65)	None
	Sprycel (dasatinib)(66)	None
	Stivarga (regorafenib)(67)	Stivarga has a boxed warning for hepatotoxicity: • Severe and sometimes fatal hepatotoxicity has occurred in clinical trials. • Monitor hepatic function prior to and during treatment. • Interrupt and then reduce or discontinue Stivarga for hepatotoxicity as manifested by elevated liver function tests or hepatocellular necrosis, depending upon severity and persistence. Stivarga has no contraindications of use.
	Sutent (sunitinib)(68)	Sutent has a boxed warning for hepatotoxicity: • Hepatotoxicity may be severe, and in some cases, fatal. Monitor hepatic function and interrupt, dose reduce, or discontinue Sutent as recommended. Sutent has no contraindications of use.

	Tabrecta (capmatinib)(69)	None
	Tafinlar (dabrafenib)(70)	None
	Tagrisso (osimertinib)(71)	None
	Talzenna (talazoparib)(72)	None
	Tarceva (erlotinib)(73)	None
	Targretin (bexarotene) capsules(74)	Targretin capsules has a boxed warning for birth defects: • It is a member of the retinoid class of drugs that is associated with birth defects in humans. Targretin must not be administered to a pregnant woman. Contraindicated in the following: • Pregnancy. Targretin can cause fetal harm when administered to a pregnant female. • Patients with a known serious hypersensitivity to bexarotene or other components of the product.
	Targretin (bexarotene) gel(75)	Contraindicated in the following: • Pregnancy. Targretin can cause fetal harm when administered to a pregnant female. • Patients with known hypersensitivity to bexarotene

	or other components of the product.
Tasigna (nilotinib)(76)	Tasigna has a boxed warning for QT prolongation and sudden death: • Tasigna prolongs the QT interval. Prior to Tasigna administration and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies. Obtain ECGs to monitor the QTc at baseline, seven days after initiation, and periodically thereafter, and following any dose adjustments. • Sudden deaths have been reported in patients receiving Tasigna. Do not administer Tasigna to patients with hypokalemia, hypomagnesemia, or long QT syndrome. • Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors. Avoid food 2 hours before and 1 hour after taking the dose. Contraindicated in patients with known hypokalemia, hypomagnesemia, or long QT syndrome.
Tazverik (tazemetostat)(77)	None
Temodar (temozolomide)(78)	Contraindicated in patients with history of serious hypersensitivity to

		temozolomide or any other ingredients in Temodar and dacarbazine.
	Tepmetko (tepotinib)(79)	None
	Thalomid (thalidomide)(80)	Thalomid has a boxed warning for embryo-fetal toxicity and venous thromboembolism: • If Thalomid is taken during pregnancy, it can cause severe birth defects or embryo-fetal death and should never be used by females who are pregnant or who could become pregnant while taking the drug. Even a single dose (regardless of strength) taken by a pregnant woman during her pregnancy can cause severe birth defects. • The use of Thalomid in multiple myeloma results in an increased risk of venous thromboembolism, such as deep venous thrombosis and pulmonary embolism. This risk increases significantly when Thalomid is used in combination with standard chemotherapeutic agents including dexamethasone. Thalomid is available through the Thalomid REMS program approved by the FDA. Contraindicated in the following:

		• Females who are pregnant. • Patients who have demonstrated hypersensitivity to the drug or its components.
	Tibsovo (ivosidenib)(81)	Tibsovo has a boxed warning for differentiation syndrome in AML and MDS: • Patients treated with Tibsovo have experienced symptoms of differentiation syndrome, which can be fatal. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution. Tibsovo has no contraindications of use.
	Tretinoin capsule(82)	Tretinoin has a boxed warning for embryo-fetal toxicity and differentiation syndrome: • Tretinoin can cause embryo-fetal loss and malformations when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Females of reproductive potential must have a

		negative pregnancy test before initiating tretinoin. • Differentiation Syndrome, which can be life-threatening or fatal, occurred in about 26% of patients with APL who received tretinoin. At first signs or symptoms of this syndrome, immediately initiate high-dose corticosteroid therapy and hemodynamic monitoring until resolution of signs and symptoms. Consider withholding tretinoin for moderate and severe Differentiation Syndrome until resolution. Contraindicated in patients with known hypersensitivity to tretinoin, any of its components, or other retinoids.
	Truqap (capivasertib)(117)	Contraindicated in patients with severe hypersensitivity to Truqap or any of its components.
	Truseltiq (infigratinib)(83)	None
	Tukysa (tucatinib)(84)	None
	Turalio (pexidartinib)(85)	Turalio has a boxed warning for hepatotoxicity: • Turalio can cause serious and potentially fatal liver injury. Monitor liver tests prior to initiation of Turalio and at specified intervals during treatment. Withhold and dose reduce or permanently

		discontinue Turalio based on severity of hepatotoxicity. Turalio is available only through a restricted program called the Turalio REMS Program. Turalio has no contraindications of use.
	Tykerb (lapatinib)(83)	Tykerb has a boxed warning for hepatotoxicity: • Hepatotoxicity has been observed in clinical trials and postmarketing experience. The hepatotoxicity may be severe and deaths have been reported. Causality of the deaths is uncertain. Contraindicated in patients with known hypersensitivity to lapatinib or its components.
	Vanflyta (quizartinib)(113)	Vanflyta has a boxed warning for QT prolongation, torsades de pointes, and cardiac arrest: • Vanflyta prolongs the QT interval in a dose- and concentration-related manner. Prior to Vanflyta administration and periodically, monitor for hypokalemia or hypomagnesemia, and correct deficiencies. Perform ECGs to monitor the QTc at baseline, weekly during induction and consolidation therapy, weekly for at least the first month of

		maintenance, and periodically thereafter. • Torsades de pointes and cardiac arrest have occurred in patients receiving Vanflyta. Do not administer Vanflyta to patients with severe hypokalemia, severe hypomagnesemia, or long QT syndrome. • Do not initiate treatment with Vanflyta or escalate the Vanflyta dose if the QT interval corrected by Fridericia's formula (QTcF) is greater than 450 ms. • Monitor ECGs more frequently if concomitant use of drugs known to prolong the QT interval is required. • Reduce the Vanflyta dose when used concomitantly with strong CYP3A inhibitors, as they may increase quizartinib exposure. • Because of the risk of QT prolongation, Vanflyta is available only through a restricted program under the Vanflyta REMS program. Contraindicated in patients with severe hypokalemia, severe hypomagnesemia, long QT syndrome, or in patients with a history of ventricular arrhythmias or torsades de pointes.
	Venclexta (venetoclax)(88)	Contraindicated in concomitant use with strong CYP3A inhibitors at initiation and during ramp-up phase

		in patients with CLL/SLL is contraindicated.
	Verzenio (abemaciclib)(89)	None
	Vitrakvi (larotrectinib)(90)	None
	Vizimpro (dacomitinib)(91)	None
	Vonjo (pacritinib)(106)	Contraindicated in concomitant use with a strong CYP3A4 inhibitor or inducer.
	Voranigo(1)	None
	Votrient (pazopanib)(92)	Votrient has a boxed warning for hepatotoxicity: • Severe and fatal hepatotoxicity has been observed in clinical trials. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. Votrient has no contraindications of use.
	Welireg (belzutifan)(93)	Welireg has a boxed warning for embryo-fetal toxicity: • Exposure to Welireg during pregnancy can cause embryo-fetal harm. • Verify pregnancy status prior to the initiation of Welireg. • Advise patients of these risks and the need for effective non-hormonal contraception. Welireg can render some

		hormonal contraceptives ineffective. Welireg has no contraindications of use.
	Xalkori (crizotinib)(94)	None
	Xeloda (capecitabine)(95)	Xeloda has a boxed warning for increased risk of bleeding with concomitant use of vitamin K antagonists: • Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking Xeloda concomitantly with oral vitamin K antagonists, such as warfarin. • Clinically significant increases in prothrombin time (PT) and international normalized ratio (INR) have been reported in patients who were on stable doses of a vitamin K antagonist at the time Xeloda was introduced. These events occurred within several days and up to several months after initiating Xeloda and, in a few cases, within 1 month after stopping Xeloda. These events occurred in patients with and without liver metastases. Monitor INR more frequently and adjust the dose of the vitamin K antagonist as appropriate.

		Contraindicated in patients with a severe hypersensitivity to fluorouracil or capecitabine.
	Xospata (gilteritinib)(96)	Xospata has a boxed warning for differentiation syndrome: • Patients treated with Xospata have experienced symptoms of differentiation syndrome, which can be fatal or life-threatening if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, or renal dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution. Contraindicated in patients with hypersensitivity to gilteritinib or any of the excipients.
	Xpovio (selinexor)(97)	None
	Xtandi (enzalutamide)(98)	None
	Yonsa (abiraterone acetate)(99)	None
	Zejula (niraparib)(100,112)	None
	Zelboraf (vemurafenib)(101)	None
	Zolinza (vorinostat)(102)	None
	Zydelig (idelalisib)(103)	Zydelig has a boxed warning for fatal and serious toxicities: hepatic, severe

			diarrhea, colitis, pneumonitis, infections, and intestinal perforation: • Fatal and/or serious hepatotoxicity occurred in 16% of Zydelig-treated patients. Monitor hepatic function prior to and during treatment. Interrupt and then reduce or discontinue Zydelig as recommended. • Fatal and/or serious and severe diarrhea or colitis occurred in 20% of Zydelig-treated patients. Monitor for the development of severe diarrhea or colitis. Interrupt and then reduce or discontinue Zydelig as recommended. • Fatal and/or serious pneumonitis occurred in 4% of Zydelig-treated patients. Monitor for pulmonary symptoms and bilateral interstitial infiltrates. Interrupt or discontinue Zydelig as recommended. • Fatal and/or serious infections occurred in 48% of Zydelig-treated patients. Monitor for signs and symptoms of infection. Interrupt Zydelig if infection is suspected. • Fatal and serious intestinal perforation can occur in Zydelig-treated patients across clinical trials.

		Discontinue Zydelig for intestinal perforation. Contraindicated in patients with a history of serious allergic reactions to idelalisib, including anaphylaxis and toxic epidermal necrolysis with any drug.
	Zykadia (ceritinib)(104)	None
	Zytiga (abiraterone)(105)	None

REFERENCES

Number	Reference
1	Voranigo prescribing information. Servier Pharmaceutical LLC. August 2024.
2	Lazcluze prescribing information. Janssen Biotech, Inc. August 2024.
3	Afinitor/Afinitor Disperz prescribing information. Novartis Pharmaceuticals Corporation. February 2022.
4	Alecensa prescribing information. Genentech, Inc. April 2024.
5	Alunbrig prescribing information. Takeda Pharmaceuticals America, Inc. February 2022.
6	Ayvakit prescribing information. Blueprint Medicines Corp. May 2023.
7	Balversa prescribing information. Janssen Products, LP. January 2024.
8	BESREMi prescribing information. Pharmaessentia USA. April 2024.
9	Bosulif tablets and capsules prescribing information. Pfizer Laboratories Div of Pfizer Inc. September 2023.

Number	Reference
10	Braftovi prescribing information. Array BioPharma Inc. October 2023.
11	Brukinsa prescribing information. BeiGene, USA, Inc. June 2024.
12	Cabometyx prescribing information. Exelixis, Inc. September 2023.
13	Calquence tablet prescribing information. AstraZeneca Pharmaceuticals LP. June 2024.
14	Caprelsa prescribing information. Genzyme Corporation. April 2024.
15	Cometriq prescribing information. Exelixis, Inc. August 2023.
16	Copiktra prescribing information. Secura Bio, Inc. February 2022.
17	Cotellic prescribing information. Genentech, Inc. May 2023.
18	Daurismo prescribing information. Pfizer Laboratories Div Pfizer Inc. March 2023.
19	Erivedge prescribing information. Genentech, Inc. March 2023.
20	Erleada prescribing information. Janssen Products, LP. July 2024.
21	Reference no longer used
22	Reference no longer used
23	Fotivda prescribing information. Aveo Pharmaceuticals, Inc. March 2021.
24	Gavreto prescribing information. Genentech Inc. March 2024.
25	Gilotrif prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. April 2022.
26	Gleevec prescribing information. Novartis Pharmaceuticals Corporation. March 2024.
27	Hycamtin prescribing Information. Novartis Pharmaceuticals Corporation. September 2018.
28	Ibrance prescribing information. Pfizer Inc. September 2023.

Number	Reference
29	Iclusig prescribing information. Takeda Pharmaceuticals America, Inc. March 2024.
30	Idhifa prescribing information. Celgene Corporation. December 2023.
31	Imbruvica prescribing information. Pharmacyclics LLC. May 2024.
32	Inlyta prescribing information. Pfizer Laboratories Div Pfizer Inc. September 2022.
33	Inqovi prescribing information. Taiho Pharmaceutical Co., LTD. March 2022.
34	Inrebic prescribing information. Celgene Corporation. May 2023.
35	Iressa prescribing information. AstraZeneca Pharmaceuticals LP. February 2023.
36	Jakafi prescribing information. Incyte Corporation. January 2023.
37	Kisqali Femara Pack prescribing information. Novartis Pharmaceuticals Corporation. August 2023.
38	Kisqali prescribing information. Novartis Pharmaceuticals Corporation. August 2023.
39	Koselugo prescribing information. AstraZeneca Pharmaceuticals LP. January 2024.
40	Lenvima prescribing information. Eisai Inc. June 2024.
41	Lonsurf prescribing information. Taiho Pharmaceutical Co., Ltd. August 2023.
42	Lorbrena prescribing information. Pfizer Laboratories Div Pfizer Inc. April 2023.
43	Lumakras prescribing information. Amgen Inc. June 2024.
44	Lynparza prescribing information. AstraZeneca Pharmaceuticals LP. November 2023.
45	Lysodren prescribing information. HRA Pharma Rare Diseases. January 2024.
46	Matulane prescribing information. Leadiant Biosciences. November 2023.
47	Mekinist prescribing information. Novartis Pharmaceuticals Corporation. March 2024.

Number	Reference
48	Mektovi prescribing information. Array BioPharma Inc. October 2023.
49	Nerlynx prescribing information. Puma Biotechnology, Inc. March 2022.
50	Nexavar prescribing information. Bayer HealthCare Pharmaceuticals Inc. August 2022.
51	Ninlaro prescribing information. Takeda Pharmaceuticals America, Inc. July 2024.
52	Nubeqa prescribing information. Bayer HealthCare Pharmaceuticals Inc. October 2023.
53	Odomzo prescribing information. Sun Pharmaceutical Industries, Inc. August 2023.
54	Onureg prescribing information. Celgene Corporation. October 2022.
55	Orgovyx prescribing information. Sumitomo Pharma America, Inc. August 2023.
56	Pemazyre prescribing information. Incyte Corporation. June 2023.
57	Piqray prescribing information. Novartis Pharmaceuticals Corp. January 2024.
58	Pomalyst prescribing information. Celgene Corporation. March 2023.
59	Qinlock prescribing information. Deciphera Pharmaceuticals, LLC. October 2023.
60	Retevmo prescribing information. Eli Lilly and Company. May 2024.
61	Revlimid prescribing information. Celgene Corporation. March 2023.
62	Rozlytrek prescribing information. Genentech USA, Inc. January 2024.
63	Rubraca prescribing information. Clovis Oncology, Inc. December 2022.
64	Rydapt prescribing information. Novartis Pharmaceuticals Corporation. May 2023.
65	Scemblix prescribing information. Novartis Pharmaceuticals Corporation. April 2024.
66	Sprycel prescribing information. E.R. Squibb & Sons, L.L.C. February 2023.

Number	Reference
67	Stivarga prescribing information. Bayer Healthcare Pharmaceuticals Inc. December 2020.
68	Sutent prescribing information. Pfizer Laboratories Div Pfizer Inc. August 2021.
69	Tabrecta prescribing information. Novartis Pharmaceuticals Corp. March 2024.
70	Tafinlar prescribing information. Novartis Pharmaceuticals Corporation. March 2024.
71	Tagrisso prescribing information. AstraZeneca Pharmaceuticals LP. April 2024.
72	Talzenna prescribing information. Pfizer Laboratories Div Pfizer Inc. March 2024.
73	Tarceva prescribing information. Genentech inc. October 2016.
74	Targretin capsule prescribing information. Bausch Health US, LLC. April 2020.
75	Targretin gel prescribing information. Bausch Health US, LLC. February 2020.
76	Tasigna prescribing information. Novartis Pharmaceuticals Corporation. February 2024.
77	Tazverik prescribing information. Epizyme Inc. December 2023.
78	Temodar prescribing Information. Merck Sharp & Dohme LLC. September 2023.
79	Tepmetko prescribing information. EMD Serono, Inc. February 2024.
80	Thalomid prescribing information. Celgene Corporation. March 2023.
81	Tibsovo prescribing information. Servier Pharmaceuticals LLC, Inc. October 2023.
82	Tretinoin prescribing information. Glenmark Pharmaceuticals, Inc, USA. April 2023.
83	Truseltiq prescribing information. QED Therapeutics Inc. May 2021.
84	Tukysa prescribing information. Seagen Inc. January 2023.
85	Turalio prescribing information. Daiichi Sankyo, Inc. November 2023.

Number	Reference
86	Tykerb prescribing information. Novartis Pharmaceuticals Corporation. March 2022.
87	Reference is no longer used
88	Venclexta prescribing information. AbbVie Inc. July 2024.
89	Verzenio prescribing information. Eli Lilly and Company. January 2024.
90	Vitrakvi prescribing information. Bayer HealthCare Pharmaceuticals Inc. November 2023.
91	Vizimpro prescribing information. Pfizer Laboratories Div Pfizer Inc. December 2020.
92	Votrient prescribing information. Novartis Pharmaceuticals Corporation. January 2024.
93	Welireg prescribing information. Merck Sharp & Dohme LLC. December 2023.
94	Xalkori prescribing information. Pfizer Laboratories Div Pfizer Inc. September 2023.
95	Xeloda prescribing information. Genentech, Inc. April 2023.
96	Xospata prescribing information. Astellas Pharma US, Inc. January 2022.
97	Xpovio prescribing information. Karyopharm Therapeutics Inc. July 2022.
98	Xtandi prescribing information. Astellas Pharma US, Inc. November 2023.
99	Yonsa prescribing information. Sun Pharmaceuticals Industries, Inc. March 2022.
100	Zejula capsule prescribing information. GlaxoSmithKline. May 2024.
101	Zelboraf prescribing information. Genentech, Inc. May 2020.
102	Zolinza prescribing information. Merck Sharp & Dohme LLC. July 2022.
103	Zydelig prescribing information. Gilead Sciences, Inc. February 2022.
104	Zykadia prescribing information. Novartis Pharmaceuticals Corporation. October 2021.

Number	Reference
105	Zytiga prescribing information. Janssen Biotech, Inc. August 2021.
106	Vonjo prescribing information. CTI Biopharma Corp. August 2023.
107	Lytgobi prescribing information. Taiho Pharmaceutical Co., LTD. April 2024.
108	Rezlidhia prescribing information. Rigel Pharmaceuticals, Inc. December 2022.
109	Krazati prescribing information. Mirati Therapeutics, Inc. June 2024.
110	Jaypirca prescribing information. Eli Lilly and Company. June 2024.
111	Orserdu prescribing information. Stemline Therapeutics, Inc. November 2023.
112	Zejula tablet prescribing information. GlaxoSmithKline. May 2024.
113	Vanflyta prescribing information. Daiichi Sankyo Inc. June 2024.
114	Akeega prescribing information. Janssen Biotech, Inc. August 2023.
115	Ojjaara prescribing information. GlaxoSmithKline LLC. September 2023.
116	Fruzaqla prescribing information. Takeda Pharmaceuticals U.S.A., Inc. November 2023
117	Truqap prescribing information. AstraZeneca Pharmaceuticals LP. November 2023.
118	Augtyro prescribing information. E.R Squibb & Sons, LLC. June 2024.
119	Ogsiveo prescribing information. SpringWorks Therapeutics, Inc. November 2023.
120	Iwilfin prescribing information.US Worldmeds (USWM), LCC. December 2023.
121	Ojemda prescribing information. Day One Biopharmaceuticals, Inc. June 2024.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td>PA</td><td>Preferred agent options are determined by client:
<table>
<tr><th>Indication</th><th>Number of Preferred Agents Required</th><th>Preferred Agent(s)*</th><th>Non-Preferred Agent(s)</th></tr>
<tr><td>Advanced or metastatic breast cancer</td><td>1</td><td>Kisqali, Kisqali Femara Pack, Verzenio</td><td>Ibrance</td></tr>
<tr><td>Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase</td><td>1</td><td>imatinib (generic), Sprycel (dasatinib)</td><td>Bosulif, Tasigna</td></tr>
<tr><td>Ph+ CML in chronic phase with the T315I mutation</td><td>1</td><td>Iclusig</td><td>Scemblix</td></tr>
<tr><td>Desmoid tumors</td><td>1</td><td>sorafenib (generic)</td><td>Ogsiveo</td></tr>
<tr><td>Metastatic ROS1-positive non-small cell lung cancer (NSCLC)</td><td>1</td><td>Rozlytrek, Xalkori</td><td>Augtyro</td></tr>
</table>
NOTE: brand Gleevec and brand Nexavar to be managed through generic before brand requirement</td></tr>
</table>

Module	Clinical Criteria for Approval
	*Preferred Agents may be targeted in another utilization management program and require Prior Authorization **Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has been treated with the requested agent within the past 180 days **OR** B. The prescriber states the patient is being treated with the requested agent within the past 180 days AND is at risk if therapy is changed **OR** C. ALL of the following: 1. ONE of the following: A. The patient has an FDA labeled indication for the requested agent and route of administration **OR** B. The patient has an indication that is supported in compendia for the requested agent and route of administration (i.e., indication must be supported in compendia by ALL requirements [e.g., performance status, disease severity, previous failures, monotherapy vs. combination therapy]) **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. ONE of the following: A. The requested indication does NOT require specific genetic/diagnostic testing per FDA labeling or compendia for the requested agent **OR** B. The requested indication requires specific genetic/diagnostic testing per FDA labeling or compendia for the requested agent AND BOTH of the following: 1. Specific genetic/diagnostic testing has been completed **AND** 2. The results of the specific genetic/diagnostic testing indicate therapy with the requested agent is appropriate **AND** 4. ONE of the following: A. The requested agent will be used as monotherapy AND is approved for use as monotherapy within FDA labeling or compendia for the requested indication **OR** B. The requested agent will be used as combination therapy with all agents and/or treatments (e.g., radiation) AND is approved for use as

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
combination therapy with all agents and/or treatments within FDA labeling or compendia for the requested indication AND
5. ONE of the following:
A. The requested agent will be used as first-line therapy AND is a first-line agent within FDA labeling or compendia for the requested indication OR
B. The patient has tried and had an inadequate response to the appropriate number and types of prerequisite agents within FDA labeling or compendia for the requested indication OR
C. The patient has an intolerance or hypersensitivity to the appropriate number and types of prerequisite agents within FDA labeling or compendia for the requested indication OR
D. The patient has an FDA labeled contraindication to ALL of the required prerequisite agents within FDA labeling or compendia for the requested indication AND
6. If the client has preferred products* for the requested indication (*Preferred agents are determined by the client and may include brand and generic agents), then ONE of the following:
<table>
<tr><th>Indication</th><th>Preferred Agents</th><th>Non-Preferred Agents</th></tr>
<tr><td></td><td></td><td></td></tr>
</table>
A. The requested agent is a preferred agent for the requested indication OR
B. The requested agent is a non-preferred agent for the requested indication AND ONE of the following:
1. The patient has a medication history of use of ONE preferred agent for the requested indication OR
2. The patient has an intolerance or hypersensitivity to ONE preferred agent for the requested indication OR
3. The patient has an FDA labeled contraindication to ALL preferred agents for the requested indication OR
4. BOTH of the following:
A. NCCN does NOT specify the plan preferred agent as a preferred regimen for the requested indication AND
B. NCCN specifies the requested agent as a preferred regimen for the requested indication OR
</td></tr>
</table>

Module	Clinical Criteria for Approval
	5. There is support for the non-preferred agent over the preferred agent for the requested indication **OR** 6. If the requested agent is Bosulif or Tasigna for CML, then the patient has been previously treated with Bosulif OR Tasigna for CML **AND** 7. If the requested agent is Imbruvica 140 mg or 280 mg tablets, then ONE of the following: A. The patient has tried and had an inadequate response to Imbruvica 140 mg capsules **OR** B. The patient has an intolerance or hypersensitivity to Imbruvica 140 mg capsules that is not expected to occur with Imbruvica tablets **OR** C. The patient has an FDA labeled contraindication to Imbruvica 140 mg capsules that is not expected to occur with Imbruvica tablets **AND** 8. If the requested agent is Zytiga/abiraterone 500 mg, then ONE of the following: A. The patient has tried and had an inadequate response to generic abiraterone 250 mg tablets **OR** B. The patient has an intolerance or hypersensitivity to generic abiraterone 250 mg tablets that is not expected to occur with the requested agent **OR** C. The patient has an FDA labeled contraindication to generic abiraterone 250 mg tablets that is not expected to occur with the requested agent **AND** 9. If the requested agent is Mekinist oral solution, then ONE of the following: A. The patient weighs less than 26 kg **OR** B. The patient has tried and had an inadequate response to Mekinist oral tablets **OR** C. The patient has an intolerance or hypersensitivity to Mekinist oral tablets that is not expected to occur with the requested agent **OR** D. The patient has an FDA labeled contraindication to Mekinist oral tablets that is not expected to occur with the requested agent **OR** E. There is support for the use of the requested agent over Mekinist oral tablets (e.g., swallowing difficulties) **AND** 10. If the requested agent is Bosulif capsules, then ONE of the following: 1. The requested dose is less than 500 mg **OR** 2. There is support for the use of the capsules over Bosulif tablets (e.g., swallowing difficulties) **AND** 2. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:

Module	Clinical Criteria for Approval

Brand	Generic Equivalent
Afinitor	everolimus
Afinitor Disperz	everolimus
Gleevec	imatinib
Iressa	gefitinib
Nexavar	sorafenib
Sutent	sunitinib
Tarceva	erlotinib
Targretin	bexarotene
Temodar	temozolomide
Tykerb	lapatinib
Votrient	pazopanib
Xeloda	capecitabine
Zytiga	abiraterone

A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent **OR**
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent **OR**
C. There is support for the use of the requested brand agent over the generic equivalent **AND**

3. The patient does not have any FDA labeled contraindications to the requested agent **AND**
4. The patient does not have any FDA labeled limitations of use that are otherwise not supported in NCCN for the requested agent **AND**

Module	Clinical Criteria for Approval
	5. The requested quantity (dose) is within FDA labeling or supported in compendia for the requested indication **Compendia Allowed:** NCCN 1 or 2A recommended use, AHFS, or DrugDex level of evidence of 1 or 2A **Length of Approval:** titration requests or Vitrakvi - up to 3 months; all other requests - up to 12 months. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. If the requested agent is Imbruvica 140 mg or 280 mg tablets, then ONE of the following: A. The patient has tried and had an inadequate response to Imbruvica 140 mg capsules **OR** B. The patient has an intolerance or hypersensitivity to Imbruvica 140 mg capsules that is not expected to occur with Imbruvica tablets **OR** C. The patient has an FDA labeled contraindication to Imbruvica 140 mg capsules that is not expected to occur with Imbruvica tablets **AND** 3. If the requested agent is Zytiga/abiraterone 500 mg, then ONE of the following: A. The patient has tried and had an inadequate response to generic abiraterone 250 mg tablets **OR** B. The patient has an intolerance or hypersensitivity to generic abiraterone 250 mg tablets that is not expected to occur with the requested agent **OR** C. The patient has an FDA labeled contraindication to generic abiraterone 250 mg tablets that is not expected to occur with the requested agent **AND** 4. If the requested agent is Mekinist oral solution, then ONE of the following: A. The patient weighs less than 26 kg **OR** B. The patient has tried and had an inadequate response to Mekinist oral tablets **OR** C. The patient has an intolerance or hypersensitivity to Mekinist oral tablets that is not expected to occur with the requested agent **OR** D. The patient has an FDA labeled contraindication to Mekinist oral tablets that is not expected to occur with the requested agent **OR** E. There is support for the use of the requested agent over Mekinist oral tablets (e.g., swallowing difficulties) **AND** 5. If the requested agent is Bosulif capsules, then ONE of the following: 1. The requested dose is less than 500 mg **OR**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
2. There is support for the use of the capsules over Bosulif tablets (e.g., swallowing difficulties) AND
6. ONE of the following:
A. The requested agent is Vitrakvi, AND the patient has had clinical benefit (partial response, complete response, or stable disease) with the requested agent OR
B. The requested agent is NOT Vitrakvi AND
7. If the request is for one of the following brand agents with a generic equivalent (listed below), then ONE of the following:
<table>
<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Afinitor</td><td>everolimus</td></tr>
<tr><td>Afinitor Disperz</td><td>everolimus</td></tr>
<tr><td>Gleevec</td><td>imatinib</td></tr>
<tr><td>Iressa</td><td>gefitinib</td></tr>
<tr><td>Nexavar</td><td>sorafenib</td></tr>
<tr><td>Sutent</td><td>sunitinib</td></tr>
<tr><td>Tarceva</td><td>erlotinib</td></tr>
<tr><td>Targretin</td><td>bexarotene</td></tr>
<tr><td>Temodar</td><td>temozolomide</td></tr>
<tr><td>Tykerb</td><td>lapatinib</td></tr>
<tr><td>Votrient</td><td>pazopanib</td></tr>
<tr><td>Xeloda</td><td>capecitabine</td></tr>
<tr><td>Zytiga</td><td>abiraterone</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
C. There is support for the use of the requested brand agent over the generic equivalent AND
8. The patient does not have any FDA labeled contraindications to the requested agent AND
9. The patient does not have any FDA labeled limitations of use that are otherwise not supported in NCCN for the requested agent AND
10. The requested quantity (dose) is within FDA labeling or supported in compendia for the requested indication

Length of Approval: up to 12 months

FDA Companion Diagnostics: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools
</td></tr>
<tr><td>PA

QL</td><td>
Preferred agent options are determined by client:

<table>
<tr><th>Indications</th><th>Number of Preferred Agents Required</th><th>Preferred Agent(s)*</th><th>Non-Preferred Agent(s)</th></tr>
<tr><td>Advanced or metastatic breast cancer</td><td>1</td><td>Kisqali, Kisqali Femara Pack, Verzenio</td><td>Ibrance</td></tr>
<tr><td>Newly diagnosed adult and pediatric patients with Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase</td><td>1</td><td>imatinib (generic), Sprycel (dasatinib)</td><td>Bosulif, Tasigna</td></tr>
<tr><td>Ph+ CML in chronic phase</td><td>1</td><td>Iclusig</td><td>Scemblix</td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval

with the T315I mutation			
Desmoid tumors	1	sorafenib (generic)	Ogsiveo
Metastatic ROS1-positive non-small cell lung cancer (NSCLC)	1	Rozlytrek, Xalkori	Augtyro

NOTE: brand Gleevec and brand Nexavar to be managed through generic before brand requirement

*Preferred Agents may be targeted in another utilization management program and require Prior Authorization

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
    A. The patient has been treated with the requested agent within the past 180 days **OR**
    B. The prescriber states the patient is being treated with the requested agent within the past 180 days AND is at risk if therapy is changed **OR**
    C. ALL of the following:
        1. ONE of the following:
            A. The patient has an FDA labeled indication for the requested agent and route of administration **OR**
            B. The patient has an indication that is supported in compendia for the requested agent and route of administration (i.e., this indication must be supported in compendia by ALL requirements [e.g., performance status, disease severity, previous failures, monotherapy vs combination therapy]) **AND**
        2. If the patient has an FDA labeled indication, then ONE of the following:
            A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**
            B. There is support for using the requested agent for the patient's age for the requested indication **AND**
        3. ONE of the following:

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
A. The requested indication does NOT require specific genetic/diagnostic testing per FDA labeling or compendia for the requested agent OR
B. The requested indication requires specific genetic/diagnostic testing per FDA labeling or compendia for the requested agent AND BOTH of the following:
1. Specific genetic/diagnostic testing has been completed AND
2. The results of the specific genetic/diagnostic testing indicate therapy with the requested agent is appropriate AND
4. ONE of the following:
A. The requested agent will be used as monotherapy AND is approved for use as monotherapy within FDA labeling or compendia for the requested indication OR
B. The requested agent will be used as combination therapy with all agents and/or treatments (e.g., radiation) AND is approved for use as combination therapy with all agents and/or treatments within FDA labeling or compendia for the requested indication AND
5. ONE of the following:
A. The requested agent will be used as first-line therapy AND is a first-line agent within FDA labeling or compendia for the requested indication OR
B. The patient has tried and had an inadequate response to the appropriate number and types of prerequisite agents within FDA labeling or compendia for the requested indication OR
C. The patient has an intolerance or hypersensitivity to the appropriate number and types of prerequisite agents within FDA labeling or compendia for the requested indication OR
D. The patient has an FDA labeled contraindication to ALL of the required prerequisite agents within FDA labeling or compendia for the requested indication AND
6. If the client has preferred products* for the requested indication (*Preferred agents are determined by the client and may include brand and generic agents), then ONE of the following:
<table>
<tr><th>Indication</th><th>Preferred Agents</th><th>Non-Preferred Agents</th></tr>
<tr><td></td><td></td><td></td></tr>
</table>
A. The requested agent is a preferred agent for the requested indication OR
</td></tr>
</table>

Module	Clinical Criteria for Approval
	B. The requested agent is a non-preferred agent for the requested indication AND ONE of the following: 1. The patient has a medication history of use of ONE preferred agent for the requested indication **OR** 2. The patient has an intolerance or hypersensitivity to ONE preferred agent for the requested indication **OR** 3. The patient has an FDA labeled contraindication to ALL preferred agents for the requested indication **OR** 4. BOTH of the following: A. NCCN does NOT specify the plan preferred agent as a preferred regimen for the requested indication **AND** B. NCCN specifies the requested agent as a preferred regimen for the requested indication **OR** 5. There is support for the non-preferred agent over the preferred agent for the requested indication **OR** 6. If the requested agent is Bosulif or Tasigna for CML, then the patient has been previously treated with Bosulif OR Tasigna for CML **AND** 7. If the requested agent is Imbruvica 140 mg or 280 mg tablets, then ONE of the following: A. The patient has tried and had an inadequate response to Imbruvica 140 mg capsules **OR** B. The patient has an intolerance or hypersensitivity to Imbruvica 140 mg capsules that is not expected to occur with Imbruvica tablets **OR** C. The patient has an FDA labeled contraindication to Imbruvica 140 mg capsules that is not expected to occur with Imbruvica tablets **AND** 8. If the requested agent is Zytiga/abiraterone 500 mg, then ONE of the following: A. The patient has tried and had an inadequate response to generic abiraterone 250 mg tablets **OR** B. The patient has an intolerance or hypersensitivity to generic abiraterone 250 mg tablets that is not expected to occur with the requested agent **OR** C. The patient has an FDA labeled contraindication to generic abiraterone 250 mg tablets that is not expected to occur with the requested agent **AND** 9. If the requested agent is Mekinist oral solution, then ONE of the following: A. The patient weighs less than 26 kg **OR** B. The patient has tried and had an inadequate response to Mekinist oral tablets **OR**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
C. The patient has an intolerance or hypersensitivity to Mekinist oral tablets that is not expected to occur with the requested agent OR
D. The patient has an FDA labeled contraindication to Mekinist oral tablets that is not expected to occur with the requested agent OR
E. There is support for the use of the requested agent over Mekinist oral tablets (e.g., swallowing difficulties) AND
10. If the requested agent is Bosulif capsules, then ONE of the following:
A. The requested dose is less than 500 mg OR
B. There is support for the use of the capsules over the Bosulif tablets (e.g., swallowing difficulties) AND
2. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:
<table>
<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Afinitor</td><td>everolimus</td></tr>
<tr><td>Afinitor Disperz</td><td>everolimus</td></tr>
<tr><td>Gleevec</td><td>imatinib</td></tr>
<tr><td>Iressa</td><td>gefitinib</td></tr>
<tr><td>Nexavar</td><td>sorafenib</td></tr>
<tr><td>Sutent</td><td>sunitinib</td></tr>
<tr><td>Tarceva</td><td>erlotinib</td></tr>
<tr><td>Targretin</td><td>bexarotene</td></tr>
<tr><td>Temodar</td><td>temozolomide</td></tr>
<tr><td>Tykerb</td><td>lapatinib</td></tr>
<tr><td>Votrient</td><td>pazopanib</td></tr>
<tr><td>Xeloda</td><td>capecitabine</td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval

Zytiga	abiraterone

A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent **OR**
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent **OR**
C. There is support for the use of the requested brand agent over the generic equivalent **AND**

3. The patient does not have any FDA labeled contraindications to the requested agent **AND**
4. The patient does not have any FDA labeled limitations of use that are otherwise not supported in NCCN for the requested agent

Compendia Allowed: NCCN 1 or 2A recommended use, AHFS, or DrugDex level of evidence of 1 or 2A

Length of Approval*: titration requests over the program quantity limit or Vitrakvi - up to 3 months; all other requests - up to 12 months.

*Approve starter packs and loading doses where appropriate and maintenance dose for the remainder of the authorization.

NOTE: if Quantity Limit applies, please refer to Quantity Limit Criteria.

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND**
2. If the requested agent is Imbruvica 140 mg or 280 mg tablets, then ONE of the following:
   A. The patient has tried and had an inadequate response to Imbruvica 140 mg capsules **OR**
   B. The patient has an intolerance or hypersensitivity to Imbruvica 140 mg capsules that is not expected to occur with Imbruvica tablets **OR**
   C. The patient has an FDA labeled contraindication to Imbruvica 140 mg capsules that is not expected to occur with Imbruvica tablets **AND**
3. If the requested agent is Zytiga/abiraterone 500 mg, then ONE of the following:

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
1. The patient has tried and had an inadequate response to generic abiraterone 250 mg tablets OR
2. The patient has an intolerance or hypersensitivity to generic abiraterone 250 mg tablets that is not expected to occur with the requested agent OR
3. The patient has an FDA labeled contraindication to generic abiraterone 250 mg tablets that is not expected to occur with the requested agent AND

4. If the requested agent is Mekinist oral solution, then ONE of the following:
   1. The patient weighs less than 26 kg OR
   2. The patient has tried and had an inadequate response to Mekinist oral tablets OR
   3. The patient has an intolerance or hypersensitivity to Mekinist oral tablets that is not expected to occur with the requested agent OR
   4. The patient has an FDA labeled contraindication to Mekinist oral tablets that is not expected to occur with the requested agent OR
   5. There is support for the use of the requested agent over Mekinist oral tablets (e.g., swallowing difficulties) AND
5. If the requested agent is Bosulif capsules, then ONE of the following:
   A. The requested dose is less than 500 mg OR
   B. There is support for the use of the capsules over the Bosulif tablets (e.g., swallowing difficulties) AND
6. ONE of the following:
   A. The requested agent is Vitrakvi, AND the patient has had clinical benefit (partial response, complete response, or stable disease) with the requested agent OR
   B. The requested agent is NOT Vitrakvi AND
7. If the request is for one of the following brand agents with a generic equivalent (listed below), then ONE of the following:

<table>
<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Afinitor</td><td>everolimus</td></tr>
<tr><td>Afinitor Disperz</td><td>everolimus</td></tr>
<tr><td>Gleevec</td><td>imatinib</td></tr>
<tr><td>Iressa</td><td>gefitinib</td></tr>
<tr><td>Nexavar</td><td>sorafenib</td></tr>
<tr><td>Sutent</td><td>sunitinib</td></tr>
</table>
</td></tr>
</table>

Module	Clinical Criteria for Approval

Tarceva	erlotinib
Targretin	bexarotene
Temodar	temozolomide
Tykerb	lapatinib
Votrient	pazopanib
Xeloda	capecitabine
Zytiga	abiraterone

A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent **OR**
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent **OR**
C. There is support for the use of the requested brand agent over the generic equivalent **AND**

8. The patient does not have any FDA labeled contraindications to the requested agent **AND**
9. The patient does not have any FDA labeled limitations of use that are otherwise not supported in NCCN for the requested agent

Length of Approval: up to 12 months

NOTE: if Quantity Limit applies, please refer to Quantity Limit Criteria.

FDA Companion Diagnostics: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools

Module	Ops Set Up	Validation Options	Other Explanation
PA	Validation: Apply Baseline and go to Validation Options	Age Verification;Continuation of Therapy;Contraind., intolerance, or hypersensitivity to prereq.;Diagnosis;Other (see Other explanation field);Prerequisites	*Verify info - any criteria point that requires confirmation from FDA labeling or allowed compendia [exceptions: 1) FDA labeled contraindications to the requested agent, and 2) FDA labeled limitations to the requested agent] *Combination therapy: request info from prescriber to verify with FDA labeling or compendia *Review info - support for non-preferred agent over the preferred agent *Review info - support for brand over the generic *Review info - support for Mekinist oral solution over tablets *Review info - support for Bosulif tablets over capsules for doses of 500 mg or more *Verify info - the requested quantity is within FDA labeling or compendia supported dosing
PA QL	Validation: Apply Baseline and go to Validation Options	Age Verification;Continuation of Therapy;Contraind., intolerance, or hypersensitivity to prereq.;Diagnosis;Other (see Other explanation field);Prerequisites	*Verify info - any criteria point that requires confirmation from FDA labeling or allowed compendia [exceptions: 1) FDA labeled contraindications to the requested agent, and 2) FDA labeled limitations to the requested agent]

Module	Ops Set Up	Validation Options	Other Explanation
			*Combination therapy: request info from prescriber to verify with FDA labeling or compendia *Review info - support for non-preferred agent over the preferred agent *Review info - support for brand over the generic *Review info - support for Mekinist oral solution over tablets *Review info - support for Bosulif tablets over capsules for doses of 500 mg or more

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Samsca (tolvaptan)

Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Samsca® (tolvaptan)* Tablet	Treatment of clinically significant hypervolemic and euvolemic hyponatremia (serum sodium <125 mEq/L or less marked hyponatremia that is symptomatic and has resisted correction with fluid restriction), including patients with heart failure and Syndrome of Inappropriate Antidiuretic Hormone (SIADH) Limitations of Use: Patients requiring intervention to raise serum sodium urgently to prevent or to treat serious neurological symptoms should not be treated with Samsca It has not been established that raising serum sodium with Samsca provides a symptomatic benefit to patients	*generic available	1

CLINICAL RATIONALE

Hyponatremia	Hyponatremia is the most common disorder of body fluid and electrolyte balance in clinical practice, occurring in up to 15-30% of acute and chronically hospitalized patients. While many cases are considered mild and relatively asymptomatic, hyponatremia is clinically important for the following reasons: untreated acute severe hyponatremia can cause substantial morbidity and mortality; adverse outcomes, including mortality, are higher in patients with a wide range of underlying conditions; and correction of serum sodium that is too fast may cause severe neurologic damage and death.(2,3) Hyponatremia can be classified as hypotonic, hypertonic, or isotonic. Hypotonic hyponatremia being further classified based on a patient's extracellular fluid volume as hypovolemic hyponatremia, hypervolemic hyponatremia, or euvolemic hyponatremia. Hypovolemic hyponatremia is associated with fluid depletion and can arise from a number of conditions. Hypervolemic hyponatremia is caused by fluid overload, as in advanced cirrhosis, renal disease, or congestive heart failure.

	Euvolemic hyponatremia is most commonly associated with Syndrome of Inappropriate Antidiuretic Hormone (SIADH).(2) Appropriate treatment should be based on the type of hyponatremia, the underlying etiology, the serum sodium (Na+) level, and the severity of symptoms. Treatment strategies can include fluid restriction, diuretic therapy, sodium supplementation, demeclocycline, urea, and vasopressin receptor antagonists (vaptans). The 2013 expert panel recommendations note that, at the time that fluid restriction is first started, medications known to be associated with SIADH should be discontinued or changed.(2) Medications associated with SIADH are: antidepressants (SSRIs, tricyclics, MAOIs, venlafaxine), anticonvulsants (carbamazepine, oxcarbazepine, sodium valproate, lamotrigine), antipsychotics (phenothiazines, butyrophenones), anticancer (vinca alkaloids, platinum compounds, ifosfamide, melphalan, cyclophosphamide, methotrexate, pentostatin), antidiabetic (chlorpropamide, tolbutamide), vasopressin analogues (desmopressin, oxytocin, terlipressin, vasopressin), miscellaneous (amiodarone, clofibrate, interferon, NSAIDs, levamisole, linezolid, monoclonal antibodies, nicotine, opiates, PPIs). Discontinuing these medications can lead to the rapid reversal of SIADH.(3)
Safety	Samsca is contraindicated in the following conditions:(1) • Patients with autosomal dominant polycystic kidney disease (ADPKD) outside of FDA-approved REMS • Unable to sense or respond to thirst • Hypovolemic hyponatremia • Taking strong CYP3A inhibitors • Anuria • Hypersensitivity (e.g., anaphylactic shock, rash generalized) to tolvaptan or any component of the product Samsca has the following boxed warning:(1) 1) Samsca should be initiated and re-initiated in patients only in a hospital where serum sodium can be monitored closely. Too rapid correction of hyponatremia (e.g., >12 mEq/L/24 hours) can cause osmotic demyelination resulting in dysarthria, mutism, dysphagia, lethargy, affective changes, spastic quadriparesis, seizures, coma and death. In

	susceptible patients, including those with severe malnutrition, alcoholism or advanced liver disease, slower rates of correction may be advisable. 2) Because of the risk of hepatotoxicity, tolvaptan should not be used for ADPKD outside of the FDA-approved REMS program.

REFERENCES

Number	Reference
1	Samsca Prescribing Information. Otsuka Pharmaceutical Co., Ltd. April 2021.
2	Verbalis, J. G., Goldsmith, S. R., Greenberg, A., Korzelius, C., Schrier, R. W., Sterns, R. H., & Thompson, C. J. (2013). Diagnosis, evaluation, and treatment of hyponatremia: Expert panel recommendations. *The American Journal of Medicine*, *126*(10). https://doi.org/10.1016/j.amjmed.2013.07.006
3	Spasovski, G., Vanholder, R., Allolio, B., Annane, D., Ball, S., Bichet, D., Decaux, G., Fenske, W., Hoorn, E. J., Ichai, C., Joannidis, M., Soupart, A., Zietse, R., Haller, M., van der Veer, S., Van Biesen, W., & Nagler, E. (2014). Clinical practice guideline on diagnosis and treatment of hyponatraemia. *Nephrology Dialysis Transplantation*, *29*(suppl_2), i1–i39. https://doi.org/10.1093/ndt/gfu040

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL Standalone	**Quantity limit for the Target Agent(s)** will be approved when the following is met: 1. The patient has had an additional hospitalization for hyponatremia for initiation of the requested agent **Length of Approval:** 30 tablets/365 days of the 15 mg tablets 60 tablets/365 days of the 30 mg tablets

Sodium-glucose Co-transporter (SGLT) Inhibitors and Combinations

Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Brenzavvy®, Bexagliflozin Tablet	An adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitation of Use: Not recommended in patients with type 1 diabetes mellitus. May increase the risk of diabetic ketoacidosis in these patients.		19
Farxiga® (dapagliflozin) Tablet	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factor To reduce the risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and either established cardiovascular disease or multiple cardiovascular risk factors. To reduce the risk of sustained eGFR decline, end stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression		2

Agent(s)	FDA Indication(s)	Notes	Ref#
	Limitations of Use: • Not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus. • Not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m^2. Farxiga is likely to be ineffective in this setting based upon its mechanism of action • Not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for the treatment of kidney disease. Farxiga is not expected to be effective in these populations.		
Glyxambi® (empagliflozin/linagliptin) Tablet	To improve glycemic control in adults with type 2 diabetes mellitus. To reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. Limitations of Use: • Not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients. Has not been studied in patients with a history of pancreatitis.	DPP-4 Inhibitor Combinations	14

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2.		
Inpefa™ (sotagliflozin) Tablet	To reduce the risk of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit in adults with: • heart failure or • type 2 diabetes mellitus, chronic kidney disease, and other cardiovascular risk factors		18
Invokamet® (canagliflozin/metformin) Tablet	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Canagliflozin is indicated to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease Canagliflozin is indicated to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria Limitations of Use: Not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus		3
Invokamet XR® (canagliflozin/metformin ER) Tablet	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus		3

Agent(s)	FDA Indication(s)	Notes	Ref#
	Canagliflozin is indicated to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease Canagliflozin is indicated to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria Limitations of Use: Not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus		
Invokana® (canagliflozin) Tablet	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus To reduce the risk of major cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease To reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria Limitations of Use: • Not recommended in patients with type 1 diabetes mellitus • Not recommended for use to improve glycemic control in adults with type 2 diabetes mellitus with		1

Agent(s)	FDA Indication(s)	Notes	Ref#
	an eGFR less than 30 mL/min/1.73 m^2		
Jardiance® (empagliflozin) Tablet	To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure. To reduce the risk of sustained decline in eGFR, end-stage kidney disease, cardiovascular death, and hospitalization in adults with chronic kidney disease at risk of progression. To reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease. As an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients aged 10 years and older with type 2 diabetes mellitus. Limitations of Use: • Not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients. • Not recommended for use to improve glycemic control in patients with type 2 diabetes mellitus with an eGFR less than 30 mL/min/1.73 m^2. • Not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of intravenous		4

Agent(s)	FDA Indication(s)	Notes	Ref#
	immunosuppressive therapy or greater than 45 mg of prednisone or equivalent for kidney disease.		
Qtern® (dapagliflozin/saxagliptin) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitation of use: Not recommended for patients with type 1 diabetes mellitus.	DPP-4 Inhibitor Combinations	15
Segluromet® (ertugliflozin/metformin) Tablet	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitation of use: Not for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis		9
Steglatro® (ertugliflozin) Tablet	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitation of Use: Not recommended in patients with type 1 diabetes mellitus		8
Steglujan® (ertugliflozin/sitagliptin) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Limitations of Use: • Not recommended for patients with type 1 diabetes mellitus • Has not been studied in patients with a history of pancreatitis.	DPP-4 Inhibitor Combinations	16
Synjardy® (empagliflozin/metformin)	As an adjunct to diet and exercise to improve glycemic control in adults and		6

Agent(s)	FDA Indication(s)	Notes	Ref#
Tablet	pediatric patients aged 10 years and older with type 2 diabetes mellitus Empagliflozin, when used as a component of Synjardy or Synjardy XR, is indicated in adults with type 2 diabetes mellitus to reduce the risk of: • Cardiovascular death in adults with established cardiovascular disease. • Cardiovascular death and hospitalization for heart failure in adults with heart failure. Limitations of Use: • Not recommended for use in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients. • Because of the metformin component, Synjardy and Synjardy XR are not recommended for use in patients with heart failure without type 2 diabetes mellitus.		
Synjardy®XR (empagliflozin/metformin) Tablet	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Empagliflozin, when used as a component of Synjardy or Synjardy XR, is indicated in adults with type 2 diabetes mellitus to reduce the risk of: • Cardiovascular death in adults with established cardiovascular disease.		7

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Cardiovascular death and hospitalization for heart failure in adults with heart failure. Limitations of Use: • Not recommended for use in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients. • Because of the metformin component, Synjardy and Synjardy XR are not recommended for use in patients with heart failure without type 2 diabetes mellitus.		
Trijardy XR™ (empagliflozin/linaglipin/metformin) Tablet	Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease Limitations of Use: • Not recommended in patients with type 1 diabetes. • Has not been studied in patients with a history of pancreatitis	DPP-4 Inhibitor Combinations	17
Xigduo® XR (dapagliflozin/metformin) Tablet	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Dapagliflozin is indicated to reduce:		5

Agent(s)	FDA Indication(s)	Notes	Ref#
	• The risk of hospitalization for heart failure in adults with type 2 diabetes mellitus and established cardiovascular disease or multiple cardiovascular risk factors. • The risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction. • The risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death and hospitalization for heart failure in adults with chronic kidney disease at risk of progression. Limitations of Use: • Not recommended for use to improve glycemic control in patients with type 1 diabetes mellitus. • Because of the metformin component, the use of Xigduo XR is limited to adults with type 2 diabetes mellitus for all indications. • Not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for the treatment of kidney disease. Xigduo XR is not expected to be effective in these populations.		

CLINICAL RATIONALE

Overview	The American Diabetes Association (ADA) recommends the following guidelines:(10,11) • Healthy lifestyle behaviors, diabetes self-management education and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. • In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardiorenal risk. • Pharmacologic approaches that provide adequate efficacy to achieve and maintain treatment goals should be considered, such as metformin or other agents, including combination therapy. • Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals. • Metformin should be continued upon initiation of insulin therapy (unless contraindicated or not tolerated) for ongoing glycemic and metabolic benefits. A Early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure. • The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (greater or equal to 300 mg/dL) are very high. • A person-centered approach should guide the choice of pharmacologic agents. Consider the effects on cardiovascular and renal comorbidities, efficacy, hypoglycemia risk, impact on weight, cost and access, risk for side effects, and individual preferences. • Among individuals with type 2 diabetes who have established atherosclerotic cardiovascular disease or indicators of high cardiovascular risk, established kidney disease, or heart failure, a sodium–glucose cotransporter 2 inhibitor and/or glucagon-like peptide 1 receptor agonist with demonstrated cardiovascular disease benefit is recommended as part of the glucose-lowering regimen and comprehensive cardiovascular risk reduction, independent of A1C and in consideration of person-specific factors. • In adults with type 2 diabetes, a glucagon-like peptide 1 receptor agonist is preferred to insulin when possible.

	Healthy lifestyle behaviors, diabetes self-management, education, and support, avoidance of clinical inertia, and social determinants of health should be considered in the glucose-lowering management of type 2 diabetes. Pharmacologic therapy should be guided by person-centered treatment factors, including comorbidities and treatment goals. Pharmacotherapy should be started at the time type 2 diabetes is diagnosed unless there are contraindications. Pharmacologic approaches that provide the efficacy to achieve treatment goals should be considered, such as metformin or other agents, including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals. In adults with type 2 diabetes and established/high risk of atherosclerotic cardiovascular disease (ASCVD), heart failure (HF), and/or chronic kidney disease (CKD), the treatment regimen should include agents that reduce cardiorenal risk.(11) Pharmacologic approaches that provide the efficacy to achieve treatment goals should be considered, specified as metformin or agent(s), including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals. In general, higher-efficacy approaches have greater likelihood of achieving glycemic goals, with the following considered to have very high efficacy for glucose lowering: the GLP-1 RAs dulaglutide (high dose) and semaglutide, the gastric inhibitory peptide (GIP) and GLP-1 RA tirzepatide, insulin, combination oral therapy, and combination injectable therapy. Weight management is an impactful component of glucose-lowering management in type 2 diabetes. The glucose-lowering treatment regimen should consider approaches that support weight management goals, with very high efficacy for weight loss seen with semaglutide and tirzepatide.(11) Metformin is effective and safe, is inexpensive, and may reduce risk of cardiovascular events and death. Metformin is available in an immediate-release form for twice-daily dosing or as an extended-release form that can be given once daily. Compared with sulfonylureas, metformin as first-line therapy has beneficial effects on A1C, weight, and cardiovascular mortality. For people with type 2 diabetes and established ASCVD or indicators of high ASCVD risk, HF, or CKD, an SGLT2 inhibitor and/or GLP-1 RA with demonstrated CVD benefit is recommended as part of the glucose-lowering regimen independent of A1C, independent of metformin use and in consideration of person-specific factors. For people without established ASCVD, indicators of high ASCVD risk, HF, or CKD, medication choice is guided by efficacy in support of individualized glycemic and weight management goals, avoidance of side effects (particularly hypoglycemia and weight gain), cost/access, and individual preferences.(11)

	Dapagliflozin and empagliflozin have been shown to significantly reduce the risk of worsening heart failure or cardiovascular death independently of diabetes status.(2,4) Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), angiotensin receptor-neprilysin inhibitors (ARNIs), funny current channel inhibitors (e.g., Corlanor), aldosterone antagonists, beta blockers, isosorbide dinitrate and hydralazine are all medications commonly used for heart failure with reduced ejection fraction (HFrEF).(12,13)
Safety	Invokamet, Invokamet XR, Segluromet, Synjardy, Synjardy XR, Trijardy XR, and Xigduo XR all have a black box warning for lactic acidosis due to their metformin component:(3,5-7,9,17) • Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Symptoms included malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities included elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. • Risk factors include renal impairment, concomitant use of certain drugs, age more than 65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Steps to reduce the risk of and manage metformin-associated lactic acidosis in these high-risk groups are provided in the Full Prescribing Information. • If lactic acidosis is suspected, discontinue the medication and institute general supportive measures in a hospital setting. Prompt hemodialysis is recommended. Brenzavvy, Farxiga, Invokana, Jardiance, Steglatro, and Glyxambi are contraindicated in patients on dialysis.(1,2,4,8,14,19) Inpefa is contraindicated in history of serious hypersensitivity reaction to Inpefa.(18) Invokamet and Invokamet XR are contraindicated in patients with severe renal impairment, acute or chronic metabolic acidosis, including diabetic ketoacidosis.(3) Segluromet, Synjardy, Synjardy XR, Xigduo XR, and Trijardy XR are contraindicated in patients with severe renal impairment, end stage renal disease

	(ESRD), patients on dialysis, and patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis.(5-7,9,17) Steglujan and Qtern are contraindicated in patients with severe renal impairment, end stage renal disease (ESRD), or on dialysis.(5-7,9,17)

REFERENCES

Number	Reference
1	Invokana prescribing information. Janssen Pharmaceuticals, Inc. July 2023.
2	Farxiga prescribing information. Astra Zeneca. September 2023.
3	Invokamet and Invokamet XR prescribing information. Janssen Pharmaceuticals, Inc. July 2023.
4	Jardiance prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc. September 2023.
5	Xigduo XR prescribing information. AstraZeneca Pharmaceuticals LP. September 2023.
6	Synjardy prescribing information. Boehringer Ingelheim. March 2022.
7	Synjardy XR prescribing information. Boehringer Ingelheim. March 2022.
8	Steglatro prescribing information. Merck & Co, Inc. March 2022.
9	Segluromet prescribing information. Merck Sharp & Dohme Corp. May 2022.
10	American Diabetes Association. Standards of Medical Care in Diabetes-2022. Available at: https://care.diabetesjournals.org/content/45/Supplement_1.
11	Nuha A. ElSayed, et. al, American Diabetes Association, 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2023. Diabetes Care 1 January 2023; 46 (Supplement_1): S140–S157. https://doi.org/10.2337/dc23-S009.
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13	Yancy CW, Jessup M, Bozkurt B, et. al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017;136:e137-e161. Available at: https://www.ahajournals.org/doi/full/10.1161/CIR.0000000000000509.
14	Glyxambi prescribing information. Boehringer Ingelheim Pharmaceuticals, Inc and Eli Lilly and Company. October 2022.
15	Qtern prescribing information. Astra Zeneca. September 2023.
16	Steglujan prescribing information. Merck & Co., Inc. June 2022.
17	Trijardy XR prescribing information. Boehringer Ingelheim International GmbH. October 2022.
18	Inpefa Prescribing Information. Lexicon Pharmaceuticals, Inc. May 2023.
19	Brenzavvy prescribing information. TheracosBio, LLC. September 2023.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity Limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR**

Module	Clinical Criteria for Approval
	C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Skyclarys (omaveloxolone)

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Skyclarys® (omaveloxolone) Capsule	Treatment of Friedreich's ataxia in adults and adolescents aged 16 years and older		1

CLINICAL RATIONALE

Friedreich Ataxia	Friedreich ataxia (FA, FRDA) is a progressive autosomal recessive genetic neurodegenerative disorder affecting approximately 5,000 patients in the United States and 22,000 patients globally.(4,5) FA is caused by a biallelic trinucleotide (GAA) repeat expansion in the first intron of the *FXN* gene, which impairs transcription and significantly reduces the amount of functional frataxin protein. The pathological consequences of frataxin deficiency include disruption of iron–sulfur cluster biosynthesis, cellular iron dysregulation, mitochondrial dysfunction, and increased sensitivity to oxidative stress leading to the clinical features of FA.(2,3,4,5) Ataxia is the most common clinical feature in FA, reflecting both proprioceptive loss and cerebellar disease. Patients can also develop spasticity, visual and hearing loss, and non-neurological features such as cardiomyopathy, diabetes, and scoliosis. In most patients, symptoms begin between 5 and 15 years of age, and patients lose the ability to ambulate by their mid-20s. FA shortens life span, most often through consequences of cardiomyopathy; average age at death is 37 years.(4,5) Genetic testing for the triplet repeat expansions in the first intron of the frataxin (*FXN*) gene that cause Friedreich ataxia should be performed in all patients with progressive cerebellar ataxia and autosomal recessive inheritance.(2,3,4,5) In individuals who are ambulant, clinical management guidelines recommend regular monitoring of ambulation and contributing physical and non-physical factors for mobility decline (e.g., balance, strength, lower limb spasticity, fear of

	falling) at least once per year. For non-ambulant individuals, regular monitoring of mobility (including ability to transfer) and contributing factors for mobility decline (e.g., balance, strength, lower limb spasticity, environmental set-up) is recommended at least once per year.(6) Until omaveloxolone was approved by the FDA for treatment of FA, there was no specific disease-modifying therapy available. The management of patients with this disorder requires a multidisciplinary team of special services. An occupational and physical therapy program should be initiated early. Periodic evaluation of cardiac function is required. Similarly, patients should be monitored for the development of dysphagia, scoliosis, vision loss, hearing loss, bladder dysfunction, sleep apnea, and diabetes mellitus.(4,5)
Efficacy	Omaveloxolone is an activator of the Nuclear factor-like (Nrf2) pathway, which is involved in the cellular response to oxidative stress.(1) Treatment with omaveloxolone in vitro restores mitochondrial function in fibroblasts from Friedreich ataxia patients and in neurons from multiple mouse models.(4,5) In a larger international randomized trial, 103 patients with Friedreich ataxia (median age, 21 to 22 years; mean disease duration, approximately 4.5 years) were randomly assigned to omaveloxolone 150 mg daily or placebo for 48 weeks. Efficacy data were presented for 82 patients (80%) who received 48 weeks of treatment and had completed primary outcome measurements on the mFARs. Among these patients, mFARS scores improved by 1.55 points in the omaveloxolone group and worsened by 0.85 points in the placebo group (mean difference between groups -2.4 points, 95% CI -4.3 to -0.5). Adverse effects that occurred more commonly with omaveloxolone than placebo included elevated aminotransferase levels (37 versus 2%; no cases of clinical liver injury), headache (37 versus 25%), and nausea (33 versus 14%).(1) Although the trial had limitations and the effect size was relatively modest, Friedreich ataxia is a slowly progressive disease, and small differences in functional progression over one to two years could translate to meaningful differences over the course of the disease.(5)

REFERENCES

Number	Reference
1	Skyclarys prescribing information. Reata Pharmaceuticals, Inc. February 2023.

Number	Reference
2	Rummey C, Corben LA, Delatycki M, et al. Natural History of Friedreich Ataxia. Neurology. 2022 Oct;99(14):e1499-e1510.
3	Pandolfo M. Friedreich Ataxia. Arch Neurol. 2008 Oct;65(10):1296-1303.
4	Lynch DR, Chin MP, Delatycki MB, et al. Safety and Efficacy of Omaveloxolone in Friedreich Ataxia (MOXIe Study). Ann Neurol. 2021 Feb;89(2):212-225.
5	Opal P, Zoghbi H, et al. Friedreich Ataxia. UpToDate. Last updated November 2023. Literature review current through December 2023.
6	Corben LA, Collins V, Milne S, et al. Clinical Management Guidelines for Friedreich Ataxia: Best Practice in Rare Diseases. Orphanet J Rare Dis. 2022;17:415.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** Skyclarys 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. ALL of the following:

Module	Clinical Criteria for Approval
	1. The patient has a diagnosis of Friedreich ataxia (FA, FRDA) with genetic analysis confirming mutation in the frataxin (FXN) gene **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber has assessed baseline status (prior to therapy with the requested agent) of the patient's symptoms (e.g., mobility, balance, strength, lower limb spasticity) **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, geneticist, neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval**: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had improvements or stabilization with the requested agent (e.g., mobility, balance, strength, lower limb spasticity) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, geneticist, neurologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval**: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support of therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Selective Serotonin Inverse Agonist (SSIA)

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Nuplazid® (pimavanserin) Capsule Tablet	Treatment of hallucinations and delusions associated with Parkinson's disease psychosis		1

CLINICAL RATIONALE

Parkinson's Disease	Parkinson's disease (PD) is a chronic, progressive neurodegenerative disease characterized by bradykinesia, hypokinesia, rest tremor, and/or rigidity. In addition to these typical motor features, patients with PD may experience nonmotor symptoms related to the disease itself or to the medications used to treat it. A frequent nonmotor complication of PD is psychosis, characterized mainly by visual hallucinations and delusions which are often paranoid in nature. Hallucinations are the most common manifestation and can affect up to 40% of patients with PD, particularly those at an advanced stage of illness. Underlying dementia predisposes to hallucinations and delusions, and psychosis is a risk factor for nursing home placement and mortality.(2-4) Management of PD psychosis (PDP) involves identifying and treating the underlying causes and contributory factors, thus requiring a multidisciplinary team to be involved (e.g., psychiatrists and other mental health professionals, neurologists).(3) Psychosis may be triggered by infection, delirium, dementia, or medications. Anticholinergics can contribute to confusion and exacerbate psychosis in PD. Psychoactive medications, including sedatives, anxiolytics, and antidepressants, are potential culprits and should be reduced or stopped if possible. The adverse effects of antiparkinsonian medications, the dopamine agonists in particular, are probably the most important cause of psychosis in patients with PD. Stopping all potentially offending antiparkinsonian drugs is usually not an option, although dose reduction can frequently be accomplished

	with the amelioration of hallucinations and little loss of drug-related benefit. Antiparkinsonian drugs may be reduced or stopped in an order that balances their potency and their likelihood of exacerbating disabling hallucinations. The suggested sequence begins with anticholinergic drugs, followed by amantadine, dopamine agonists, monoamine oxidase type B (MAO B) inhibitors, and catechol-O-methyl transferase (COMT) inhibitors. Levodopa, usually combined with a peripheral decarboxylase inhibitor (e.g., carbidopa-levodopa), should be the last of a drug combination to be reduced, since it is the most effective antiparkinsonian agent and least likely to cause psychosis.(2-4) For refractory hallucinations or delusions treatment options are scarce, in part because many antipsychotics are known to worsen motor symptoms or are not effective. Quetiapine is the most widely prescribed despite evidence of efficacy in PD patients being mixed. Clozapine has demonstrated the highest efficacy of the second-generation antipsychotics in this setting but is underutilized because of the burdensome requirement of hematologic monitoring (agranulocytosis).(2-4)
Efficacy	In 2016, pimavanserin (Nuplazid) became the first antipsychotic FDA-approved to treat PDP. Pimavanserin is a second-generation antipsychotic that acts as a selective serotonin 5-HT2A receptor inverse agonist. Pimavanserin's efficacy in hallucinations and delusions associated with PDP was studied in a 6-week, randomized, placebo-controlled, parallel-group study with 199 patients. Pimavanserin was statistically significantly superior to placebo in decreasing the frequency and/or severity of hallucinations and delusions in patients with PDP as measured by central, independent, and blinded raters using the PD-adapted Scale for the Assessment of Positive Symptoms (SAPS-PD) scale. An effect was seen on both the hallucinations and delusions components of the SAPS-PD scale. Notably, pimavanserin did not negatively impact motor function, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS). Initial concerns of higher rates of mortality were shown to be no higher than those in this already frail patient group.(1,4)
Safety	Pimavanserin has the following boxed warnings:(1) • Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. • Nuplazid is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis. And has the following contraindication:(1)

	• Known hypersensitivity to Nuplazid or any of its components. All antipsychotic drugs appear to be associated with a small increase in all-cause mortality and cardiovascular events when used to treat behavioral disorders in older adults with dementia. However, these risks must be balanced with the high morbidity and mortality of untreated psychosis.

REFERENCES

Number	Reference
1	Nuplazid prescribing information. Acadia Pharmaceuticals Inc. September 2023.
2	Taddei RN, Cankaya S, Dhaliwal S, Chaudhuri KR. Management of Psychosis in Parkinson's Disease: Emphasizing Clinical Subtypes and Pathophysiological Mechanisms of the Condition. J Parkinsons Dis 2017;2017:3256542. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5613459/.
3	Chen JJ. Treatment of Psychotic Symptoms in Patients with Parkinson Disease. Ment Health Clin 2017;7(6):262-270. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6007727/.
4	Weil RS, Reeves S. Hallucinations in Parkinson's disease: new insights into mechanisms and treatments. Adv Clin Neurosci Rehabil. 2020;19(4):ONNS5189. Published 2020 Jul 13. doi:10.47795/ONNS5189.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of hallucinations or delusions associated with Parkinson's disease psychosis AND ONE of the following: 1. The patient has tried and had an inadequate response to clozapine or quetiapine **OR** 2. The patient has an intolerance or hypersensitivity to clozapine or quetiapine **OR** 3. The patient has an FDA labeled contraindication to BOTH clozapine and quetiapine **OR** B. The patient has another FDA labeled indication for the requested agent **AND**

Module	Clinical Criteria for Approval
	2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within the FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist, psychiatrist or other mental health professional) or the prescriber has consulted with a specialist in the area of the patient's diagnosis for the requested indication **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support of therapy with a higher dose for the requested indication **Length of Approval**: 12 months

Strensiq

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Strensiq® (asfotase alfa) Subcutaneous injection	Treatment of patients with perinatal/infantile-onset and juvenile-onset hypophosphatasia (HPP)		1

CLINICAL RATIONALE

Hypophosphatasia	Hypophosphatasia (HPP) is a rare genetic disease caused by mutations in the tissue non-specific alkaline phosphatase (TNSALP) gene, which reduce its activity. This causes disruption of mineralization, a process in which calcium and phosphorous are deposited in developing bones and teeth.(5) TNSALP controls skeletal and dental mineralization by hydrolyzing inorganic pyrophosphate, an inhibitor of hydroxyapatite crystal growth. Insufficient activity can lead to chest wall instability and respiratory complications in perinatal and infantile forms. Natural substrates of TNSALP that accumulate in hypophosphatasia include inorganic pyrophosphate (PPi), phosphoethanolamine (PEA), and pyridoxal 5'-phosphate (PLP), the principal circulating form of vitamin B6.(4) Perinatal HPP features extreme skeletal disease obvious at birth; survival beyond birth is rare. Infantile HPP develops prior to 6 months of age and has an estimated 50% mortality during infancy typically due to respiratory complications. Patients with infantile HPP develop rickets, failure to thrive, hypotonia, myopathy, and the condition is often complicated by hypercalcemia, nephrocalcinosis, craniosynostosis, and vitamin B6-dependent seizures. Although spontaneous improvement sometimes occurs in infantile hypophosphatasia, substantial bone disease and weakness often persist. Skeletal deterioration typically results in death from respiratory insufficiency. In both forms, hypomineralization leads to thoracic instability, fractures, and deformities, and sometimes even pulmonary hypoplasia in perinatal HPP.(3)

	Juvenile HPP tends to be less severe than those that appear in infancy. Affected children may have short stature, bowed legs, enlarged wrist and ankle joints (metaphyseal flares that appear as “swollen joints”), muscle weakness, and abnormal skull shape.(3) A diagnosis of HPP is based upon identification of characteristic signs and symptoms, a detailed patient history, a thorough clinical evaluation, and a variety of laboratory tests including routine x-ray and biochemical studies. Proper diagnosis of HPP is easy for physicians who are familiar or experienced with this disorder. Molecular genetic testing can support a diagnosis of HPP. Molecular genetic testing can detect mutations in the ALPL gene known to cause the disorder, but it is only available as a diagnostic service at specialized laboratories.(4) Individuals with HPP have reduced serum alkaline phosphatase (ALP) activity for their age, except for the extremely rare individual with pseudohypophosphatasia who has normal activity levels. The range of serum alkaline phosphatase (ALP) activity varies by age and healthy children normally have higher ALP levels than healthy adults. Identification of deficient ALP activity is consistent with HPP, but not conclusive since other conditions can result in this finding.(4) Individuals with HPP also have elevated levels of pyridoxal 5’-phosphate (PLP: the active form of vitamin B6) in the blood because PLP is normally broken down by TNSALP. Previously, blood or urine was tested for increased amounts of phosphoethanolamine (PEA), another chemical normally broken down by TNSALP. Elevated PEA is not specific to HPP, can be associated with other metabolic bone diseases, or some individuals with HPP have normal PEA levels. Screening for elevated PLP is preferred over screening for PEA because it is more sensitive, more precise, and less expensive. In the most severe cases of HPP, specifically the perinatal and infantile forms, x-ray studies can reveal diagnostic changes within the bones. However, these changes may not be recognized as being associated with HPP except by radiologists familiar with the disorder.(2,4) Periodic assessments should be performed to monitor the safety and effectiveness of Strensiq. Assessment includes the monitoring of symptoms, growth, radiographs, and laboratory tests, (e.g., PEA, PLP, or PPi). Other than asfotase alpha, the primary way to manage HPP is through supportive care.(2,4)
Efficacy	Strensiq is the first approved therapy for perinatal, infantile and juvenile-onset HPP. Strensiq is a formulation of asfotase alfa, which is a soluble glycoprotein composed of two identical polypeptide chains. Strensiq is a tissue nonspecific alkaline phosphatase produced by recombinant DNA technology in a Chinese hamster ovary cell line.(1)

	Strensiq was evaluated in two studies for perinatal/infantile-onset hypophosphatasia (HPP) identified in the label as study 1 and study 2. Study 1 was a 24-week prospective single-arm trial in 11 patients with severe perinatal/infantile-onset HPP. Study 2 was a prospective open-label study in 59 patients with perinatal/infantile-onset HPP. Survival and invasive ventilation-free survival were compared in both study 1 and study 2 with a historical cohort of untreated patients with similar clinical characteristics. In the Strensiq treated populations, 91% were alive at the point of last contact vs 27% of historical controls. The Kaplan-Meier estimate of alive at age 1 year (week 48) was 97% in the Strensiq treated populations and 42% in the historical controls. The percentage of patients that were alive and not on ventilation at the point of last contact was 85% in the Strensiq treated population and 25% in the historical controls. The Kaplan-Meier estimate of alive and not on ventilation at age 1 year (week 48) was 96% in the Strensiq treated population and 31% in the historical controls.(1) Study 3 (as identified in the prescribing information) was a prospective open-label 24-week trial that included 8 juvenile-onset HPP and 5 perinatal/infantile-onset HPP patients. Growth and skeletal manifestations were compared with a historical cohort of 32 untreated patients with similar clinical characteristics. Strensiq treated patients showed better z-scores for height and weight compared to the historical cohorts. All 8 Strensiq treated patients were rated as responders (defined as a 2 or higher on the Radiographic Global Impression of Change scale by month 54) of treatment for skeletal manifestations.(1) Gait was also assessed using a modified Performance Oriented Mobility Assessment-Gait (MPOMA-G) scale in all 8 patients and using the 6-minute walk test in 7 of the 8 patients in this study. Step length improved by at least 1 point in either foot in 6 out of the 8 patients compared to 1 out of 6 control patients. The proportion of patients who had 6-minute walk test percent predicted values within the normal range for age, sex, and height-matched peers increased from 0 out of 8 patients at baseline to 6 patients by month 48. All 6 of these patients were also able to walk longer distances at this time point compared to baseline.(1) Prenatal/infantile and juvenile-onset HPP patients treated with Strensiq had reductions in plasma TNSALP substrates, PPi and PLP within 6 to 12 weeks of treatment. Reductions in plasma PPi and PLP levels did not correlate with clinical outcomes.(1)
Safety	The 80 mg/0.8 mL vial of Strensiq should not be used in pediatric patients weighing less than 40 kg because the systemic exposure of asfotase alfa

	achieved with the 80 mg/0.8 mL (higher concentration) is lower than that achieved with the other strength vials (lower concentration). A lower exposure may not be adequate for this subgroup of patients. Patients with HPP are at increased risk for developing ectopic calcifications. Events of ectopic calcification, including ophthalmic and renal, have been reported in clinical trials experience with Strensiq. Although there was insufficient information to determine whether or not the reported events were consistent with the disease or due to Strensiq, ophthalmology examinations and renal ultrasounds are recommended at baseline and periodically during treatment to monitor for signs and symptoms of ectopic calcifications and for changes in vision or renal function.(1)

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Number	Reference
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2	Kishani PS, Rush ET, Arundel P, et al. Monitoring guidance for patients with hypophosphatasia treated with asfotase alfa. Molecular Genetics and Metabolism 112 (2017) 4-17.
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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met:

Module	Clinical Criteria for Approval
	1. The patient has a diagnosis of either perinatal/infantile- OR juvenile-onset hypophosphatasia (HPP) AND ALL of the following: A. The patient was less than 18 years of age at onset **AND** B. The patient is experiencing active disease (e.g., bone pain, fractures, gait problems) **AND** C. The patient has/had clinical manifestations consistent with hypophosphatasia at the age of onset prior to age 18 (e.g., vitamin B6-dependent seizures, fractures, lost teeth with roots, skeletal abnormalities: such as rachitic chest deformity leading to respiratory problems or bowed arms/legs, "failure to thrive") **AND** D. The patient has/had radiographic imaging confirming the diagnosis of hypophosphatasia at the age of onset prior to age 18 (e.g., infantile rickets, alveolar bone loss, craniosynostosis) **AND** E. Molecular genetic testing has been completed confirming mutations in the *ALPL* gene that encodes the tissue nonspecific isoenzyme of ALP (TNSALP) **AND** F. The patient has reduced activity of unfractionated serum alkaline phosphatase (ALP) in the absence of bisphosphonate therapy (i.e., below the normal lab reference range for age and sex) **AND** G. ONE of the following: 1. Elevated serum concentration of pyridoxal 5'-phosphate (PLP) in the absence of vitamin supplements within one week prior to the test **OR** 2. Elevated urine concentration of phosphoethanolamine (PEA) **OR** 3. Elevated urinary inorganic pyrophosphate (PPi) **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient has had an ophthalmology examination and renal ultrasound at baseline (prior to starting therapy with the requested agent) **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 5. The requested quantity (dose) is within FDA labeled dosing for the requested indication based on the patient's weight **Length of Approval:** 6 months **Renewal Evaluation** **Target Agent(s)** will be approved when ALL the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND**

Module	Clinical Criteria for Approval
	2. The patient has had a decrease from baseline (before treatment with the requested agent) in at least ONE of the following: A. Serum concentration of pyridoxal 5'-phosphate (PLP) in the absence of vitamin supplements within one week prior to the test **OR** B. Urine concentration of phosphoethanolamine (PEA) **OR** C. Urinary inorganic pyrophosphate (PPi) **AND** 3. The patient has had clinical improvement from baseline (prior to starting therapy with the requested agent) in at least ONE of the following: A. Respiratory status **OR** B. Growth **OR** C. Radiographic findings **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient has been monitored for signs and symptoms of ophthalmic and renal calcifications and for changes in vision or renal function **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 7. The requested quantity (dose) is within FDA labeled dosing for the requested indication based on the patient's weight **Length of Approval:** 12 months

Substrate Reduction Therapy

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Cerdelga® (eliglustat) Capsule	Long-term treatment of adult patients with Gaucher disease type 1 who are CYP2D6 extensive metabolizers (EMs), intermediate metabolizers (IMs), or poor metabolizers (PMs) as detected by an FDA-cleared test for determining CYP2D6 genotype Limitations of Use: • CYP2D6 ultra-rapid metabolizers (URMs) may not achieve adequate concentrations of Cerdelga to achieve a therapeutic effect • A specific dosage cannot be recommended for those patients whose CYP2D6 genotype cannot be determined (indeterminate metabolizers)		1
Opfolda™ (miglustat) Capsule	Treatment of adult patients with late-onset Pompe disease (lysosomal acid alpha-glucosidase [GAA] deficiency) weighing greater than or equal to 40 kg and who are not improving on their current enzyme replacement therapy (ERT); Opfolda (an enzyme stabilizer) is indicated in combination with Pombiliti (a hydrolytic lysosomal glycogen-specific enzyme)		11
Zavesca® (miglustat)* Capsule	Monotherapy for treatment of adult patients with mild to moderate type 1 Gaucher disease for whom enzyme replacement therapy is not a therapeutic option (e.g., due to allergy, hypersensitivity, or poor venous access)	* Generic available	2

CLINICAL RATIONALE

Gaucher Disease	Gaucher disease (GD), the most common of the lysosomal storage disorders (LSDs), is a rare autosomal recessive metabolic disorder affecting only 1 in 40,000 in the general United States population.(4,7) Mutations in the *GBA* (glucocerebrosidase) gene cause reduced activity of the lysosomal enzyme

	glucocerebrosidase (also known as acid beta-glucosidase), resulting in the accumulation of harmful quantities of the glycolipid glucocerebroside (also known as glucosylceramide, or GLC) and other related sphingolipids. This multisystemic accumulation of GLC in various tissues, especially in lysosomes of macrophages, compromises the bone marrow, spleen, and liver, and less often the lungs, skin, kidneys, and heart.(3,4,7,8,9,10) GD is classified into 3 clinical types, distinguished by their clinical features, management, and prognosis. However, as with most genetic diseases, there is a continuum of clinical findings and overlap within and between types, resulting in identification of additional subtypes.(4,5,7,9) GD Type 1 (GD1) is distinguished from GD Types 2 (GD2) and 3 (GD3) by the lack of characteristic involvement of the central nervous system (CNS).(3,4,5,7,8) As such, it is also known as non-neuronopathic GD.(3,4,7) In the United States, Europe, and Israel, 90% of GD patients have GD1, with a high carrier frequency in the Ashkenazi-Jewish population.(3,4,5,7,8) Age of onset for GD1 is variable, with some patients presenting between 12 and 24 months of age and others having no clinical signs until late adulthood.(3,4,7) Manifestation in the first or second decades of life typically results in more aggressive and severe symptoms than those manifesting at a later stage of life.(7) Presentation of symptoms among patients with GD1 is variable. Splenomegaly is the most common symptom; hepatomegaly is also common, but the liver increases relatively less than the spleen. Other common presenting symptoms are anemia, thrombocytopenia, bone disease, and delayed growth.(3,4,5,7,8,10) GD2 is an acute neuronopathic form of GD characterized by early onset, typically in the first year after birth. Neurologic complications are extensive and severe, with limited psychomotor development. Death occurs within the first 2 years of life, usually due to respiratory failure.(3,5,7) GD3 is the subacute or chronic neuronopathic form, has later onset than GD2, and has slower disease progression with patients typically surviving to second or third decades of life. The distinction between GD2 and GD3 is difficult.(3,4) A diagnosis of GD should be considered in patients with unexplained anemia and easy bruising, particularly if they have enlargement of the spleen and liver.(3) Definitive diagnosis of GD can be confirmed by the finding of reduced glucocerebrosidase activity in leukocytes, fibroblasts, or other nucleated cells.(3,4,5,7,9,10) This enzyme assay test is typically known as BGL (beta-glucosidase leukocyte), and a finding of 15% or less of mean normal glucocerebrosidase enzyme activity is indicative of GD.(4,5) If BGL results are not conclusive and/or further confirmatory testing is desired, genetic testing is an option. Identification of two pathogenic alleles in the *GBA* gene can also

	determine diagnosis of GD.(3,4,5,9) The presence of neurologic complications has critical implications for prognosis and treatment and should be determined as soon as possible after diagnosis. Neuronopathic symptoms indicative of GD2 and GD3 include bulbar signs (e.g., stridor, strabismus, swallowing difficulty), pyramidal signs (e.g., opisthotonus, head retroflexion, spasticity, trismus), oculomotor apraxia, tonic-clonic seizures, myoclonic epilepsy, dementia, and ataxia. If not already performed as part of the diagnostic process, baseline measurement of hemoglobin level, platelet count, liver volume, and spleen volume should be documented.(4,5,7,10) When possible, management of a patient with GD should occur with a multidisciplinary team at a Comprehensive Gaucher Treatment Center(5) (list of facilities nationwide available at www.gaucherdisease.org. Goals of treatment are elimination or improvement of symptoms, prevention of irreversible complications, and improvement in overall health and quality of life. An additional goal in children is optimization of growth.(3,6,8) Currently, two different therapeutic approaches for the treatment of GD1 are used: enzyme replacement therapy (ERT) [Cerezyme (imiglucerase), VPRIV (velaglucerase alfa), Elelyso (taliglucerase alfa)] and substrate reduction therapy (SRT) [Cerdelga (eliglustat), Zavesca (miglustat)].(3,5,6,8,9) ERT, intravenously administered, targets macrophages and increases the breakdown of accumulated glycolipids.(8) SRT, orally administered, reduces the amount of synthesized GLC to a level that can be effectively cleared by the mutated enzyme's residual activity.(5,6,8) The decision to offer ERT or SRT in patients with GD1 is based upon disease severity and/or significant disease progression.(6,7,8,10) To begin treatment with ERT or SRT, clinically significant manifestations must be present. Thrombocytopenia of sufficient magnitude to justify initiation of treatment is defined by platelet counts less than 100,000 microliter, as well as symptomatic presentation of splenomegaly, anemia, bone disease, and/or delayed growth.(3,4,5,7,8,9)
Pompe Disease	Pompe disease, also known as acid maltase deficiency (AMD) or glycogen storage disease type II (GSDII), is an autosomal recessive disorder caused by mutations in the *GAA* gene for enzyme acid alpha-glucosidase (GAA).(12,13) Deficiency of lysosomal enzyme GAA leads to accumulation of glycogen in lysosomes and cytoplasm, resulting in tissue destruction.(13) Infantile-onset Pompe disease (IOPD) is characterized by cardiomyopathy, severe generalized hypotonia, respiratory distress typically requiring ventilator support, and failure to thrive. Most patients with this form die within the first

	year or two of life without treatment. The juvenile-adult form (late onset Pompe disease [LOPD]) is characterized by skeletal myopathy, delayed gross-motor development, and respiratory insufficiency and/or failure.(12,13) Diagnosis can be confirmed by demonstration of reduced acid alpha-glucosidase glycogen enzyme activity in dried blood spots or leukocytes (skin fibroblasts or skeletal muscle tissue are also options). *GAA* gene mutational analysis is the preferred test to confirm the diagnosis (with two pathogenic alleles), since it is routinely available, less invasive, and may help predict cross-reactive immunologic material (CRIM) status.(12,13,14) Prenatal diagnosis is possible by DNA analysis of cultured amniocytes or chorionic villus samples, if the mutation in the family is known.(13,14) Guidelines note that a trial of ERT may be considered in patients who receive invasive ventilation support, if there are predefined outcomes which can be evaluated and which, if achieved, would improve the functional status of the patient. After one year, decisions regarding the continuation of ERT in patients receiving invasive ventilation support should be made on a case-by-case basis.(15,16) Opfolda (miglustat) in combination with Pombiliti (an ERT; cipaglucosidase alfa) was approved by the FDA in September 2023 as a new treatment for adults with LOPD. Pombiliti provides an exogenous source of GAA, which exerts enzymatic activity in cleaving accumulating glycogen. Opfolda binds with, stabilizes, and reduces inactivation of Pombiliti in the blood after infusion.(11)
Efficacy - Gaucher Disease	Until the FDA approval of the SRT Cerdelga in 2014, ERT was the mainstay of therapy in patients with GD1. A 12-month phase 3, open-label, noninferiority study (ENCORE) in 106 adults (18 years of age and older) with GD1, stable after greater than or equal to 3 years of ERT with Cerezyme or VPRIV, found Cerdelga noninferior to Cerezyme in maintaining stability of four component domains (i.e., hemoglobin level, platelet count, liver volume, spleen volume). A 9-month randomized, double-blind, placebo-controlled study (ENGAGE) in 40 treatment-naïve GD1 patients 16 years of age and older, demonstrated that treatment with Cerdelga led to greater improvements in spleen and liver volume, platelet count, and hemoglobin level compared to placebo. These findings provided Cerdelga its designation as first-line or maintenance therapy in adult patients with GD1.(1,5,6,8) The SRT Zavesca, approved in 2003, is indicated only for GD1 patients for whom ERT is not an option (e.g., due to allergy, hypersensitivity, or poor venous access). Studies of Zavesca have demonstrated significant reductions from baseline in

	liver and spleen volume, and a non-significant increase from baseline in hemoglobin level and platelet count.(2,5,6)
Efficacy - Pompe Disease	PROPEL was a randomized, double-blind, active-controlled, international, multi-center clinical trial (NCT#03729362) in patients greater than or equal to 18 years old diagnosed with late-onset Pompe disease (LOPD). Patients were randomized 2:1 to receive Pombiliti in combination with Opfolda, or a non-U.S.-approved alglucosidase alfa product with placebo every other week for 52 weeks. The efficacy population included a total of 123 patients of whom 95 (77%) had received prior treatment with U.S.-approved alglucosidase alfa or a non-U.S.-approved alglucosidase alfa product (ERT-experienced) and 28 (23%) were ERT-naïve. More than two thirds (n=64, 67%) of ERT-experienced patients had been on ERT treatment for more than 5 years prior to entering the trial (mean of 7.4 years). Demographics, baseline sitting forced vital capacity (FVC) (% predicted), and 6-minute walk distance (6MWD) were generally similar between the 2 treatment groups. Key efficacy endpoints included assessment of sitting FVC (% predicted) and 6MWD. The ERT-experienced patients treated with Pombiliti in combination with Opfolda showed a numerically favorable change in sitting FVC from baseline at Week 52 (p=0.006).(11) Patients treated with combination Pombiliti and Opfolda walked on average 21 meters farther from baseline as compared to those treated with a non-U.S.-approved alglucosidase alfa product with placebo who walked 8 meters farther from baseline; the estimated treatment difference was 14 meters (95% CI: -1, 28). The ERT-experienced patients treated with Opfolda in combination with Pombiliti showed a numerically favorable change in 6MWD from baseline at Week 52 (p=0.047).(11) Opfolda in combination with Pombiliti is not approved for use in ERT-naïve patients with LOPD. The ERT-naïve patient subgroup enrolled too few patients to conclusively interpret the data.(11) A U.S.-approved alglucosidase alfa product was not used in this clinical trial. Conclusions cannot be drawn from this clinical trial regarding comparative effectiveness between a U.S.-approved alglucosidase alfa product and Opfolda in combination with Pombiliti for the treatment of adult patients with LOPD.(11)
Safety	Cerdelga (eliglustat) is contraindicated in the following patients based on CYP2D6 metabolizer status due to the risk of cardiac arrhythmias from prolongation of the PR, QTc, and/or QRS cardiac intervals:(1) • Extensive metabolizers (EMs):

	○ Taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor ○ Moderate or severe hepatic impairment ○ Mild hepatic impairment taking a strong or moderate CYP2D6 inhibitor • Intermediate metabolizers (IMs): ○ Taking a strong or moderate CYP2D6 inhibitor concomitantly with a strong or moderate CYP3A inhibitor ○ Taking a strong CYP3A inhibitor ○ Any degree of hepatic impairment • Poor metabolizers (PMs): ○ Taking a strong CYP3A inhibitor ○ Any degree of hepatic impairment Opfolda in combination with Pombiliti is contraindicated in pregnancy.(11) Zavesca (miglustat) has no contraindications.(2)

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Cerdelga, Zavesca	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND BOTH of the following: **Agents Eligible for Continuation of Therapy** All target agents are eligible for continuation of therapy 1. ONE of the following: A. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** B. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **AND** 2. The prescriber has assessed current status of the following: spleen volume, hemoglobin level, liver volume, platelet count, growth, bone pain or crisis **OR** B. ALL of the following: 1. The patient has a diagnosis of Gaucher disease type 1 (GD1) **AND** 2. ONE of the following: A. The patient has baseline (prior to therapy for the requested indication) glucocerebrosidase enzyme activity of less than or equal to 15% of mean normal in fibroblasts, leukocytes, or other nucleated cells **OR** B. Genetic analysis confirmed two (2) pathogenic alleles in the glucocerebrosidase (*GBA*) gene **AND** 3. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 4. The patient does NOT have any neuronopathic symptoms indicative of Gaucher disease type 2 or type 3 [e.g., bulbar signs (e.g., stridor, strabismus, swallowing difficulty), pyramidal signs (e.g., opisthotonos, head retroflexion, spasticity,

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trismus), oculomotor apraxia, tonic-clonic seizures, myoclonic epilepsy, dementia, ataxia] AND
5. The prescriber has assessed baseline (prior to therapy for the requested indication) status of hemoglobin level, platelet count, liver volume, and spleen volume AND
6. The patient has at least ONE of the following clinical presentations at baseline (prior to therapy for the requested indication):
A. Anemia defined as mean hemoglobin (Hb) level below the testing laboratory's lower limit of the normal range based on age and gender OR
B. Thrombocytopenia (platelet count less than 100,000/microliter on at least 2 measurements) OR
C. Hepatomegaly OR
D. Splenomegaly OR
E. Growth failure (i.e., growth velocity is below the standard mean for age) OR
F. Evidence of bone disease with other causes ruled out AND
7. If the requested agent is Zavesca or miglustat, enzyme replacement therapy (ERT) is NOT a therapeutic option (e.g., due to allergy, hypersensitivity, poor venous access, previous ERT failure) AND
2. If the requested agent is Cerdelga or eliglustat, the patient is a CYP2D6 extensive metabolizer (EM), intermediate metabolizer (IM), or poor metabolizer (PM), as detected by an FDA-cleared test for determining CYP2D6 genotype AND
3. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:
A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
C. There is support for the use of the requested brand agent over the generic equivalent AND
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<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Zavesca</td><td>miglustat</td></tr>
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4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND
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5. The patient will NOT be using the requested agent in combination with another substrate reduction therapy agent (e.g., Cerdelga, Opfolda, Zavesca) for the requested indication AND
6. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 12 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. The patient has been previously approved for the requested agent through the plan’s Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] AND
2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following:
   A. Spleen volume OR
   B. Hemoglobin level OR
   C. Liver volume OR
   D. Platelet count (sufficient to decrease the risk of bleeding) OR
   E. Growth OR
   F. Bone pain or crisis AND
3. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:
   A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
   B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
   C. There is support for the use of the requested brand agent over the generic equivalent AND

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<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Zavesca</td><td>miglustat</td></tr>
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<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of patient's diagnosis AND
5. The patient will NOT be using the requested agent in combination with another substrate reduction therapy agent (e.g., Cerdelga, Opfolda, Zavesca) for the requested indication AND
6. The patient does NOT have any FDA labeled contraindications to the requested agent

Length of Approval: 12 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.</td></tr>
<tr><td>Opfolda</td><td>Initial Evaluation

Opfolda will be approved when ALL of the following are met:

1. ONE of the following:
A. The requested agent is eligible for continuation of therapy AND ONE of the following:

<table><tr><th>Agents Eligible for Continuation of Therapy</th></tr><tr><td>Opfolda</td></tr></table>
1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days OR
2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed OR
B. ALL of the following:
1. The patient has a diagnosis of late-onset Pompe disease (acid maltase deficiency [AMD]; glycogen storage disease type II [GSDII]) confirmed by at least ONE of the following:
A. Genetic analysis confirms biallelic mutation (two pathogenic variants) in the GAA gene OR
B. The patient has deficient acid alpha-glucosidase glycogen enzyme activity in dried blood spots, leukocytes, skin fibroblasts, and/or skeletal muscle tissue AND
2. The patient is not improving on their current enzyme replacement therapy (ERT) AND
3. The requested agent will be taken in combination with Pombiliti AND</td></tr>
</table>

Module	Clinical Criteria for Approval
	4. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The prescriber has assessed current status of the following: gross motor function (e.g., walking distance), pulmonary function (e.g., forced vital capacity [FVC]) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval**: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit criteria. **Renewal Evaluation** **Opfolda** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had improvements or stabilization with the requested agent as indicated by ONE of the following: A. Gross motor function (e.g., walking distance) **OR** B. Pulmonary function (e.g., forced vital capacity [FVC]) **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval**: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support of therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Sucraid (sacrosidase)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Sucraid® (sacrosidase) Oral solution	Oral replacement therapy for treatment of genetically determined sucrase deficiency, which is part of congenital sucrase-isomaltase deficiency (CSID)		1

CLINICAL RATIONALE

CSID	Congenital sucrase-isomaltase deficiency (CSID) is a rare, chronic, autosomal recessive disorder characterized by the absence or deficiency of the enzymes sucrase and isomaltase.(3) Patients with CSID have two defective copies of the sucrase-isomaltase (SI) gene. The SI enzyme complex is naturally produced in the brush border lining of the small intestine and assists in the breakdown of certain sucrose and products of starch digestion (dextrins). When sucrase-isomaltase is absent or deficient, non-absorbed carbohydrates enter the distal small intestine and colon where they are fermented, leading to the excessive production of short-chain fatty acids and gases such as hydrogen, methane, and hydrogen sulfide. This in turn can lead to abdominal distension, cramping, pain, excessive flatulence, nausea/vomiting, and osmotic diarrhea. If left untreated, significant sucrase-isomaltase deficiency (SID) can result in inadequate growth and failure to thrive in children as well as weight loss in adults.(4) The gold standard for the diagnosis of CSID remains small intestinal biopsy specimens assayed for lactase, sucrase, isomaltase, and maltase activity. Criteria to make the diagnosis of CSID include normal small bowel morphology in the presence of markedly reduced or absent sucrase activity, isomaltase activity varying from zero to full activity, and reduced maltase activity. Lactase activity can be normal or reduced in children with a sucrase:lactase ratio of less than 1.0. Genetic sequencing of the SI gene can identify homozygous and compound heterozygous mutations responsible for CSID. A number of noninvasive diagnostic tests can also help establish the diagnosis, including the sucrose challenge test, lactose breath test, and hydrogen-methane breath test. However,

	many of these tests have limitations including false-positive results, false-negative results, and lack of validation data.(2) Previously, treatment of CSID has required lifelong adherence to a sucrose-free diet.(2-4) Data suggest that even after diagnosis and dietary treatment, major gastrointestinal symptoms persists, and there is a high frequency of decreased weight for height and age in these patients.(5) Treatment has improved considerably with the availability of enzyme replacement therapy (sacrosidase) which has allowed consumption of a more normal diet and decreased the high incidence of chronic gastrointestinal problems.(2-5) Access to a physician or dietician who is knowledgeable about CSID is essential for guiding patients and their families.(4)
Safety	Sucraid is contraindicated in patients known to be hypersensitive to yeast, yeast products, glycerin (glycerol), or papain.(1)

REFERENCES

Number	Reference
1	Sucraid prescribing information. QOL Medical, LLC. December 2023.
2	Treem WR. Clinical Aspects and Treatment of Congenital Sucrase-Isomaltase Deficiency. *Journal of Pediatric Gastroenterology and Nutrition*. 2012;55(S2). doi:10.1097/01.mpg.0000421401.57633.90
3	Congenital Sucrase-Isomaltase Deficiency - Symptoms, Causes, treatment | NORD. National Organization for Rare Disorders. https://rarediseases.org/rare-diseases/disaccharide-intolerance-i/
4	Congenital Sucrase-Isomaltase Deficiency: What, when, and how? – Gastroenterology & Hepatology. https://www.gastroenterologyandhepatology.net/supplements/congenital-sucrase-isomaltase-deficiency-what-when-and-how/
5	Treem WR, McAdams L, Stanford L, Kastoff G, Justinich C, Hyams J. Sacrosidase Therapy for Congenital Sucrase-Isomaltase Deficiency. *Journal of Pediatric Gastroenterology and Nutrition*. 1999;28(2):137-142. doi:10.1097/00005176-199902000-00008

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of congenital sucrase-isomaltase deficiency (CSID) confirmed by ONE of the following: A. Genetic testing of the sucrase-isomaltase (SI) gene indicates a pathogenic mutation **OR** B. Endoscopic biopsy of the small bowel indicates normal small bowel morphology in the presence of decreased (or absent) sucrase activity, isomaltase activity varying from decreased to normal activity, and decreased maltase activity **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, geneticist, endocrinologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 3 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., gastroenterologist, geneticist, endocrinologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Sunosi

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Sunosi® (solriamfetol) Tablet	Improve wakefulness in adult patients with excessive daytime sleepiness associated with narcolepsy or obstructive sleep apnea (OSA) Limitations of Use: Not indicated to treat the underlying airway obstruction in OSA. Ensure that the underlying airway obstruction is treated (e.g., with continuous positive airway pressure [CPAP]) for at least one month prior to initiating Sunosi for excessive daytime sleepiness. Modalities to treat the underlying airway obstruction should be continued during treatment with Sunosi. Sunosi is not a substitute for these modalities.		1

CLINICAL RATIONALE

Excessive daytime sleepiness	Excessive daytime sleepiness (EDS) is characterized by persistent sleepiness regardless of how much sleep an individual gets at night. In between sleep attacks, individuals have normal levels of alertness, particularly if doing activities that keep their attention.(2) The most common causes of EDS include narcolepsy, obstructive sleep apnea, shift work disorder, sleep deprivation, medication effects, and other medical and psychiatric conditions.(5)
Narcolepsy	Narcolepsy is a chronic neurological disorder caused by the inability to regulate sleep-wake cycles. At various times throughout the day, patients with narcolepsy experience irresistible bouts of sleep and could fall asleep. If left undiagnosed or untreated, narcolepsy can interfere with psychological, social, and cognitive function and development and can inhibit academic, work, and social activities. Symptoms may include excessive daytime sleepiness, cataplexy, sleep paralysis, and hallucinations. All patients diagnosed with narcolepsy will have excessive daytime sleepiness. However, sleepiness in narcolepsy is more like a “sleep attack”, where an overwhelming sense of sleepiness comes on quickly.(2) There

	is limited evidence to advise on treatment of special populations such as children, pregnant women, and breastfeeding mothers.(4)
	
	The American Family Physician recommends referral to a sleep clinic if narcolepsy is suspected.(3) The American Academy of Sleep Medicine (AASM) indicates treatment goals should be to alleviate daytime sleepiness and produce the fullest possible return of normal function for patients at work, school, home, and socially.(4)
	
	AASM 2021 guidelines combined the recommendations for narcolepsy with cataplexy and EDS associated with narcolepsy. The AASM recommend the following for the pharmacologic treatment with narcolepsy:(8)
	
	• Strong treatment recommendations:
	  ○ Modafinil
	  ○ Pitolisant
	  ○ Sodium oxybate
	  ○ Solriamfetol
	• Conditional treatment recommendations:
	  ○ Armodafinil
	  ○ Dextroamphetamine
	  ○ Methylphenidate
	• There was insufficient evidence to make recommendations for SSRI and SNRIs for the treatment of narcolepsy.(8)

Obstructive Sleep Apnea (OSA)	Obstructive sleep apnea (OSA) is a prevalent condition with serious health consequences, including EDS, cognitive disturbances, depression, hypertension, and cardiovascular and cerebrovascular disease.(7) Guidelines from the American College of Physicians (ACP) on management of OSA do not include modafinil/armodafinil in their recommendations for treatment. ACP guidelines state that pharmacologic therapy is not currently supported by evidence and should not be prescribed for OSA treatment.(7) AASM practice parameters recommend modafinil in patients with OSA for the treatment of residual excessive daytime sleepiness despite effective positive airway pressure treatment and who are lacking any other identifiable cause for their sleepiness.(7) Both guidelines recommend weight loss for obese and overweight patients and continuous positive airway pressure treatment as initial therapy.(6,7) A review on the treatment of OSA suggested pharmacologic agents play a minimal role in the treatment of breathing itself in patients with a sleep

	disorder. Modafinil and armodafinil are considered adjunctive therapies to improve wakefulness in these patients. These agents are recommended for patients who experience residual sleepiness despite optimal CPAP therapy, provided CPAP compliance is closely monitored. Modafinil or armodafinil do not treat the OSA itself but only the associated symptoms of sleepiness. The majority of patients (75%) with severe sleepiness at baseline still had mean multiple sleep latency times of less than 10 minutes despite the addition of modafinil to effective therapy with CPAP. This suggests that these drugs do not necessarily eliminate the risk of motor vehicle and other accidents in the OSA population. Concern also exists that the use of pharmacotherapy to treat excessive sleepiness associated with OSA may lead to subsequent reduction in CPAP compliance.(6)
Efficacy	**Excessive Daytime Sleepiness (EDS) in Patients with Narcolepsy** The efficacy of Sunosi in improving wakefulness and reducing excessive daytime sleepiness was demonstrated in a 12-week, multi-center, randomized, double-blind, placebo controlled, parallel-group study (Study 1; NCT02348593) in adult patients with a diagnosis of narcolepsy according to the ICSD-3 or DSM-5 criteria.(1) Wakefulness and sleepiness were assessed using the Maintenance of Wakefulness Test(MWT) and the Epworth Sleepiness Scale (ESS). Compared to the placebo group, patients randomized to 150 mg Sunosi showed statistically significant improvements on the MWT and on the ESS at Week 12.(1) **Excessive Daytime Sleepiness (EDS) in Patients with Obstructive Sleep Apnea (OSA)** The efficacy of Sunosi in improving wakefulness and reducing excessive daytime sleepiness in patients with OSA was demonstrated in a 12-week multi-center, randomized, double-blind, placebo-controlled study (Study 2; NCT02348606) in adults diagnosed with OSA according to ICSD 3 criteria.(1) Compared to the placebo group, patients randomized to 37.5 mg, 75 mg, and 150 mg Sunosi showed statistically significant improvements on the MWT and ESS. At Week 12, 37.5 mg, 75 mg, and 150 mg of Sunosi all demonstrated improvements i wakefulness compared to placebo as assessed in test sessions 1 (approximately hour post-dose) through 5 (approximately 9 hours post-dose) of the MWT.(1)
Safety	Sunosi is contraindicated in patients receiving concomitant treatment with monoamine oxidase inhibitors (MAOI), or within 14 days following discontinuation of MOAI, due to the risk of hypertensive reactions.(1)

REFERENCES

Number	Reference
1	Sunosi prescribing Information. Axsome Therapeutics, Inc. June 2023.
2	National Institute of Neurological Disorders and Stroke. Narcolepsy. NIH Publication No. 17-1637. Available at: https://www.ninds.nih.gov/health-information/disorders/narcolepsy. Last updated September 2023. Accessed October 2023.
3	Ramar, Kannan MD and Olson, Eric MD. Management of Common Sleep Disorders. Am Fam Physician. 2013 Aug 15; 88(4): 231-238.
4	Krahn, Lois MD, et al. Quality Measures for the Care of Patients with Narcolepsy. *Journal of Clinical Sleep Medicine*. 2015; Vol. 11(3).
5	Pagel J. Excessive daytime sleepiness. Am Fam Physician. 2009;79(5): 391-395.
6	Qaseem A, Holty J, Owens D, et al. Management of obstructive sleep apnea in adults: A clinical practice guideline from the American College of Physicians. Ann Intern Med. 2013;159:471–483.
7	Morgenthaler TI, Kapen S, Lee-Chiong T, Alessi C, Boehlecke B, Brown T, et al. Practice parameters for the medical therapy of obstructive sleep apnea. Sleep (2006) 29:1031–5.
8	Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2021;17(9):1881-1893.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of excessive daytime sleepiness associated with obstructive sleep apnea (OSA) AND ALL of the following:

Module	Clinical Criteria for Approval
	1. The underlying airway obstruction has been treated (e.g., continuous positive airway pressure [CPAP]) for at least 1-month prior to initiating therapy with the requested agent **AND** 2. The modalities to treat the underlying airway obstruction (e.g., continuous positive airway pressure [CPAP]) will be continued during treatment with the requested agent **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response after 1-month of therapy with armodafinil OR modafinil **OR** B. The patient has an intolerance or hypersensitivity to armodafinil OR modafinil **OR** C. The patient has an FDA labeled contraindication to BOTH armodafinil AND modafinil **OR** B. The patient has a diagnosis of excessive daytime sleepiness associated with narcolepsy AND ONE of the following: 1. The patient has tried and had an inadequate response after 1-month of therapy with armodafinil OR modafinil **OR** 2. The patient has an intolerance or hypersensitivity to armodafinil OR modafinil **OR** 3. The patient has an FDA labeled contraindication to BOTH armodafinil AND modafinil **AND** 2. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist, psychiatrist, pulmonologist, sleep disorder specialist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months Note: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation**

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. If the diagnosis is excessive daytime sleepiness associated with obstructive sleep apnea (OSA), the modalities to treat the underlying airway obstruction (e.g., continuous positive airway pressure [CPAP]) will be continued during treatment with the requested agent **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist, psychiatrist, pulmonologist, sleep disorder specialist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months Note: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR**

Module	Clinical Criteria for Approval
	C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval: up to 12 months**

Tarpeyo

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Tarpeyo® (budesonide) Delayed release capsule	Reduce the loss of kidney function in adults with primary immunoglobulin A nephropathy (IgAN) who are at risk for disease progression		1

CLINICAL RATIONALE

Immunoglobulin A Nephropathy	Immunoglobulin A nephropathy (IgAN), also known as Berger's disease, is a kidney disease that occurs when IgA deposits build up in the kidneys, causing inflammation that damages the glomeruli, in turn causing the kidneys to leak blood and protein into the urine. The damage may lead to scarring of the nephrons that progresses slowly over may years. Eventually, IgAN can lead to end-stage renal disease (ESRD).(3) Kidney biopsy is required to confirm the diagnosis of IgAN as there are no validated diagnostic serum or urine biomarkers for IgAN. Biopsy is indicated when a patient has signs of a severe or progressive disease. After a diagnosis has been established, guidelines recommend that all patients with IgAN be assessed for secondary causes (e.g., liver cirrhosis, HIV, hepatitis, inflammatory bowel disease).(3) The primary focus of IgAN management should be optimized supportive care [e.g., blood pressure management, maximally tolerated angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin II blocker (ARB), lifestyle modification, address cardiovascular risk]. Guidelines recommend that all patients with proteinuria greater than 0.5 g/d be treated with an ACEI or ARB irrespective of whether they have hypertension.(3) Guidelines define high risk of progression in IgAN as proteinuria greater than

	0.75–1 g/d despite at least 90 days of optimized supportive care. It is suggested that patients who remain at high risk despite maximal supportive care be considered for a 6 month course of glucocorticoid therapy. They stress the importance of discussing treatment-emergent toxicity, particularly those who have an estimated glomerular filtration rate (eGFR) less than 50 mL/min/1.73 m^2. It is further noted that glucocorticoids should be given with extreme caution or avoided entirely in the following situations:(3) • eGFR less than 30 mL/min/1.73 m^2 • Diabetes • Obesity (BMI greater than 30 kg/m^2) • Latent infections (e.g., viral hepatitis, tuberculosis) • Secondary disease (e.g., cirrhosis) • Active peptic ulceration • Uncontrolled psychiatric illness • Severe osteoporosis The goal of treatment for these patients that remain at high risk for progressive disease is a reduction of proteinuria to less than 1 g/d.(3)
Efficacy	The effect of Tarpeyo on proteinuria and kidney function was assessed in a randomized, double-blind, phase 3, 2-part, multicenter study (NefIgArd, NCT: 03643965) in adult patients (n=364) with biopsy-proven IgAN, eGFR greater than or equal to 35 mL/min/1.73 m^2 , and proteinuria (defined as either greater than or equal to 1 g/day or urine protein to creatinine ratio (UPCR) greater than or equal to 0.8 g/g) who were on a stable dose of maximally-tolerated renin-angiotensin-system (RAS) inhibitor therapy. Patients with other glomerulopathies, nephrotic syndrome, or those who had been treated with systemic immunosuppressive medications were excluded. Patients were randomized 1:1 to either Tarpeyo 16 mg once daily or placebo and treated for 9 months followed by a 2-week taper of either Tarpeyo 8 mg once daily or placebo. Patients were then observed for 15 months, during which no study drug was administered. At baseline, the mean eGFR was approximately 58 mL/min/1.73 m^2 and the mean UPCR was 1.5 g/g. The median age was 43 years (range from 20-73 years). At baseline, 98% of patients were treated with an ACEI or ARB.(1,2) The primary outcome for Part A of the study was the ratio (reduction) of UPCR (based on 24-hour urine collections) at 9 months compared to baseline. An interim analysis was based on the first 199 randomized patients who completed the Month 9 visit. A 31% reduction in UPCR was seen in patients treated with Tarpeyo 16mg daily compared to a 5% reduction in the placebo group (95% CI:

	16% to 42% reduction; p=0.0001). The final analysis of all 364 patients was consistent with the results of the interim analysis.(1,2) The primary outcome for Part B of the study was a time-weighted average of the log ratio of eGFR at each time point over 2 years relative to baseline to assess the effect of Tarpeyo on long-term kidney function. After 2 years there was a 5.9 mL/min/1.73 m^2 difference in mean change from baseline in eGFR (95% CI: 3.3 to 8.5 mL/min/1.73 m^2; p less than 0.0001). This treatment effect at 2 years was consistent across key subgroups, including baseline disease characteristics (e.g., baseline proteinuria).(1)
Safety	Tarpeyo is contraindicated in patients with hypersensitivity to budesonide or any of the ingredients of Tarpeyo. Serious hypersensitivity reactions, including anaphylaxis have occurred with other budesonide formulations.(1)

REFERENCES

Number	Reference
1	Tarpeyo prescribing information. Calliditas Therapeutics AB. December 2023.
2	Barratt J, Lafayette RA, Kristensen JK, et al. Results from part A of the multi-center, double-blind, randomized, placebo-controlled NefIgArd trial, which evaluated targeted-release formulation of budesonide for the treatment of primary immunoglobulin A nephropathy. *Kidney International*. 2023;103(2):391-402. doi:10.1016/j.kint.2022.09.017
3	Rovin BH, Adler SG, Barratt J, et al. KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases. *Kidney International*. 2021;100(4):S1-S276. doi:10.1016/j.kint.2021.05.021
4	Reference no longer used.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of primary immunoglobulin A nephropathy (IgAN) confirmed by kidney biopsy **AND**

Module	Clinical Criteria for Approval
	2. The requested agent will be used to reduce the loss of kidney function in a patient at risk for disease progression **AND** 3. ONE of the following: A. The patient has a urine protein-to-creatinine ratio (UPCR) greater than or equal to 0.8 g/g **OR** B. The patient has proteinuria greater than or equal to 1 g/day **AND** 4. The patient's eGFR is greater than or equal to 30 mL/min/1.73 m^2 **AND** 5. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 6. ONE of the following: A. BOTH of the following: 1. The patient has tried and had an inadequate response after at least 3 months of therapy with maximally tolerated ACEI or ARB (e.g., benazepril, lisinopril, losartan), or a combination medication containing an ACEI or ARB **AND** 2. The patient will be using an ACEI or ARB or a combination medication containing an ACEI or ARB in combination with the requested agent **OR** B. The patient has an intolerance or hypersensitivity to an ACEI or ARB, or a combination medication containing an ACEI or ARB **OR** C. The patient has an FDA labeled contraindication to ALL ACEI or ARB **AND** 7. ONE of the following: A. The patient has an intolerance or hypersensitivity to oral generic budesonide that is not expected to occur with the requested agent **OR** B. The patient has an FDA labeled contraindication to oral generic budesonide that is not expected to occur with the requested agent **AND** 8. ONE of the following: A. The patient has not previously been treated with a course of therapy (9 months) with the requested agent **OR** B. The patient has previously been treated with a course of therapy with the requested agent, AND there is support for an additional course of therapy with the requested agent **AND** 9. The prescriber is a specialist in the area of the patient's diagnosis (e.g., nephrologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 10. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 10 months NOTE: If Quantity Limit applies, please refer to Quantity Limit criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 10 months

Tezspire (tezepelumab-ekko)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Tezspire® (tezepelumab-ekko) Subcutaneous injection	Add-on maintenance treatment of adult and pediatric patients 12 years and older with severe asthma Limitation of use: • Not for the relief of acute bronchospasm or status asthmaticus		1

CLINICAL RATIONALE

Asthma	Asthma is a chronic inflammatory disorder of the airways.(2,3) It is characterized by variable and recurring clinical symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation.(2) Symptoms of asthma include wheezing, coughing, recurrent difficulty breathing, shortness of breath, and chest tightness. Generally, these symptoms will occur or worsen with exposure to allergens and irritants, infections, exercise, changes in weather, stress, or menstrual cycles. Guidelines recommend the use of detailed medical history, physical examination, and spirometry to make a diagnosis of asthma.(2,3) The Global Initiative for Asthma (GINA) guidelines recommend a stepwise approach for managing asthma. Long-term goals for asthma management are to achieve good control of symptoms, maintain normal activity level, and to minimize the future risk of exacerbations, fixed airflow limitation, and side-effects.(3) IgE is the antibody responsible for activation of allergic reactions and is important to the pathogenesis of allergic asthma and the development and persistence of inflammation. GINA guidelines define moderate asthma as that which is well controlled with Step 3 or Step 4 treatment (e.g., low- or medium-dose inhaled corticosteroids [ICS] in combination with a long-acting beta agonist [LABA] in either treatment track). Severe asthma is defined as asthma that remains uncontrolled despite optimized treatment with high-dose ICS-LABA, or

	that requires high-dose ICS-LABA to prevent it from becoming uncontrolled. Severe asthma must be distinguished from asthma that is difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity, as they need very different treatment compared with if asthma is relatively refractory to high-dose ICS-LABA or even oral corticosteroids (OCS). Early initiation of low dose ICS in patients with asthma has led to greater improvement in lung function than initiation of ICS after symptoms have been present for more than 2 to 4 years. The 2023 GINA guidelines recommend every adult and adolescent with asthma should receive ICS-containing controller medication to reduce the risk of serious exacerbation, even in patients with infrequent symptoms.(3)
	
	2023 GINA STEP recommendations for adults and adolescents (12 years of age and over) are intended to reduce the risk of serious exacerbations and are broken into two tracks based on reliever therapy.
	
	Track 1 is the preferred approach recommended by GINA, because using low dose ICS-formoterol as reliever reduces the risk of exacerbations compared with regimens with short-acting β2-agonist (SABA) as reliever, and is a simpler regimen. Note ICS-formoterol should not be used as the reliever by patients taking any other (non-formoterol) ICS-LABA or ICS-LAMA:(3)
	
	• Step 1:
	  ○ As-needed low dose ICS-formoterol
	• Step 2:
	  ○ As-needed low dose ICS-formoterol
	• Step 3: address and treat modifiable risk factors (e.g., adherence, technique) before considering step up
	  ○ Maintenance: low dose ICS-formoterol
	  ○ Reliever: as-needed low dose ICS-formoterol
	• Step 4:
	  ○ Maintenance: medium dose ICS-formoterol
	  ○ Reliever: as-needed low dose ICS-formoterol
	• Step 5: patients with uncontrolled symptoms and/or exacerbations despite Step 4 treatment should be assessed for contributory factors, have their treatment optimized, and be referred for expert assessment including severe asthma phenotype, and potential add on treatment
	  ○ Maintenance: consider high dose ICS-formoterol
	  ○ Reliever: as-needed low dose ICS-formoterol
	  ○ Add-on LAMA for patients greater than or equal to 18 years (greater than or equal to 6 years for tiotropium) in separate or combination inhalers

	○ Refer for phenotypic assessment +/- biologic therapy ▪ Add-on anti-IgE for severe allergic asthma • SC omalizumab in patients greater than or equal to 6 years ▪ Add-on anti-interleukin (IL)5 or anti-IL5R or anti-IL4R for severe eosinophilic/Type 2 asthma • Anti-IL5: SC mepolizumab for patients greater than or equal to 6 years OR IV reslizumab for patients greater than or equal to 18 years of age • Anti-IL5R: SC benralizumab for patients greater than or equal to 12 years • Anti-IL4R: SC dupilumab for patients greater than or equal to 6 years ▪ Add-on anti-thymic stromal lymphopoietin (TSLP) for severe asthma • SC tezepelumab for patients greater than or equal to 12 years ○ Add-on azithromycin three days/week reduces exacerbations, but increases antibiotic resistance ○ Maintenance oral corticosteroids (OCS) should be used only as last resort, because short-term and long-term systemic side-effects are common and serious **Track 2** is an alternative approach if Track 1 is not possible or is not preferred by a patient with no exacerbations on their current therapy. Before considering a regimen with SABA reliever, the clinician should consider whether the patient is likely to be adherent with their controller therapy; if not, they will be exposed to the higher risk of exacerbations with SABA-only treatment:(3) • Step 1: ○ Take ICS whenever SABA taken ○ Reliever: as-needed ICS-SABA or as needed SABA • Step 2: ○ Preferred maintenance: low dose ICS ○ Preferred reliever: as-needed ICS-SABA or as-needed SABA ○ Alternative options with limited indications, or less evidence for efficacy and/or safety: ▪ Low dose ICS whenever SABA taken ▪ Daily LTRA. These are less effective than daily ICS, particularly for preventing exacerbations and there is a US FDA boxed warning about the risk of serious mental health effects with montelukast

	▪ Daily low-dose ICS-LABA as initial therapy leads to faster improvement in symptoms and FEV1 than ICS alone but is costlier, and the reduction in exacerbations compared with SABA is similar to that with ICS ▪ For adults with rhinitis who are allergic to house dust mite and have FEV1 > 70% predicted, consider adding sublingual immunotherapy (SLIT) • Step 3: address and treat modifiable risk factors (e.g., adherence, technique) before considering step up o Preferred maintenance: low dose ICS-LABA o Preferred reliever: as-needed ICS-SABA or as-needed SABA o Alternative options: ▪ Medium dose ICS ▪ Low-dose ICS plus LTRA but review US FDA boxed warning ▪ For adults with rhinitis who are allergic to house dust mite and have FEV1 > 70% predicted, consider adding SLIT • Step 4: o Preferred maintenance: medium/high dose ICS-LABA o Preferred reliever: as-needed ICS-SABA or as-needed SABA o Alternative options: ▪ Add-on LAMA for patients greater than or equal to 18 years (greater than or equal to 6 years for tiotropium my mist inhaler) ▪ Before considering add-on LAMA for patients with exacerbations, increase ICS dose to at least medium ▪ For adults with rhinitis who are allergic to house dust mite and have FEV1 > 70% predicted, consider adding sublingual immunotherapy (SLIT) • Step 5: patients with uncontrolled symptoms and/or exacerbations despite Step 4 treatment should be assessed for contributory factors, have their treatment optimized, and be referred for expert assessment including severe asthma phenotype, and potential add on treatment o Maintenance: medium/high dose ICS-LABA o Reliever: as-needed ICS-SABA or as-needed SABA o Add-on LAMA for patients greater than or equal to 18 years (greater than or equal to 6 years for tiotropium) in separate or combination inhalers o Refer for phenotypic assessment +/- biologic therapy ▪ Add-on anti-IgE for severe allergic asthma • SC omalizumab in patients greater than or equal to 6 years

	▪ Add-on anti-interleukin (IL)5 or anti-IL5R or anti-IL4R for severe eosinophilic/Type 2 asthma • Anti-IL5: SC mepolizumab for patients greater than or equal to 6 years OR IV reslizumab for patients greater than or equal to 18 years of age • Anti-IL5R: SC benralizumab for patients greater than or equal to 12 years • Anti-IL4R: SC dupilumab for patients greater than or equal to 6 years ▪ Add-on anti-thymic stromal lymphopoietin (TSLP) for severe asthma • SC tezepelumab for patients greater than or equal to 12 years ○ Add-on azithromycin three days/week reduces exacerbations, but increases antibiotic resistance ○ Maintenance OCS should only be used as last resort, because short-term and long-term systemic side-effects are common and serious 2023 GINA STEP recommendations for children (6 to 11 years of age) are intended to reduce the risk of serious exacerbations:(3) • Step 1: ○ Low dose ICS taken whenever SABA taken ○ Reliever: as needed SABA • Step 2: ○ Preferred: daily low dose ICS ○ Preferred reliever: as needed SABA ○ Alternative options: ▪ Low-dose ICS whenever SABA is taken using separate inhalers ▪ Daily LTRA are less effective for exacerbation reduction. Advise parents about US FDA warning on montelukast • Step 3: after checking inhaler technique and adherence, and treating modifiable risk factors (any of the following): ○ Medium-dose ICS maintenance plus as-needed SABA ○ Low-dose ICS-LABA maintenance plus as-needed SABA ○ Maintenance and reliever therapy (MART) with a very low dose of budesonide-formoterol DPI • Step 4: Individual children's responses vary, so each of the Step 3 options may be tried before considering a step-up to Step 4. Refer for expert advice

	○ Preferred: medium dose ICS-LABA plus as-needed SABA ○ Preferred: low dose ICS-formoterol MART plus as-needed low-dose ICS-formoterol ○ Alternative options: ▪ Add-on tiotropium ▪ Add-on LTRA • Step 5: ○ Refer for phenotypic assessment with or without higher dose ICS-LABA ○ Reliever: as needed SABA (or ICS-formoterol reliever for MART) ○ Add on therapy with anti-IgE or anti-IL4R, anti-IL5 ○ As a last resort consider add on low dose OCS but consider side effects **Severe Asthma Phenotype and Eosinophilic Asthma Subphenotype** Roughly 3% to 10% of adults with asthma have severe asthma as defined by the GINA 2023 guidelines.(3) The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014; updated 2020) and the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group mirror the GINA definition of severe asthma, and defined uncontrolled asthma for adult and pediatric patients 5 years of age and over:(2,4) • Frequent severe exacerbations (i.e., two or more bursts of systemic corticosteroids within the past 12 months) • Serious exacerbations (i.e., at least one hospitalization, intensive care unit stay, or mechanical ventilation in the past 12 months) • Airflow limitation (i.e., FEV1 less than 80% predicted) • Asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids A specialist, preferably in a multidisciplinary severe asthma clinic (if available) performs further assessment, which includes the patient's inflammatory phenotype (i.e., Type 2 or non-Type 2).(3) Type 2 inflammation is characterized by the presence of cytokines such as interleukin (IL)-4, IL-5, and IL-13, which are often produced by the adaptive immune system on recognition of allergens. It is also characterized by eosinophilia or increased fraction of exhaled nitric oxide (FeNO) and may be accompanied by atopy. In many patients with asthma, Type 2 inflammation rapidly improves when ICS are taken regularly and correctly; this is classified as mild or moderate asthma. In severe asthma, Type 2 inflammation may be

	relatively refractory to high dose ICS. Type 2 inflammation is considered refractory if any of the following are found while the patient is taking high dose ICS or daily OCS:(3)
	
	• Blood eosinophils greater than or equal to 150 cells/microliter
	• FeNO greater than or equal to 20 ppb
	• Sputum eosinophils greater than or equal to 2%
	• Asthma is clinically allergen-driven
	
	Biologic agents should be considered as add-on therapy for patients with refractory Type 2 inflammation with exacerbations or poor symptom control despite taking at least high dose ICS/LABA, and who have allergic or eosinophilic biomarkers or need maintenance OCS.(3) 2023 GINA recommends the biologics below based on patient eligibility factors:
	
	• Anti-IgE (omalizumab):
	  ○ Sensitization on skin prick testing or specific IgE
	  ○ Total serum IgE and weight within dosage range
	  ○ Exacerbations in the last year
	• Anti-IL5/Anti-IL5R (benralizumab, mepolizumab, reslizumab):
	  ○ Exacerbations in the last year
	  ○ Blood eosinophils greater than or equal to 150 cells/microliter (for benralizumab and mepolizumab) or greater than or equal to 300 cells/microliter (for reslizumab)
	• Anti-IL4R (dupilumab):
	  ○ Exacerbations in the last year
	  ○ Blood eosinophil greater than or equal to 150 cells/microliter but less than or equal to 1500 cells/microliter, or FeNO greater than or equal to 25 ppb, or taking maintenance OCS
	• Anti-TSLP (tezepelumab):
	  ○ Exacerbations in the last year
	
	Patient response should be evaluated 4 months after initiating therapy and follow up should occur every 3 to 6 months thereafter. 2023 GINA recommends the following step-down therapy process in patients responding well to targeted biologic therapy:(3)
	
	Reevaluate the need for each asthma medication every 3 to 6 months, but inhaled therapy should not be completely stopped

	Oral treatments: gradually decreased starting with OCS due to significant adverse effects. Inhaled treatments: consider reducing ICS dose after 3 to 6 months, but do not completely stop inhaled therapy. Continue at least medium dose ICS and remind patients of the importance of continued inhaled controller therapy Biologic treatments: trial withdrawal after 12 months of treatment and only if patient's asthma remains well controlled on medium dose ICS, and for allergic asthma, there is no further exposure to a previous allergic trigger
Efficacy	The efficacy of Tezspire was evaluated in two randomized, double-blind, parallel group, placebo-controlled clinical trials (PATHWAY [NCT02054130] and NAVIGATOR [NCT03347279]) of 52 weeks duration. The two trials enrolled a total of 1609 patients 12 years of age and older with severe asthma.(1) PATHWAY was a 52-week dose-ranging exacerbation trial that enrolled 550 adult patients with severe asthma who received treatment with tezepelumab-ekko 70 mg subcutaneously every 4 weeks, Tezspire 210 mg subcutaneously every 4 weeks, tezepelumab-ekko 280 mg subcutaneously every 2 weeks, or placebo subcutaneously. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or injectable corticosteroid treatment or 1 asthma exacerbation resulting in hospitalization in the past 12 months.(1) NAVIGATOR was a 52-week exacerbation trial that enrolled 1061 patients (adult and pediatric patients 12 years of age and older) with severe asthma who received treatment with Tezspire 210 mg subcutaneously every 4 weeks or placebo subcutaneously every 4 weeks. Patients were required to have a history of 2 or more asthma exacerbations requiring oral or injectable corticosteroid treatment or resulting in hospitalization in the past 12 months.(1) In both PATHWAY and NAVIGATOR, patients were required to have an Asthma Control Questionnaire 6 (ACQ-6) score of 1.5 or more at screening and reduced lung function at baseline [pre-bronchodilator forced expiratory volume in 1 second (FEV1) below 80% predicted in adults, and below 90% predicted in adolescents]. Patients were required to have been on regular treatment with medium or high-dose inhaled corticosteroids (ICS) and at least one additional asthma controller, with or without oral corticosteroids (OCS). Patients continued background asthma therapy throughout the duration of the trials. In both trials, patients were enrolled without requiring a minimum baseline level of blood eosinophils or FeNO.(1)

	The primary endpoint for PATHWAY and NAVIGATOR was the rate of clinically significant asthma exacerbations measured over 52 weeks. Clinically significant asthma exacerbations were defined as worsening of asthma requiring the use of or increase in oral or injectable corticosteroids for at least 3 days, or a single depo-injection of corticosteroids, and/or emergency department visits requiring use of oral or injectable corticosteroids and/or hospitalization. In both PATHWAY and NAVIGATOR, patients receiving Tezspire had significant reductions in the annualized rate of asthma exacerbations compared to placebo. There were also fewer exacerbations requiring emergency room visits and/or hospitalization in patients treated with Tezspire compared with placebo. In NAVIGATOR, patients receiving Tezspire experienced fewer exacerbations than those receiving placebo regardless of baseline levels of blood eosinophils or FeNO and similar results were seen in PATHWAY. The time to first exacerbation was longer for the patients receiving Tezspire compared with placebo in NAVIGATOR and similar findings were seen in PATHWAY. Change from baseline in FEV1 was assessed as a secondary endpoint in PATHWAY and NAVIGATOR. Compared with placebo, Tezspire provided clinically meaningful improvements in the mean change from baseline in FEV1 in both trials. In NAVIGATOR, improvement in FEV1 was seen as early as 2 weeks after initiation of treatment and was sustained through week 52.(1) Changes from baseline in Asthma Control Questionnaire 6 (ACQ-6) and Standardized Asthma Quality of Life Questionnaire for ages 12 and older [AQLQ(S)+12] were also assessed as secondary endpoints in PATHWAY and NAVIGATOR. In both trials, more patients treated with Tezspire compared to placebo had a clinically meaningful improvement in ACQ-6 and AQLQ(S)+12. Clinically meaningful improvement (responder rate) for both measures was defined as improvement in score of 0.5 or more at end of trial. In NAVIGATOR, the ACQ-6 responder rate for Tezspire was 86% compared with 77% for placebo (OR=1.99; 95% CI 1.43, 2.76) and the AQLQ(S)+12 responder rate for Tezspire was 78% compared with 72% for placebo (OR=1.36; 95% CI 1.02, 1.82). Similar findings were seen in PATHWAY.(1) In an additional randomized, double-blind, parallel group, placebo-controlled clinical trial, the effect of Tezspire (210 mg subcutaneously every 4 weeks) on reducing the use of maintenance OCS was evaluated. The trial enrolled 150 adult patients with severe asthma who required treatment with daily OCS (7.5 mg to 30 mg per day) in addition to regular use of high-dose ICS and a long-acting beta-agonist with or without additional controller(s). The primary endpoint was categorized percent reduction from baseline of the final OCS dose at Week 48 (greater than or equal to 90% reduction, greater than or equal to 75% to less than 90% reduction, greater than or equal to 50% to less than 75% reduction, greater

	than 0% to less than 50 reduction, and no change or no decrease in OCS), while maintaining asthma control. Tezspire did not demonstrate a statistically significant reduction in maintenance OCS dose compared with placebo (cumulative OR=1.28; 95% CI 0.69, 2.35).(1)
Safety	Tezepelumab-ekko is contraindicated in patients who have a known hypersensitivity to Tezepelumab-ekko or any of its excipients.(1)

REFERENCES

Number	Reference
1	Tezspire prescribing information. Amgen Inc. May 2023.
2	International European Respiratory Society (ERS)/American Thoracic Society (ATS) Guidelines on Management of Severe Asthma. Eur Resp J. 2020;55:1900588. Available at https://erj.ersjournals.com/content/55/1/1900588.
3	Global Initiative for Asthma (GINA). Global Strategy For Asthma Management and Prevention. 2023. Available at www.ginasthma.org.www.ginasthma.org.
4	National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. 2020 Focused updates to the asthma management guidelines. National Heart, Lung, and Blood Institute, 2007. Available at: https://www.nhlbi.nih.gov/health-topics/all-publications-and-resources/2020-focused-updates-asthma-management-guidelines

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy**

Module	Clinical Criteria for Approval
	All target agents are eligible for continuation of therapy 1. Information has been provided that indicates the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. The patient has a diagnosis of severe asthma **AND** 2. The patient has a history of uncontrolled asthma while on asthma control therapy as demonstrated by ONE of the following: A. Frequent severe asthma exacerbations requiring two or more courses of systemic corticosteroids (steroid burst) within the past 12 months **OR** B. Serious asthma exacerbations requiring hospitalization, mechanical ventilation, or visit to the emergency room or urgent care within the past 12 months **OR** C. Controlled asthma that worsens when the doses of inhaled and/or systemic corticosteroids are tapered **OR** D. The patient has baseline (prior to therapy with the requested agent) Forced Expiratory Volume (FEV1) that is less than 80% of predicted **OR** C. The patient has another FDA approved indication for the requested agent and route of administration **OR** D. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has a diagnosis of severe asthma, ALL of the following: A. ONE of the following: 1. The patient is NOT currently being treated with the requested agent AND is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **OR** 2. The patient is currently being treated with the requested agent AND ONE of the following: A. Is currently treated with an inhaled corticosteroid for at least 3 months that is adequately dosed to control symptoms **OR** B. Is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **OR**

Module	Clinical Criteria for Approval
	3. The patient has an intolerance or hypersensitivity to inhaled corticosteroid therapy **OR** 4. The patient has an FDA labeled contraindication to ALL inhaled corticosteroids **AND** B. ONE of the following: 1. The patient is currently being treated for at least 3 months with ONE of the following: A. A long-acting beta-2 agonist (LABA) **OR** B. Long-acting muscarinic antagonist (LAMA) **OR** C. A leukotriene receptor antagonist (LTRA) **OR** D. Theophylline **OR** 2. The patient has an intolerance or hypersensitivity to therapy with long-acting beta-2 agonists (LABA), long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonist (LTRA), or theophylline **OR** 3. The patient has an FDA labeled contraindication to ALL long-acting beta-2 agonists (LABA) AND long-acting muscarinic antagonists (LAMA) **AND** C. The patient will continue asthma control therapy (e.g., ICS, ICS/LABA, LTRA, LAMA, theophylline) in combination with the requested agent **AND** 3. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. ONE of the following (Please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. The prescriber has provided information in support of combination therapy (submitted copy required, e.g., clinical trials, phase III studies, guidelines required) **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use

Module	Clinical Criteria for Approval
	Length of Approval: 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. ONE of the following: A. The patient has a diagnosis of severe asthma AND BOTH of the following: 1. The patient has had improvements or stabilization with the requested agent from baseline (prior to therapy with the requested agent) as indicated by ONE of the following: A. The patient has had an increase in percent predicted Forced Expiratory Volume (FEV1) **OR** B. The patient has had a decrease in the dose of inhaled corticosteroids required to control the patient's asthma **OR** C. The patient has had a decrease in need for treatment with systemic corticosteroids due to exacerbations of asthma **OR** D. The patient has had a decrease in number of hospitalizations, need for mechanical ventilation, or visits to urgent care or emergency room due to exacerbations of asthma **AND** 2. The patient is currently treated and is compliant with asthma control therapy [e.g., inhaled corticosteroids, ICS/long-acting beta-2 agonist (ICS/LABA), leukotriene receptor antagonist (LTRA), long-acting muscarinic antagonist (LAMA), theophylline] **OR** B. The patient has another FDA approved indication for the requested agent and route of administration AND has had clinical benefit with the requested agent **OR** C. The patient has another indication that is supported in compendia for the requested agent and route of administration AND has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. ONE of the following (Please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR**

Module	Clinical Criteria for Approval
	B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. The prescriber has provided information in support of combination therapy (submitted copy required, e.g., clinical trials, phase III studies, guidelines required) **AND** 5. The patient does NOT have an FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Evaluation **Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. The prescriber has provided information in support of therapy with a higher dose for the requested indication **Length of approval:** Initial - 6 months; Renewal - 12 months

CONTRAINDICATION AGENTS

Contraindicated as Concomitant Therapy
Agents NOT to be used Concomitantly Abrilada (adalimumab-afzb) Actemra (tocilizumab) Adalimumab Adbry (tralokinumab-ldrm) Amjevita (adalimumab-atto) Arcalyst (rilonacept) Avsola (infliximab-axxq) Benlysta (belimumab) Bimzelx (bimekizumab-bkzx) Cibinqo (abrocitinib) Cimzia (certolizumab) Cinqair (reslizumab) Cosentyx (secukinumab) Cyltezo (adalimumab-adbm) Dupixent (dupilumab) Enbrel (etanercept) Entyvio (vedolizumab) Fasenra (benralizumab) Hadlima (adalimumab-bwwd) Hulio (adalimumab-fkjp) Humira (adalimumab) Hyrimoz (adalimumab-adaz) Idacio (adalimumab-aacf) Ilaris (canakinumab) Ilumya (tildrakizumab-asmn) Inflectra (infliximab-dyyb) Infliximab Kevzara (sarilumab) Kineret (anakinra) Leqselvi (deuruxolitinib) Litfulo (ritlecitinib) Nemluvio (nemolizumab-ilto) Nucala (mepolizumab) Olumiant (baricitinib) Omvoh (mirikizumab-mrkz) Opzelura (ruxolitinib)

Contraindicated as Concomitant Therapy
Orencia (abatacept)
Otezla (apremilast)
Pyzchiva (ustekinumab-ttwe)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rinvoq (upadacitinib)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Saphnelo (anifrolumab-fnia)
Selarsdi (ustekinumab-aekn)
Siliq (brodalumab)
Simlandi (adalimumab-ryvk)
Simponi (golimumab)
Simponi ARIA (golimumab)
Skyrizi (risankizumab-rzaa)
Sotyktu (deucravacitinib)
Spevigo (spesolimab-sbzo) subcutaneous injection
Stelara (ustekinumab)
Taltz (ixekizumab)
Tezspire (tezepelumab-ekko)
Tofidence (tocilizumab-bavi)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tyenne (tocilizumab-aazg)
Tysabri (natalizumab)
Velsipity (etrasimod)
Wezlana (ustekinumab-auub)
Xeljanz (tofacitinib)
Xeljanz XR (tofacitinib extended release)
Xolair (omalizumab)
Yuflyma (adalimumab-aaty)
Yusimry (adalimumab-aqvh)
Zeposia (ozanimod)
Zymfentra (infliximab-dyyb)

Thrombopoietin Receptor Agonists and Tavalisse

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Alvaiz™ (eltrombopag) Tablet	• Treatment of thrombocytopenia in adult and pediatric patients 6 years and older with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Alvaiz should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding. • Treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. Alvaiz should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy • Treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy Limitations of Use: • Alvaiz is not indicated for the treatment of patients with myelodysplastic syndrome (MDS) • Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection		16
Doptelet® (avatrombopag)	• Treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure		1

Agent(s)	FDA Indication(s)	Notes	Ref#
Tablet	• Treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia who have had an insufficient response to previous treatment		
Mulpleta® (lusutrombopag) Tablet	• Treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure		2
Nplate® (romiplostim) Subcutaneous injection	• Treatment of thrombocytopenia in adult patients with immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy • Treatment of thrombocytopenia in pediatric patients 1 year of age and older with ITP for at least 6 months who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy • Increase survival in adults and in pediatric patients (including term neonates) acutely exposed to myelosuppressive doses of radiation (Hematopoietic Syndrome of Acute Radiation Syndrome [HS-ARS]) Limitations of Use: • Nplate is not indicated for the treatment of thrombocytopenia due to myelodysplastic syndrome (MDS) or any cause of thrombocytopenia other than ITP • Nplate should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding • Nplate should not be used in an attempt to normalize platelet counts		3
Promacta® (eltrombopag) Tablet	• Treatment of thrombocytopenia in adult and pediatric patients 1 year and older with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Promacta should		4

Agent(s)	FDA Indication(s)	Notes	Ref#
Powder for oral suspension	be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increase the risk for bleeding • Treatment of thrombocytopenia in patients with chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy. Promacta should be used only in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon-based therapy or limits the ability to maintain interferon-based therapy • In combination with standard immunosuppressive therapy for the first-line treatment of adult and pediatric patients 2 years and older with severe aplastic anemia • Treatment of patients with severe aplastic anemia who have had an insufficient response to immunosuppressive therapy Limitations of Use: • Promacta is not indicated for the treatment of patients with myelodysplastic syndrome (MDS) • Safety and efficacy have not been established in combination with direct-acting antiviral agents used without interferon for treatment of chronic hepatitis C infection		
Tavalisse® (fostamatinib) Tablet	• Treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment		5

CLINICAL RATIONALE

ITP	Immune (idiopathic) thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by a low platelet count resulting from platelet destruction and impaired platelet production. ITP can be an isolated primary condition, or it may be secondary to other conditions. The goal of all treatment strategies for

	ITP is to achieve a platelet count that is associated with adequate hemostasis, rather than a normal platelet count. Bleeding events are often unpredictable and patients with ITP, even in the setting of severe thrombocytopenia, may not exhibit bleeding beyond bruising and petechiae. However, more serious mucosal bleeding may occur, including menorrhagia, epistaxis, gastrointestinal hemorrhage, hematuria, or, rarely, intra-cranial hemorrhage. The decision as to whether a patient can be observed or requires further intervention is highly complex and varies based on comorbidities, medications, and age, which all impact the risk of bleeding. In addition, management approaches may vary based on disease duration, access to care, quality-of-life implications, and patient and provider preferences, among other factors. An International Working Group consensus panel defines ITP as newly diagnosed (diagnosis to 3 months), persistent (3-12 months from diagnosis), or chronic (lasting for more than 12 months).(6) The American Society of Hematology (ASH) 2019 guidelines for immune thrombocytopenia separate treatments into adult and pediatric categories as well as initial vs secondary treatments in both groups.(6) In adults with newly diagnosed ITP and a platelet count of less than 30 X 10^9/L who are asymptomatic or have minor mucocutaneous bleeding, ASH suggests corticosteroids rather than management with observation. There may be a subset of patients within this group for whom observation might be appropriate. This should include consideration of the severity of thrombocytopenia, additional comorbidities, use of anticoagulant or antiplatelet medications, need for upcoming procedures, and age of the patient.(6) In adults with newly diagnosed ITP and a platelet count greater than or equal to 30 X 10^9/L who are asymptomatic or have minor mucocutaneous bleeding, the ASH panel recommends against corticosteroids and in favor of management with observation. For patients with a platelet count at the lower end of this threshold, for those with additional comorbidities, anticoagulant or antiplatelet medications, or upcoming procedure, and for elderly (greater than 60 years old), treatment with corticosteroids may be appropriate.(6) In adult patients with ITP for greater than or equal to 3 months who are corticosteroid dependent or do not have a response to corticosteroids, the ASH panel suggests treatment with a thrombopoietin receptor agonist (the guidelines suggest either eltrombopag or romiplostim but also acknowledge no therapies available after 2017 were included in these guidelines), rituximab, or a splenectomy. The panel suggests use of a thrombopoietin receptor agonist over

	rituximab or a splenectomy and rituximab over a splenectomy. Each of these second-line treatments may be effective therapy and therefore the choice of treatment should be individualized based on duration of ITP, frequency of bleeding episodes requiring hospitalization or rescue medication, comorbidities, age of patient, medication adherence, medical and social support networks, patient values and preferences, cost, and availability.(6)
	
	In children with newly diagnosed ITP who have non-life-threatening mucosal bleeding and/or diminished health related quality of life (HRQoL), the panel suggests corticosteroids over IVIG or anti-D immunoglobulin but does suggest that IVIG or anti-D immunoglobulin could be used in certain situations.(6)
	
	In children with ITP who have non-life-threatening mucosal bleeding and/or diminished HRQoL and do not respond to first-line treatment, the ASH panel suggests the use of thrombopoietin receptor agonists over rituximab or splenectomy, and rituximab over splenectomy.(6)
	
	Given the impact of corticosteroids on mental health, the treating prescriber should assess HRQoL (e.g., depression, fatigue, mental status) while patients are receiving corticosteroids. Based on clinical experience, the ASH panel agreed there was likely trivial benefit in continuing corticosteroids in adults beyond 6 weeks. For the majority of patients, a trial of 6 weeks of corticosteroids should determine whether a patient is going to enter remission or will require additional therapy. For patients who require additional therapy, consideration of alternative therapy is preferred over ongoing exposure to corticosteroids. In children, the ASH panel advises against courses of corticosteroids longer than 7 days.(6)
	
	Recommendations from the 2011 ASH guidelines that were not prioritized to be addressed, discussed or updated by the 2019 guideline panel were as follows:(6)
	
	• First-line treatment of adult ITP:
	  ○ IVIG with corticosteroids can be used when a more rapid increase in platelet count is required
	  ○ Either IVIG or anti-D (in appropriate patients) can be used as a first-line treatment if corticosteroids are contraindicated

HCV associated thrombocytopenia	A number of studies have suggested an association between hepatitis C virus (HCV) infection and immune thrombocytopenia (ITP) and/or autoimmune hemolytic anemia, either as a consequence of interferon therapy or in the setting of chronic infection without therapy. One of the largest studies included 120,691 United States veterans with chronic HCV who were matched with 454,905

	controls. HCV was associated with ITP in both treated and untreated patients (hazard ratio 1.8).(11)
Aplastic anemia	Aplastic anemia (AA) is a diagnosis of exclusion. There is no single test that can be used to consistently diagnose AA from the multiple of other causes of bone marrow failure and the diagnostic evaluation must assess for and exclude these alterative etiologies. At initial presentation many patients exhibit fatigue, weakness, pallor, and headaches due to anemia. Often patients have petechiae of the skin and mucous membranes, epistaxis, and/or gum bleeding related to severe thrombocytopenia. Fever and infections can also be seen in these patients as a result of low white blood cell counts and neutropenia. AA patients identified earlier in the course of the disease by abnormalities found on routine laboratory testing may not have any physical manifestations of their disease.(15) AA is further classified clinically by the severity of the depression of the peripheral blood counts. Severe AA is defined by a decrease in blood counts involving greater than or equal to 2 hematopoietic lineages (i.e., absolute reticulocyte count <60 x 10^9/L, absolute neutrophil count <0.5 X 10^9/L, platelet count <20 x 10^9/L) and bone marrow hypocellularity (<25% of the normal cellularity). Very severe AA has an absolute neutrophil count <0.2 x 10^9/L and moderate AA is characterized by the depression of blood counts not fulfilling the definition of severe disease.(15) The British Journal of Haematology guidelines for the diagnosis and management of adult aplastic anaemia define severe aplastic anemia as severe hypocellularity <25% (or moderate hypocellularity of 25-50% with hematopoietic cells representing <30% of residual cells) and at least 2 of the following blood criteria: neutrophils <0.5 X 10^9/L, platelets <20 X 10^9/L, absolute reticulocyte level of <20 X 10^9/L.(10) The standard treatment for AA is immunosuppressive therapy with horse antithymocyte globulin (ATG) and cyclosporine, and hematologic responses are observed in about two thirds of patients. Patients with disease that is refractory to immunosuppression and those who have a relapse after treatment may undergo allogeneic hematopoietic stem-cell transplantation (HSCT). However, 20 to 40% of patients without a suitable donor for HSCT continue to have severe cytopenias and are at risk for life-threatening hemorrhage due to thrombocytopenia and severe infections due to neutropenia.(8) No standard therapies are available for patients who have AA that is refractory to immunosuppression and are ineligible for HSCT, other than transfusions and treatment of infections. More than 40% of patients with disease that is refractory

	to immunosuppression die from bleeding or infection within 5 years after diagnosis. Although readministration of immunosuppressive therapy has been effective as salvage therapy in some patients, intensification of the regimen with more potent agents, such as rabbit ATG, sirolimus, or mycophenolate, has not improved the response rate.(8)
Thrombocytopenia in liver disease	Patients with acute and chronic liver disease frequently acquire unique changes in hemodynamic and hemostatic pathways that may result in life-threatening bleeding and thrombosis. Additionally, activation of hemostatic pathways may play a role in disease progression through prechymal extinction, or organ atrophy, recruitment of inflammatory cells and activation of stellate cells.(12) Traditional coagulation measures, including pro-thrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), and bleeding time (BT) do not measure bleeding risk in cirrhosis. In addition, platelet count alone provides an incomplete guide to bleeding risk in cirrhosis. However, values below 50,000/μL may be associated with a higher risk of bleeding.(12) Procedure-related bleeding is common in cirrhosis patients but estimates of incidence vary widely. For many years, the PT/INR served as a surrogate marker for estimating bleeding risk in cirrhosis. However, use of INR and arbitrary “cut-offs” as a clinical target is not recommended or supported by scientific evidence. Assessment of individual patient characteristics is also essential as clinical factors, such as acute kidney injury or infection may alter bleeding risk in certain clinical scenarios. In elective and planned settings, such as planned dental extractions or other invasive procedures with moderate or high risk, thrombopoietin receptor agonists are an alternative means to increase platelets prior to invasive procedures.(12)
Hematopoietic syndrome of ARS	Acute radiation syndrome (ARS) (sometimes known as radiation toxicity or radiation sickness) is an acute illness caused by irradiation of the entire body (or most of the body) by a high dose of penetrating radiation in a very short period of time (usually a matter of minutes). The major cause of this syndrome is depletion of immature parenchymal stem cells in specific tissues. The three classic ARS syndromes are hematopoietic syndrome, gastrointestinal (GI) syndrome, and cardiovascular (CV)/central nervous system (CNS) syndrome. Of the 3, the hematopoietic syndrome is the only one that may be reversed through medical intervention preventing death. The survival rate of patient with bone marrow syndrome decreases with increasing dose. The primary cause of death is the destruction of the bone marrow resulting in infection and hemorrhage.(14) The required conditions for ARS are:(14)

	• The radiation dose must be large (i.e., greater than 0.7 Gray (Gy) or 70 rads)
	  ○ Mild symptoms may be observed with doses as low as 0.3 Gy or 30 rads
	• The dose usually must be external (i.e., the source of radiation is outside of the patient's body)
	  ○ Radioactive materials deposited inside the body have produced some ARS effects only in extremely rare cases
	• The radiation must be penetrating (i.e., able to reach internal organs)
	  ○ High energy X-rays, gamma rays, and neutrons are penetrating radiations
	• The entire body (or a significant portion of it) must have received the dose
	  ○ Most radiation injuries are local, frequently involving the hands, and these local injuries seldom cause classical signs of ARS
	• The dose must have been delivered in a short time (usually a matter of minutes)
	  ○ Fractionated doses are often used in radiation therapy. These are large total doses delivered in small daily amounts over a period of time. Fractionated doses are less effective at inducing ARS than a single dose of the same magnitude

Efficacy	**Doptelet(1)** Doptelet (avatrombopag) is a thrombopoietin receptor agonist that stimulates proliferation and differentiation of megakaryocytes from bone marrow progenitor cells resulting in an increased production of platelets. The efficacy of Doptelet for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure was established in 2 identically-designed multicenter, randomized, double-blind, placebo-controlled trials (ADAPT-1 and ADAPT-2). In each study, patients were assigned to the low baseline platelet count cohort (less than 40 X 10^9/L) or high baseline platelet count cohort (greater than or equal to 40 to less than 50 X 10^9/L) based on their platelet count at baseline. In the ADAPT-1 trial 149 patients were treated with Doptelet and 82 patients were treated with placebo both once daily for 5 days. In the ADAPT-2 trial, 128 patients were treated with Doptelet and 76 patients were treated with placebo. Across both baseline platelet count cohorts and the Doptelet and placebo treatment

	groups, patients underwent a broad spectrum of types of scheduled procedures that ranged from low to high bleeding risk. The major efficacy outcome in both trials was the proportion of patients who did not require a platelet transfusion or any rescue procedure for bleeding after randomization and up to 7 days following an elective procedure. Additional secondary efficacy outcomes were the proportion of patients who achieved platelet counts of greater than or equal to 50 X 10^9/L on the day of procedure and the change in platelet count from baseline to procedure day. Responders were defined as patients who did not require a platelet transfusion or any rescue procedure (whole blood transfusion, packed red blood cell transfusion, platelet transfusion, fresh frozen plasma or cryoprecipitate administration, Vitamin K, desmopressin, recombinant activated factor VII, aminocaproic acid, tranexamic acid, or surgical or interventional radiology performed to achieve hemostasis and control blood loss) for bleeding after randomization and up to 7 days following a scheduled procedure. In both baseline platelet count cohorts, patients in the Doptelet treatment groups had a greater proportion of responders than the corresponding placebo treatment groups that was both clinically meaningful and statistically significant. The percentage of responders in the low baseline platelet count cohort and treatment group that responded in the ADAPT-1 trial was 66% in the Doptelet group and 23% in the placebo group (p-value less than 0.0001). In the Adapt-2 trial the percentage of responders was 69% in the Doptelet group and 35% in the placebo group (p-value 0.0006). The percentage of responders in the high baseline platelet count cohort in ADAPT-1 trial was 88% in the Doptelet group and 38% in the placebo group (p-value less than 0.0001). In the ADAPT-2 trial the percentage of responders was 88% in the Doptelet group and 33% in the placebo group (p-value less than 0.0001). Both trials also demonstrated a higher proportion of patients who achieved the target platelet count of greater than or equal to 50 X 10^9/L on the day of the procedure (a secondary efficacy endpoint) and a greater mean change in platelet counts from baseline to the day of the procedure (a secondary efficacy endpoint). The efficacy of Doptelet in adult patients with chronic immune thrombocytopenia was evaluated in a phase 3, multicenter, randomized, double-blind, placebo-controlled trial (NCT01438840). Patients had received one or more chronic

	immune thrombocytopenia therapies and had an average platelet count (of less than 30 X 10^9/L). The major efficacy outcome was the cumulative number of weeks in which the platelet count was greater than or equal to 50 X 10^9/L during the 6-month treatment period in the absence of rescue therapy. Doptelet-treated patients had a longer duration of platelet counts greater than or equal to 50 x10^9/L in the absence of rescue therapy than those who received placebo (median 12.4 [0, 25] vs 0 [0, 2] weeks, respectively, p less than 0.0001. In addition, a larger proportion of patients in the Doptelet treatment group had platelet counts greater than or equal to 50 X 10^9/L at Day 8 compared to placebo (21/32; 66% vs 0/17; 0.0%, respectively; p less than 0.0001). **Mulpleta(2)** Mulpleta (lusutrombopag) is an orally bioavailable TPO receptor agonist that interacts with the transmembrane domain of human TPO receptors expressed on megakaryocytes to induce the proliferation and differentiation of megakaryocytic progenitor cells from hematopoietic stem cells and megakaryocyte maturation. The efficacy of Mulpleta for the treatment of thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure was evaluated in 2 randomized, double-blind, placebo-controlled trial (L-PLUS 1 and L-PLUS 2). Patients with chronic liver disease who were undergoing an invasive procedure and had a platelet count less than 50 X 10^9/L were eligible to participate. Patients were randomized to receive 3 mg of Mulpleta or placebo once daily for up to 7 days. In L-PLUS 1 the major efficacy outcome was the proportion of patients who require no platelet transfusion prior to the primary invasive procedure. In L-PLUS 2 the major efficacy outcome was the proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding (i.e., platelet preparations, other blood preparations, including red blood cells and plasma, volume expanders) from randomization through 7 days after the primary invasive procedure. In both the L-PLUS 1 and L-PLUS 2 trials, responders were defined as patients who had a platelet count of greater than or equal to 50 X 10^9/L with an increase of greater than or equal to 20 X 10^9/L from baseline. In the L-PLUS 1 trial the percentage of patients not requiring platelet transfusion prior to invasive procedure was 78% in the Mulpleta arm and 13% in the placebo arm (95% CI, p-value less than 0.0001). The percentage of patients that

	responded during the study was 76% in the Mulpleta arm and 6% in the placebo arm (95%CI, p-value less than 0.0001). In the L-Plus 2 trial the percentage of patients not requiring platelet transfusion prior to invasive procedure or rescue therapy for bleeding from randomization through 7 days after invasive procedure was 65% in the Mulpleta arm and 29% in the placebo arm (95% CI, p-value less than 0.0001). The percentage of patients that responded during the study was 65% in the Mulpleta arm and 13% in the placebo arm (95%CI, p-value less than 0.0001). **Nplate(3)** Nplate (romiplostim) is a thrombopoietin receptor agonist that increases platelet production through binding and activation of the thrombopoietin (TPO) receptor, similar in mechanism to endogenous TPO. The safety and efficacy of Nplate were assessed in two double-blind, placebo-controlled clinical studies, in an open-label single-arm study, and in an open-label extension study. Efficacy in all studies was defined as maintaining a target platelet count greater than or equal to 50 X 10^9/L. The safety and efficacy of Nplate in pediatric patients 1 year and older with ITP for at least 6 months were assessed in two double-blind, placebo controlled clinical trials. The efficacy in both studies was defined as maintaining a target platelet count of greater than or equal to 50 X 10^9/L. Efficacy studies of Nplate could not be conducted in humans with acute radiation syndrome for ethical and feasibility reasons. Approval for this indication was based on efficacy studies conducted in animals, Nplate's effect on platelet count in healthy human volunteers, and on data supporting Nplate's effect on thrombocytopenia in patients with ITP and insufficient response to corticosteroids, immunoglobulins, or splenectomy. **Promacta(4)** Promacta (eltrombopag) interacts with the transmembrane domain of the TPO receptor (also known as cMpl) leading to increased platelet production. Safety and efficacy of Promacta in adult patients with persistent or chronic ITP were evaluated in three randomized, double-blind, placebo-controlled trials and in an open-label extension trial. Safety and efficacy of Promacta in pediatric patients 1 year and older with persistent or chronic ITP were evaluated in two

	double-blind, placebo-controlled trials. All of these trials showed clinically significant efficacy of Promacta vs placebo. Safety and efficacy of Promacta was evaluated in 2 randomized, double-blind, placebo-controlled trials for eltrombopag in treating thrombocytopenia in patients with chronic hepatitis C. One trial used peginterferon alfa-2a (Pegasys); the other used peginterferon alfa-2b (Pegintron), both were in combination with ribavirin. Approximately 30% of patients had been previously treated with interferon and ribavirin. Patients had to have platelet counts of less than 75 x10^9/L. The trials consisted of 2 phases: a pre-antiviral treatment phase and an antiviral treatment phase. Patients were allowed to be randomized for the antiviral treatment phase if they reached the platelet count threshold of greater than or equal to 90 X 10^9/L (trial 1) and greater than or equal to 100 x 10^9/L (trial 2). The maximum allowed time on open label eltrombopag was 9 weeks. The primary efficacy endpoint for both studies was sustained virologic response (SVR) defined as the percentage of patients with undetectable HCV-RNA at 24 weeks after completion of antiviral treatment. The median time to achieve the target platelet count in study 1 was approximately 2 weeks with 95% of patients initiating antiviral therapy. The safety of Promacta as first-line treatment of severe aplastic anemia was established based on a single-arm trial of 153 patients with severe aplastic anemia who had not received prior definitive immunosuppressive therapy. In this trial, Promacta was administered in combination with horse antithymocyte globulin (h-ATG) and cyclosporine. The efficacy of Promacta in combination with h-ATG and cyclosporine was established on the basis of complete hematological response at 6 months. A complete response was defined as hematological parameters meeting all 3 of the following values on 2 consecutive serial blood count measurements at least one week apart: absolute neutrophil count (ANC) greater than 1,000/microliter, platelet count greater than 100 X 10^9/L, and hemoglobin greater than 10 g/dL. A partial response was defined as blood counts no longer meeting the standard criteria for severe pancytopenia in severe aplastic anemia equivalent to 2 of the following values on 2 consecutive serial blood count measurements at least one week apart: ANC greater than 500/microliter, platelet count greater than 20 X 10^9/L, or reticulocyte count greater than 60,000/microliter. Overall response rate is defined as the number of partial responses plus complete responses. The overall response rate at month 6 was 79% (95% CI). The median duration of overall response was 70 months (95% CI). The median duration of complete response was 46 months (95% CI). Promacta was studied in a single-arm, single-center, open-label trial in 43 patients with severe aplastic anemia who had an insufficient response to at least

	one prior immunosuppressive therapy and who had a platelet count of less than or equal to 30 X 10^9/L. The efficacy was evaluated by the hematologic response assessed after 12 weeks of treatment. Hematologic response was defined as meeting 1 or more of the following criteria: 1) platelet count increases to 20 X 10^9/L above baseline, or stable platelet counts with transfusion independence for a minimum of 8 weeks; 2) hemoglobin increase by greater than 1.5 g/dL, or a reduction in greater than or equal to 4 units of red blood cell transfusions for 8 consecutive weeks; 3) ANC increase of 100% or an ANC increase greater than 0.5 X 10^9/L. Promacta was discontinued after 16 weeks if no hematologic response was observed. The response rate was 40% (95% CI) and the median of duration of response was not reached due to few events. **Alvaiz(16)** Alvaiz (eltrombopag) interacts with the transmembrane domain of the TPO receptor (also known as cMpl) leading to increased platelet production. Safety and efficacy of Alvaiz has been established based on adequate and well-controlled studies of eltrombopag olamine in adult and pediatric patients 6 years and older with persistent or chronic ITP, adult patients with chronic hepatitis C-associated thrombocytopenia, and adult patients with refractory severe aplastic anemia. These studies are listed under Promacta. **Tavalisse(5)** Tavalisse (fostamatinib) is a tyrosine kinase inhibitor with demonstrated activity against spleen tyrosine kinase. Tavalisse was studied in two placebo-controlled efficacy and safety studies (FIT-1 and FIT-2), and an open-label extension study (FIT-3). A total of 150 patients with persistent or chronic immune thrombocytopenia, who had an insufficient response to previous treatment (which included corticosteroids, immunoglobulins, splenectomy, and/or a thrombopoietin receptor agonists) were enrolled in two identical, double-blind, placebo-controlled studies that were conducted in different countries. For each study, patients were randomized to receive Tavalisse or placebo for 24 weeks. Patients who did not respond to treatment after 12 weeks, as well as patients who completed the 24-week double blind study, were eligible to enroll in the open-label extension study. The efficacy of Tavalisse was based on stable platelet response (at least 50 X 10^9/L on at least 4 of the 6 visits between weeks 14 to 24).

	The percent of patients who had a stable platelet response was 16-18% in the Tavalisse arms and 0-4% in the placebo arms. The FIT-3 extension study enrolled 123 patients who completed 24 weeks of treatment in the FIT-1 and FIT-2 studies, or who did not respond to treatment any time after 12 weeks in these studies. Patients who were designated as responders in the FIT-1 and FIT-2 studies (defined as platelet count of at least 50 X 10^9/L) at the time of rollover continued in the extension study at their current trial dose and regimen. Patients who entered the extension study as non-responders (defined as platelet count less than 50 X 10^9/L) received Tavalisse 100 mg twice daily regardless of their dose and regimen in the prior study. Stable response in this study was prospectively defined as no 2 visits, at least 4 weeks apart, with a platelet count less than 50 X 10^9/L, without an intervening visit with a platelet count of at least 50 X 10^9/L (unrelated to rescue therapy), within a period of 12 weeks following initial achievement of the target platelet count. Among the patients who achieved stable response in FIT-1, FIT-2, and FIT-3 trials, 18 patients maintained the platelet count of at least 50 X 10^9/L for 12 months or longer.
Safety	All targeted agents have no FDA labeled contraindications of use.(1-5,16)

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ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
8240506000	Nplate	romiplostim for inj	125 MCG ; 250 MCG ; 500 MCG	Max 10 mcg/kg/week			
82405060002110	Nplate	Romiplostim For Inj 125 MCG	125 MCG	Max 10 mcg/kg/week			
82405060002120	Nplate	Romiplostim For Inj 250 MCG	250 MCG	Max 10 mcg/kg/week			
82405060002130	Nplate	Romiplostim For Inj 500 MCG	500 MCG	Max 10 mcg/kg/week			

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when the ALL of the following are met: 1. ONE of the following: A. The requested agent is Doptelet AND ONE of the following: 1. The patient has a diagnosis of chronic (defined as lasting for at least 12 months) immune (idiopathic) thrombocytopenia (ITP) AND BOTH of the following: A. ONE of the following: 1. The patient has a platelet count less than or equal to 30 X 10^9/L **OR**

Module	Clinical Criteria for Approval
	2. The patient has a platelet count greater than 30 X 10^9/L but less than 50 X 10^9/L AND has symptomatic bleeding and/or an increased risk for bleeding **AND** B. ONE of the following: 1. The patient has tried and had an inadequate response to ONE corticosteroid used for the treatment of ITP **OR** 2. The patient has an intolerance or hypersensitivity to ONE corticosteroid used for the treatment of ITP **OR** 3. The patient has an FDA labeled contraindication to ALL corticosteroids used for the treatment of ITP **OR** 4. The patient has tried and had an inadequate response to another thrombopoietin receptor agonist (e.g., Nplate, Promacta) or Tavalisse **OR** 5. The patient has tried and had an inadequate response to immunoglobulins (IVIg or Anti-D) **OR** 6. The patient has had an inadequate response to a splenectomy **OR** 7. The patient has tried and had an inadequate response to rituximab **OR** 2. The patient has a diagnosis of thrombocytopenia and has chronic liver disease AND ALL of the following: A. The patient has a platelet count less than 50 X 10^9/L **AND** B. The patient is scheduled to undergo a procedure with an associated risk of bleeding (e.g., gastrointestinal endoscopy, liver biopsy, bronchoscopy, dental procedure) **AND** C. The patient would require a platelet transfusion unless platelet counts are clinically increased from baseline (prior to therapy with the requested agent) **OR** 3. The patient has another FDA labeled indication for the requested agent **OR** 4. The patient has another indication that is supported in compendia for the requested agent and route of administration **OR** B. The requested agent is Mulpleta (lusutrombopag) AND ONE of the following: 1. The patient has a diagnosis of thrombocytopenia and has chronic liver disease AND ALL of the following: A. The patient has a platelet count less than 50 X 10^9/L **AND** B. The patient is scheduled to undergo a procedure with an associated risk of bleeding (e.g., gastrointestinal endoscopy, liver biopsy, bronchoscopy, dental procedure) **AND**

Module	Clinical Criteria for Approval
	C. The patient would require a platelet transfusion unless platelet counts are clinically increased from baseline (prior to therapy with the requested agent) **OR** 2. The patient has another FDA labeled indication for the requested agent **OR** 3. The patient has another indication that is supported in compendia for the requested agent and route of administration **OR** C. The requested agent is Nplate (romiplostim) AND ONE of the following: 1. The patient has a diagnosis of hematopoietic syndrome of acute radiation syndrome (HS-ARS) **OR** 2. The patient has a diagnosis of immune (idiopathic) thrombocytopenia (ITP) AND ALL of the following: A. If the patient is a pediatric patient, then the patient has had ITP for at least 6 months **AND** B. ONE of the following: 1. The patient has a platelet count less than or equal to 30 X 10^9/L **OR** 2. The patient has a platelet count greater than 30 X 10^9/L but less than 50 x 10^9/L AND has symptomatic bleeding and/or an increased risk for bleeding **AND** C. ONE of the following: 1. The patient has tried and had an inadequate response to ONE corticosteroid used for the treatment of ITP **OR** 2. The patient has an intolerance or hypersensitivity to ONE corticosteroid used for the treatment of ITP **OR** 3. The patient has an FDA labeled contraindication to ALL corticosteroids used for the treatment of ITP **OR** 4. The patient has tried and had an inadequate response to immunoglobulins (IVIg or anti-D) **OR** 5. The patient has had an inadequate response to a splenectomy **OR** 6. The patient has tried and had an inadequate response to rituximab **OR** 3. The patient has another FDA labeled indication for the requested agent **OR** 4. The patient has another indication that is supported in compendia for the requested agent and route of administration **OR** D. The requested agent is Promacta (eltrombopag) AND ONE of the following: 1. The patient has a diagnosis of hepatitis C associated thrombocytopenia AND ONE of the following:

Module	Clinical Criteria for Approval
	A. The intent of therapy with the requested agent is to increase platelet counts sufficiently to initiate interferon therapy AND the patient's platelet count is less than 75 x 10^9/L **OR** B. The patient is on concomitant therapy with interferon AND is at risk for discontinuing hepatitis C therapy due to thrombocytopenia **OR** 2. The patient has a diagnosis of severe aplastic anemia AND ALL of the following: A. The patient has at least 2 of the following blood criteria: 1. Neutrophils less than 0.5 X 10^9/L 2. Platelets less than 30 X 10^9/L 3. Reticulocyte count less than 60 X 10^9/L **AND** B. The patient has 1 of the following marrow criteria: 1. Severe hypocellularity: less than 25% **OR** 2. Moderate hypocellularity, 25-50% with hematopoietic cells representing less than 30% of residual cells **AND** C. ONE of the following: 1. BOTH of the following: A. The patient will use the requested agent as first-line treatment **AND** B. The patient will use the requested agent in combination with standard immunosuppressive therapy (i.e., antithymocyte globulin [ATG] AND cyclosporine) **OR** 2. ONE of the following: A. The patient has tried and had an inadequate response to BOTH antithymocyte globulin (ATG) AND cyclosporine therapy **OR** B. The patient has an intolerance or hypersensitivity to BOTH ATG AND cyclosporine **OR** C. The patient has an FDA labeled contraindication to BOTH ATG AND cyclosporine **OR** 3. The patient has a diagnosis of persistent or chronic (defined as lasting for at least 3 months) immune (idiopathic) thrombocytopenia (ITP) AND BOTH of the following: A. ONE of the following: 1. The patient has a platelet count less than or equal to 30 x 10^9/L **OR** 2. The patient has a platelet count greater than 30 x 10^9/L but less than 50 x 10^9/L AND has symptomatic bleeding and/or an increased risk for bleeding **AND**

Module	Clinical Criteria for Approval
	B. ONE of the following: 1. The patient has tried and had an inadequate response to ONE corticosteroid used for the treatment of ITP **OR** 2. The patient has an intolerance or hypersensitivity to ONE corticosteroid used for the treatment of ITP **OR** 3. The patient has an FDA labeled contraindication to ALL corticosteroids used for the treatment of ITP **OR** 4. The patient has tried and had an inadequate response to immunoglobulins (IVIg or anti-D) **OR** 5. The patient has had an inadequate response to a splenectomy **OR** 6. The patient has tried and had an inadequate response to rituximab **OR** 4. The patient has another FDA labeled indication for the requested agent **OR** 5. The patient has another indication that is supported in compendia for the requested agent and route of administration **OR** E. The requested agent is Alvaiz (eltrombopag) AND ONE of the following: 1. The patient has a diagnosis of hepatitis C associated thrombocytopenia AND ONE of the following: A. The intent of therapy with the requested agent is to increase platelet counts sufficiently to initiate interferon therapy AND the patient's platelet count is less than 75 x 10^9/L **OR** B. The patient is on concomitant therapy with interferon AND is at risk for discontinuing hepatitis C therapy due to thrombocytopenia **OR** 2. The patient has a diagnosis of severe aplastic anemia AND ALL of the following: A. The patient has at least 2 of the following blood criteria: 1. Neutrophils less than 0.5 X 10^9/L 2. Platelets less than 30 X 10^9/L 3. Reticulocyte count less than 60 X 10^9/L **AND** B. The patient has 1 of the following marrow criteria: 1. Severe hypocellularity: less than 25% **OR** 2. Moderate hypocellularity, 25-50% with hematopoietic cells representing less than 30% of residual cells **AND** C. ONE of the following: 1. The patient has tried and had an inadequate response to BOTH antithymocyte globulin (ATG) AND cyclosporine therapy **OR** 2. The patient has an intolerance or hypersensitivity to BOTH ATG AND cyclosporine **OR**

Module	Clinical Criteria for Approval
	3. The patient has an FDA labeled contraindication to BOTH ATG AND cyclosporine **OR** 3. The patient has a diagnosis of persistent or chronic (defined as lasting for at least 3 months) immune (idiopathic) thrombocytopenia (ITP) AND BOTH of the following: A. ONE of the following: 1. The patient has a platelet count less than or equal to 30 x 10^9/L **OR** 2. The patient has a platelet count greater than 30 x 10^9/L but less than 50 x 10^9/L AND has symptomatic bleeding and/or an increased risk for bleeding **AND** B. ONE of the following: 1. The patient has tried and had an inadequate response to ONE corticosteroid used for the treatment of ITP **OR** 2. The patient has an intolerance or hypersensitivity to ONE corticosteroid used for the treatment of ITP **OR** 3. The patient has an FDA labeled contraindication to ALL corticosteroids used for the treatment of ITP **OR** 4. The patient has tried and had an inadequate response to immunoglobulins (IVIg or anti-D) **OR** 5. The patient has had an inadequate response to a splenectomy **OR** 6. The patient has tried and had an inadequate response to rituximab **OR** 4. The patient has another FDA labeled indication for the requested agent **OR** 5. The patient has another indication that is supported in compendia for the requested agent and route of administration **OR** F. The requested agent is Tavalisse (fostamatinib disodium hexahydrate) AND ONE of the following: 1. The patient has a diagnosis of chronic (defined as lasting for at least 12 months) immune (idiopathic) thrombocytopenia (ITP) AND BOTH of the following: A. ONE of the following: 1. The patient has a platelet count less than or equal to 30 X 10^9/L **OR** 2. The patient has a platelet count greater than 30 X 10^9/L but less than 50 x 10^9/L AND has symptomatic bleeding and/or an increased risk for bleeding **AND** B. ONE of the following:

Module	Clinical Criteria for Approval
	1. The patient has tried and had an inadequate response to ONE corticosteroid used for the treatment of ITP **OR** 2. The patient has an intolerance or hypersensitivity to ONE corticosteroid used for the treatment of ITP **OR** 3. The patient has an FDA labeled contraindication to ALL corticosteroids used for the treatment of ITP **OR** 4. The patient has tried and had an inadequate response to another thrombopoietin receptor agonist (e.g., Doptelet, Nplate, Promacta) **OR** 5. The patient has tried and had an inadequate response to immunoglobulins (IVIg or Anti-D) **OR** 6. The patient has had an inadequate response to a splenectomy **OR** 7. The patient has tried and had an inadequate response to rituximab **OR** 2. The patient has another FDA labeled indication for the requested agent **OR** 3. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. ONE of the following: A. The patient will NOT be using the requested agent in combination with another agent included in this program **OR** B. The patient will use the requested agent in combination with another agent included in this program AND BOTH of the following: 1. The requested agent is Nplate **AND** 2. The patient has a diagnosis of hematopoietic syndrome of acute radiation syndrome (HS-ARS) **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Lengths of Approval:** **Doptelet:** thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure - 1 month; all other indications - 6 months **Mulpleta:** thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure - 1 month; all other indications - 6 months

Module	Clinical Criteria for Approval
	Nplate: HS-ARS - 1 time; ITP - 4 months; all other indications - 6 months **Promacta:** ITP - 2 months; thrombocytopenia in hep C - 3 months; first-line therapy in severe aplastic anemia - 6 months; all other severe aplastic anemia - 4 months; all other indications - 6 months **Alvaiz:** ITP - 2 months; thrombocytopenia in hep C - 3 months; all other severe aplastic anemia - 4 months; all other indications - 6 months **Tavalisse:** all indications - 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review]. (Doptelet and Mulpleta for thrombocytopenia with chronic liver disease, AND Nplate for hematopoietic syndrome of acute radiation syndrome [HS-ARS] should always be reviewed under initial criteria.) **AND** 2. ONE of the following: A. The patient has a diagnosis of immune (idiopathic) thrombocytopenia (ITP) AND ONE of the following: 1. The patient's platelet count is greater than or equal to 50 x 10^9/L **OR** 2. The patient's platelet count has increased sufficiently to avoid clinically significant bleeding **OR** B. The patient has the diagnosis of hepatitis C associated thrombocytopenia AND BOTH of the following: 1. The patient will be initiating or maintaining hepatitis C therapy with interferon **AND** 2. ONE of the following: A. The patient's platelet count is greater than or equal to 90 x 10^9/L **OR** B. The patient's platelet count has increased sufficiently to initiate or maintain interferon therapy for the treatment of hepatitis C **OR** C. The patient has a diagnosis other than ITP or hepatitis C associated thrombocytopenia AND has had clinical benefit with the requested agent **AND** 3. The patient will NOT be using the requested agent in combination with another agent included in this program **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Lengths of Approval:** thrombocytopenia in hepatitis C - 6 months; all other indications - 12 months

Module	Clinical Criteria for Approval
	NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Initial Lengths of Approval:** **Doptelet:** thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure - 1 month; all other indications - up to 6 months **Mulpleta:** thrombocytopenia in patients with chronic liver disease who are scheduled to undergo a procedure - 1 month; all other indications - up to 6 months **Nplate:** HS-ARS - 1 time; ITP - up to 4 months; all other indications - up to 6 months **Promacta:** ITP - up to 2 months; thrombocytopenia in hep C - up to 3 months; first-line therapy in severe aplastic anemia - up to 6 months; all other severe aplastic anemia - up to 4 months; all other indications - up to 6 months **Alvaiz:** ITP - 2 months; thrombocytopenia in hep C - 3 months; all other severe aplastic anemia - 4 months; all other indications - 6 months **Tavalisse:** all indications - up to 6 months

Module	Clinical Criteria for Approval
	Renewal Lengths of approval: thrombocytopenia in hepatitis C - up to 6 months; all other indications - up to 12 months

Transmucosal Immediate Release Fentanyl (TIRF)

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Actiq® (fentanyl) Transmucosal lozenge*	Management of breakthrough pain in cancer patients 16 years of age and older who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent cancer pain	* - Generic available	2
Fentora®, Fentanyl Buccal tablet	Management of breakthrough pain in cancer patients 18 years of age and older who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent cancer pain		3
Lazanda® (fentanyl) Nasal spray	Management of breakthrough pain in cancer patients 18 years of age and older who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent cancer pain		4
Subsys® (fentanyl) Sublingual spray	Management of breakthrough pain in cancer patients 18 years of age and older who are already receiving, and who are tolerant to, around-the-clock opioid therapy for their underlying persistent cancer pain		5

CLINICAL RATIONALE

CLINICAL RATIONALE	Transmucosal immediate release fentanyl (TIRF) products are indicated only in patients who are already receiving opioid therapy and who are tolerant to opioid therapy. Life-threatening respiratory depression and death could occur at any dose in opioid non-tolerant patients. Patients considered opioid tolerant are those who are taking, for one week or longer, around-the-clock medicine consisting of at least 60 mg of oral morphine per day, at least 25 mcg per hour of transdermal fentanyl, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day, at least 25 mg oral oxymorphone per day, at least

	60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid daily. Patients must remain on around-the-clock opioids while taking TIRF products. TIRF products are not bioequivalent with other TIRF products. Patients should not be converted on a mcg per mcg basis from one TIRF product to another.(2-5)
Safety	TIRF products carry a boxed warning for the following:(2-5) • Life-threatening respiratory depression • Accidental ingestion, especially by children • Concomitant use with CYP3A4 inhibitors • Concomitant use with benzodiazepines and/or other CNS depressants • Risk of medication errors (e.g. conversion or substitution with other fentanyl products) • Addiction, abuse, and misuse • Risk Evaluation and Mitigation Strategy • Neonatal opioid withdrawal syndrome (i.e., prolonged use during pregnancy) TIRF products have the following contraindications:(2-5) • Opioid non-tolerant patients • Significant respiratory depression • Management of acute or postoperative pain including headache, migraines, dental pain, or use in the emergency department • Acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment • Known or suspected gastrointestinal obstruction • Known hypersensitivity to fentanyl or any other components of the agent Actiq, Fentora, Lazanda, and Subsys are available only through a restricted program called the TIRF REMS Access program. Outpatients, healthcare professionals who prescribe to outpatients, pharmacies, and distributors are required to enroll in the program.(2-5)

REFERENCES

Number	Reference
1	Reference no longer used.
2	Actiq prescribing information. Cephalon, Inc. November 2022.
3	Fentora prescribing information. Cephalon, Inc. November 2022.
4	Lazanda prescribing information. West Therapeutic Development, LLC. March 2021.
5	Subsys prescribing information. Insys Therapeutics, Inc. April 2021.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of chronic cancer pain due to active malignancy **AND** 2. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 3. The patient is currently opioid tolerant (taking, for one week or longer, around-the-clock medicine consisting of at least 60 mg of oral morphine per day, at least 25 mcg per hour of transdermal fentanyl, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day, at least 25 mg oral oxymorphone per day, at least 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid daily) **AND** 4. The patient is taking a long-acting opioid concurrently with the requested TIRF agent **AND** 5. The patient will NOT be using the requested agent with any other TIRF agent in any other strength **AND** 6. If the client has preferred generic TIRF agents, then ONE of the following: A. The request is for a generic TIRF agent **OR** B. The request is for a brand TIRF agent AND ONE of the following: 1. The patient's medication history includes use of at least ONE generic TIRF agent within the past 90 days **OR**

Module	Clinical Criteria for Approval
	2. Information has been provided that indicates the patient is currently being treated with the requested agent within the past 90 days **OR** 3. The prescriber states the patient is currently being treated with the requested agent within the past 90 days AND is at risk if therapy is changed **OR** 4. The patient has an intolerance or hypersensitivity to at least ONE generic TIRF agent that is not expected to occur with the requested agent **OR** 5. The patient has an FDA labeled contraindication to ALL generic TIRF agents that is not expected to occur with the requested agent **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** • 1 month for increased dose requests during a dose titration period • Up to 6 months for all other requests NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. ALL of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose **AND** 2. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **AND** 3. Episodes of breakthrough pain cannot be controlled by modifying the dose of the maintenance long-acting opioid used for underlying persistent pain **AND** 4. The prescriber has provided information in support of therapy with a higher quantity (dose) for the requested indication **OR** B. ALL of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose **AND** 2. Episodes of breakthrough pain cannot be controlled by modifying the dose of the maintenance long-acting opioid used for underlying persistent pain **AND**

Module	Clinical Criteria for Approval
	3. The prescriber has provided information in support of therapy with a higher quantity (dose) for the requested indication **Length of Approval:** • 1 month for increased dose requests during a dose titration period • Up to 6 months for all other requests

Topical Actinic Keratosis, Basal Cell Carcinoma, Genital Warts Agents

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Aldara® (imiquimod) 5% cream*	Topical treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratoses on the face or scalp in immunocompetent adults Topical treatment of biopsy-confirmed primary superficial basal cell carcinoma (sBCC) in immunocompetent adults, with a maximum tumor diameter of 2.0 cm, located on the trunk (excluding anogenital skin), neck, or extremities (excluding hands and feet), only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured Treatment of external genital and perianal warts (condyloma acuminata) in patients 12 years or older	* generic available	6
Carac® (fluorouracil) 0.5% cream*	Topical treatment of multiple actinic or solar keratoses of the face and anterior scalp	* generic available	2
diclofenac 3% gel	Topical treatment of actinic keratosis (AK)		1
Efudex® (fluorouracil) 5% cream*	Topical treatment of multiple actinic or solar keratoses Treatment of superficial basal cell carcinomas when conventional methods are impractical, such as with multiple lesions or difficult treatment sites	* generic available	4
Fluoroplex® (fluorouracil)	Topical treatment of multiple actinic (solar) keratoses		3

Agent(s)	FDA Indication(s)	Notes	Ref#
1% cream			
KLISYRI® (tirbanibulin) 1% ointment	Topical treatment of actinic keratosis on the face or scalp		8
Tolak® (fluorouracil) 4% cream	Topical treatment of actinic keratosis lesions of the face, ears, and/or scalp		5
Zyclara® (imiquimod) 3.75% cream*	Topical treatment of clinically typical visible or palpable actinic keratoses (AK) of the full face or balding scalp in immunocompetent adults Treatment of external genital and perianal warts (EGW)/condyloma acuminata in patients 12 years or older	* generic available	7
Zyclara® (imiquimod) 2.5% cream	Topical treatment of clinically typical visible or palpable actinic keratoses (AK) of the full face or balding scalp in immunocompetent adults		7

CLINICAL RATIONALE

Actinic Keratosis (AK)	Actinic keratoses (AK or solar keratoses) are keratotic or scaling macules, papules, or plaques resulting from the intraepidermal proliferation of atypical keratinocytes in response to prolonged exposure to ultraviolet radiation.(9) Although most AKs do not progress to squamous cell carcinoma (SCC), AKs are a concern because the majority of cutaneous SCCs arise from pre-existing AKs and AKs that will progress to SCC cannot be distinguished from AKs that will spontaneously resolve or persist.(9,10) According to NCCN guidelines, topical first-line therapies for AK include 5-fluorouracil (5-FU), imiquimod, and tirbanibulin. Topical diclofenac is considered 2B (based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate) due to varying efficacy results across large randomized trials.(10) 5-

	FU and imiquimod are considered as first-line topical therapies, and diclofenac and tirbanibulin as second-line.(15)
Superficial Basal Cell Carcinoma (BCC)	Basal cell carcinoma (BCC) is a common skin cancer that arises from the basal layer of epidermis and its appendages. Although rarely metastatic, BCC can produce substantial local destruction along with disfigurement and may involve extensive areas of soft tissue, cartilage, and bone. First-line therapy is surgical excision, however for some patients with low-risk superficial BCC, where surgery is contraindicated or impractical, topical therapies such as 5-fluorouracil (5-FU) or imiquimod may be considered, even though the cure rate may be lower.(12)
Genital Warts	Condylomomata acuminata, also known as anogenital warts or external genital / perianal warts (EGW), are a manifestation of anogenital human papillomavirus (HPV) infection. The treatment of genital warts should be guided by the extent of disease (e.g., wart size, number, and anatomic site), patient preference, cost and availability of treatment, and the experience of the health care provider. Patient-applied therapies include imiquimod 3.75% and 5%, and podophyllotoxin. The majority of genital warts respond within 3 months of therapy.(14)

REFERENCES

Number	Reference
1	Diclofenac 3% gel prescribing information. Glenmark Pharmaceuticals Inc. July 2023.
2	Carac 0.5% cream prescribing information. Bausch Health US, LLC. May 2021.
3	Fluoroplex prescribing information. Almirall, LLC. March 2022.
4	Efudex prescribing information. Bausch Health Companies Inc. March 2024.
5	Tolak prescribing information. Hill Dermaceuticals, Inc. August 2022.
6	Aldara prescribing information. Valeant Pharmaceuticals International, Inc. October 2023.
7	Zyclara prescribing information. Bausch Health US, LLC. January 2024.
8	Klisyri prescribing information. Almirall, LLC. August 2021.

Number	Reference
9	Criscione VD, Weinstock MA, et al. Actinic keratoses: Natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. Cancer 2009; 115:2523.
10	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Squamous Cell Skin Cancer. Version 1.2024.
11	Reference no longer used.
12	National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Basal Cell Skin Cancer. Version 3.2024.
13	Refernce no longer used.
14	Workowski KA, Bachmann LH, Chan PA, et al. Centers for Disease Control and Prevention (CDC) Treatment Guidelines on Sexually Transmitted Diseases. MMWR. 2021;70(4):1-187.
15	Eisen DB, Asgari MM, Bennett DD, et al. Guidelines of care for the management of actinic keratosis. J Am Acad Dermatol 2021; 85:e209.

ALLOWED EXCEPTIONS QUANTITY LIMIT

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Allowed Exceptions	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
Prior Authorization with Quantity Limit							
90374035304020		Diclofenac Sodium (Actinic Keratoses) Gel 3%	3 %	Actinic keratoses: one 100 gram tube per month for up to 90 days			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Allowed Exceptions	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
90773040003720		Imiquimod Cream 5%	5 %	Actinic keratoses: three boxes (36 packets) for up to 16 weeks External genital and perianal warts (EGW) (condyloma acuminata): 12 packets per month for up to 16 weeks Superficial basal cell carcinoma: three boxes (36 packets) for up to 6 weeks			
90372030003705	Carac	Fluorouracil Cream 0.5%	0.5 %	Multiple actinic or solar keratoses: one 30 gram tube per month for up to 4 weeks			
90372030003730	Efudex	Fluorouracil Cream 5%	5 %	Multiple actinic or solar keratoses: one 40 gram tube per month for up to 4 weeks Superficial basal cell carcinomas: two 40 gram tubes per month for up to 12 weeks			
90374580004220	Klisyri	Tirbanibulin Ointment	1 %	Actinic keratoses (face or scalp): 5 packets for up to 90 days			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Allowed Exceptions	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
90372030003725	Tolak	Fluorouracil Cream 4%	4 %	Actinic keratoses: one 40 gram tube per month for up to 4 weeks			
90773040003715	Zyclara ; Zyclara pump	Imiquimod Cream 3.75%	3.75 %	Actinic keratoses: two boxes (56 packets) for up to 6 weeks two 7.5 gm pump bottles for up to 6 weeks External genital or perianal warts (EGW) (condyloma acuminata): two boxes (56 packets) for up to 8 weeks two 7.5 gm pump bottles for up to 8 weeks			
90773040003710	Zyclara pump	Imiquimod Cream 2.5%	2.5 %	Actinic keratoses: two 7.5 gm pump bottles for up to 6 weeks			

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Target Agent(s)** will be approved when ALL of the following are met: 1. If the patient has an FDA labeled indication, then ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. ONE of the following: A. BOTH of the following: 1. The patient has a diagnosis of actinic (solar) keratoses of the face and/or scalp: **AND** 2. The requested agent is diclofenac 3% gel, Carac (Fluorouracil) 0.5% cream, Efudex (Fluorouracil) 5% cream, Fluoroplex, Tolak, imiquimod 5%, Zyclara (imiquimod) 3.75% cream, Zyclara 2.5% cream, OR Klisyri **OR** B. BOTH of the following: 1. The patient has a diagnosis of actinic (solar) keratoses of the trunk and/or extremities: **AND** 2. The requested agent is diclofenac 3% gel, Efudex (Fluorouracil) 5% cream, OR Fluoroplex **OR** C. BOTH of the following: 1. The patient has a diagnosis of superficial basal cell carcinoma **AND** 2. The requested agent is imiquimod 5% OR Efudex (Fluorouracil) 5% cream **OR** D. BOTH of the following: 1. The patient has a diagnosis of external genital and/or perianal warts (EGW) / condyloma acuminata **AND** 2. The requested agent is imiquimod 5% OR Zyclara (imiquimod) 3.75% cream **AND** 3. ONE of the following: A. For a diagnosis of actinic keratoses or superficial basal cell carcinoma, ONE of the following: 1. The patient has tried and had an inadequate response to generic imiquimod 5% cream or fluorouracil solution **OR** 2. The patient has an intolerance or hypersensitivity to therapy with generic imiquimod 5% cream or fluorouracil solution **OR** 3. The patient has an FDA labeled contraindication to generic imiquimod 5% cream AND fluorouracil solution **OR** B. For a diagnosis of external genital warts, ONE of the following: 1. The patient has tried and had an inadequate response to generic imiquimod 5% cream **OR** 2. The patient has an intolerance of hypersensitivity to therapy with generic imiquimod 5% cream **OR**

Module	Clinical Criteria for Approval
	3. The patient has an FDA labeled contraindication to generic imiquimod 5% cream **Length of Approval:** Up to duration in the program quantity limit for the requested indication; or durations above program quantity limit with appropriate supportive information for up to 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL with PA	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) and/or duration does NOT exceed the program quantity limit for the requested indication **OR** 2. There is support of therapy with the requested quantity (dose) and/or duration of therapy for the requested indication **Length of Approval:** up to duration in the program quantity limit for the requested indication; or durations above program quantity limit with appropriate supportive information for up to 12 months

Topical Corticosteroids

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Ala-Scalp®, Hydrocortisone 2% Lotion	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses		5
Amcinonide 0.1% Cream, lotion, ointment*	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses		6
ApexiCon® E (diflorasone diacetate) 0.05% Cream emollient	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses		7
Diprolene® (augmented betamethasone dipropionate) 0.05% Ointment*	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 13 years of age or older	*generic available	20
Bryhali® (halobetasol propionate) 0.01% Lotion	Treatment of plaque psoriasis in adults		9
Clobex®, Olux®, Olux-E® (clobetasol propionate) 0.05% Emulsion foam aerosol*, foam aerosol*,	Cream/lotion/ointment: Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 12 years of age or older (of the scalp for solution)	*generic available	11 ; 30 ; 31

Agent(s)	FDA Indication(s)	Notes	Ref#
lotion*, shampoo*, spray aerosol*	Shampoo: Treatment of moderate to severe forms of scalp psoriasis in patients 18 years and older Foam: Treatment of moderate to severe plaque psoriasis of the scalp and mild to moderate plaque psoriasis of non-scalp regions of the body in patients 12 years and older Spray: Treatment of moderate to severe plaque psoriasis affecting up to 20% body surface area (BSA) in patients 18 years and older		
Cloderm® (clocortolone pivalate) 0.1% Cream*	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses	*generic available	12
Cordran®, Flurandrenolide 0.05% Cream*, lotion*, ointment 0.025% Cream	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses	*generic available	13
Cordran® (flurandrenolide) 4 mcg/cm^2 Tape	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses, particularly dry, scaling localized lesions		14
Derma-Smoothe/FS® (fluocinolone acetonide) 0.01% Body oil*, scalp oil*	Body Oil: Treatment of atopic dermatitis in patients 3 months of age and older Scalp oil: Treatment of psoriasis of the scalp in adults	*generic available	16
Desonide 0.05% Gel*	Treatment of mild to moderate atopic dermatitis in patients 3 months of age and older	*generic available	17

Agent(s)	FDA Indication(s)	Notes	Ref#
DesOwen®, Tridesilon™, Verdeso® (desonide) 0.05% Cream*, foam	Cream: Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses Foam: Treatment of mild to moderate atopic dermatitis in patients 3 months of age and older	*generic available	18 ; 42
Diflorasone diacetate 0.05% Cream	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses		34
Diprolene® (betamethasone dipropionate, augmented) 0.05% Ointment*	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses	*generic available	20
Fluocinonide 0.05% Gel*	For the relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses	*generic available	21
Fluticasone propionate 0.05% Lotion*	Relief of the inflammatory and pruritic manifestations of atopic dermatitis in patients 3 months of age and older	*generic available	15
Lexette®, Ultravate® (halobetasol propionate) 0.05% Foam*, lotion	Lotion: Treatment of plaque psoriasis in patients 18 years and older Foam: Treatment of plaque psoriasis in patients 12 years and older	*generic available	26 ; 40
Halog® (halcinonide) 0.1% Cream*, ointment, solution	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses	*generic available	22
Locoid®, Hydrocortisone butyrate	Treatment of mild to moderate atopic dermatitis in pediatric patients 3 months to 18 years of age	*generic available	27

Agent(s)	FDA Indication(s)	Notes	Ref#
0.1% Lotion*, solution	Lotion: Treatment of mild to moderate atopic dermatitis in patients 3 months of age and older Solution: Relief of the inflammatory and pruritic manifestations of seborrheic dermatitis		
Impeklo™ (clobetasol propionate) 0.05% Lotion	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 18 year of age or older		23
Impoyz® (clobetasol propionate) 0.025% Cream	Treatment of moderate to severe plaque psoriasis in patients 18 years and older		24
Kenalog® (triamcinolone acetonide) Aerosol spray*	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses	*generic available	25
Locoid® Lipocream, Hydrocortisone butyrate hydrophilic 0.1% Lipo base cream*	Lipocream: • Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in adults • Treatment of mild to moderate atopic dermatitis in pediatric patients 3 months to 18 years of age	*generic available	27 ; 28
Luxiq® (betamethasone valerate) 0.12% Foam*	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses of the scalp	*generic available	29
Pandel®	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 18 years and older		32

Agent(s)	FDA Indication(s)	Notes	Ref#
(hydrocortisone probutate) 0.1% Cream			
Prednicarbate 0.1% Ointment	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses		33
Sernivo® (betamethasone dipropionate) 0.05% Spray	Treatment of mild to moderate plaque psoriasis in patients 18 years and older		35
Capex®, Synalar® (fluocinolone acetonide) 0.01% Shampoo, solution*	Solution: Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses Shampoo: Treatment of seborrheic dermatitis of the scalp	*generic available	10 ; 36
Synalar® (fluocinolone acetonide) 0.025% Cream*, ointment*	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses	*generic available	36
Texacort®, Hydrocortisone (hydrocortisone) 2.5% Lotion*, solution	For the relief of the inflammatory and pruritic manifestations of corticosteroids-responsive dermatoses		38
Topicort® (desoximetasone)	Spray: Treatment of plaque psoriasis in patients 18 years and older	*generic available	39

Agent(s)	FDA Indication(s)	Notes	Ref#
0.25% Cream*, ointment*, spray*	Cream/gel/ointment: Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses		
Topicort® (desoximetasone) 0.05% Cream*, gel*, ointment*	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses	*generic available	39
Vanos® (fluocinonide) 0.1% Cream*	Relief of the inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses in patients 12 years and older	*generic available	41

CLINICAL RATIONALE

Topical Corticosteroids	Topical steroids are the mainstay of therapy for dermatologic conditions and come in a variety of potencies and formulations. The choice of topical steroid should be individualized, and success depends on accurate diagnosis, consideration for potency and delivery vehicle, frequency of application, duration of therapy, and safety concerns.(1-4) It is essential for prescribers to make an accurate diagnosis prior to prescribing a topical corticosteroid, as fungal infections can be exacerbated by the use of corticosteroids. These agents are effective for the treatment of conditions characterized by hyperproliferation, inflammation, and immunologic involvement. They also provide symptomatic relief for burning and pruritic lesions. Higher potency corticosteroids are frequently used to treat severe atopic dermatitis, psoriasis, and severe eczema, while lower potency corticosteroids are frequently used to treat mild cases of dermatitis and on fragile skin, such as the face and eye lids.(1,2) Once or twice daily administration is recommended for most formulations. More frequent applications have not been proven to provide superior results. Chronic application of topical steroids can cause tolerance and tachyphylaxis. Super-high

	potent steroids are not recommended for use beyond three consecutive weeks. If a longer duration is required, the agent can be gradually tapered to avoid rebound symptoms, and treatment may resume after at least a one-week steroid-free period. This alternating schedule can be repeated chronically or until the condition resolves. Steroids differ in potency based on the vehicle used in formulation and should only be used on certain areas of the body. Side effects are rare when low- to high-potency steroids are used for less than three months, except in intertriginous areas, on the face and neck, and under occlusion.(1,2) A standard unit used for topical corticosteroid application is the fingertip unit. One fingertip unit is the amount of medication dispensed from a standard 5-mm nozzle over a distance from the tip of the index finger to the crease of the distal interphalangeal joint. This represents approximately 0.5 g of medication and should cover approximately 2% of the body surface area on an adult. The area of an adult patient's palm represents approximately 1% of body surface area or one-half of a fingertip unit. For example, 30 g should be sufficient for twice daily application to an area the size of two adult palms for 30 days.(2) The duration of treatment depends on the strength of the corticosteroid and the condition being treated. In general, super-high-potency topical corticosteroids should be used for no more than three weeks at a time. High- and medium-potency corticosteroids should be used for no more than 12 weeks at a time. For treatments of longer duration, a potent corticosteroid may be used intermittently or transitioned to a milder corticosteroid for ongoing control. Lesions on the face, groin, and skinfolds may be treated in one- to two-week intervals. Therapy may be discontinued when the lesions resolve.(2)
Potency	Topical corticosteroids are ranked according to their potency on a scale of 1 to 7; ranging from group 1 (I) super-high potent to group 7 (VII) least potent. Group 1 (I) corticosteroids have the greatest risk of inducing side effects such as tolerance and tachyphylaxis if used for periods extending past two weeks; medications are not generally recommended for use longer than two weeks. Group 7 (VII) corticosteroids can be used more safely for longer periods of time and on larger surface areas but they too must be used properly to prevent unwanted side effects. Some generic formulations have been shown to be less or more potent than their brand-name equivalent.(1,3,4) **Potency Ratings for Topical Corticosteroids(1.3,4)**

Potency Group	Generic	Brand
Group 1 (I) Super-high Potency	Betamethasone dipropionate (augmented) 0.05% (gel, lotion, ointment) Clobetasol propionate 0.05% (cream, cream emollient, foam, gel, lotion, ointment, shampoo, solution, spray) Fluocinonide 0.1% (cream) Flurandrenolide (tape) Halobetasol propionate 0.05% (cream, foam, lotion, ointment)	Clobex (lotion, shampoo, spray) Cordran (tape) Diprolene (ointment) Impeklo (lotion) Lexette (foam) Olux, Olux E (foam) Ultravate (lotion) Vanos (cream)
Group 2 (II) High Potency	Amcinonide 0.1% (ointment) Betamethasone dipropionate (augmented) 0.05% (cream) Betamethasone dipropionate 0.05% (ointment) Clobetasol propionate 0.025% (cream) Desoximetasone, 0.05% (gel) Desoximetasone, 0.25% (cream, ointment, spray) Diflorasone diacetate 0.05% (cream, ointment) Fluocinonide 0.05% (cream, gel, ointment, solution) Halcinonide 0.1% (cream, ointment, solution) Halobetasol propionate 0.01% (lotion)	ApexiCon E (cream) Bryhali (lotion) Diprolene AF (cream) Halog (cream, ointment, solution) Impoyz (cream) Topicort (gel, cream, ointment, spray)
Group 3 (III) Medium-high Potency	Amcinonide 0.1% (cream, lotion) Betamethasone dipropionate 0.05% (cream) Betamethasone valerate 0.1% (ointment) Betamethasone valerate 0.12% (foam) Desoximetasone 0.05%	Luxiq (foam) Topicort (cream, ointment)

		(cream, ointment) Diflorasone diacetate 0.05% (cream) Fluocinonide 0.05% (cream) Fluticasone propionate 0.005% (ointment) Mometasone furoate 0.1% (ointment) Triamcinolone acetonide 0.5% (cream, ointment)	
	Group 4 (IV) Medium Potency	Betamethasone dipropionate 0.05% (spray) Clocortolone pivalate 0.1% (cream) Fluocinolone acetonide 0.025% (ointment) Flurandrenolide 0.05% (ointment) Fluticasone propionate 0.05% (cream) Hydrocortisone valerate 0.2% (ointment) Mometasone furoate 0.1% (cream, lotion, solution) Triamcinolone acetonide 0.05% (ointment) Triamcinolone acetonide 0.1% (cream, ointment) Triamcinolone acetonide 0.2 mg (spray)	Cloderm (cream) Cordran (ointment) Kenalog (spray) Sernivo (spray) Synalar (ointment)
	Group 5 (V) Lower-mid Potency	Betamethasone dipropionate 0.05% (lotion) Betamethasone valerate 0.1% (cream) Desonide 0.05% (gel) Fluocinolone acetonide 0.025% (cream) Flurandrenolide 0.05% (cream, lotion) Flurandrenolide 0.025% (cream)	Cordran (cream, lotion) Locoid (lotion, solution) Locoid Lipocream (cream) Pandel (cream) Synalar (cream)

		Fluticasone propionate 0.05% (cream, lotion) Hydrocortisone butyrate 0.1% (cream, lotion, ointment, solution) Hydrocortisone probutate 0.1% (cream) Hydrocortisone valerate 0.2% (cream) Prednicarbate 0.1% (ointment) Triamcinolone acetonide 0.1% (lotion) Triamcinolone acetonide 0.025%	
	Group 6 (VI) Low Potency	Alclometasone dipropionate 0.05% (cream, ointment) Betamethasone valerate 0.1% (lotion) Desonide 0.05% (cream, foam, lotion, ointment) Fluocinolone acetonide 0.01% (cream, oil, shampoo, solution) Triamcinolone acetonide 0.025% (cream, lotion)	Capex (shampoo) Derma-Smoothe/FS (oil) DesOwen, Tridesilon (cream) Synalar (solution) Verdeso (foam)
	Group 7 (VII) Least Potent	Hydrocortisone 0.5% to 2.5% Hydrocortisone acetate 0.5% to 2.5%	Ala-Scalp (lotion) Texacort (solution)
Safety	Prolonged use of topical corticosteroids may result in adverse effects. It is difficult to quantify the incidence of side effects caused by topical corticosteroids, given their differences in potency. According to a post-marketing safety review, the most frequently reported side effects were local irritation (66%), skin discoloration (15%), and striae or skin atrophy (15%). Side effects occur more often with higher potencies. Using the least potent corticosteroid for the shortest time while still maintaining efficacy, reduces the risk of adverse effects. Other side effects from the use of topical corticosteroids include permanent dermal atrophy, telangiectasia, rosacea, hypopigmentation, and induction of contact dermatitis. High and super-high potent corticosteroids have		

	been reported to cause systemic side effects. Hypothalamic-pituitary-adrenal suppression, glaucoma, septic necrosis of the femoral head, hyperglycemia, hypertension, and other systemic side effects have been reported.(1-4) In general, topical corticosteroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparation.(5-18,20-36,38-42)

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2	Stacey SK, McEleney M. Topical Corticosteroids: Choice and Application. Am Fam Physician. 2021 Mar 15;103(6):337-343. PMID: 33719380.
3	Topical Steroid Potency Chart. National Psoriasis Foundation. https://www.psoriasis.org/potency-chart/. Last updated October 2022.
4	“Topical Steroid Potencies.” MPR, www.empr.com/clinical-charts/topical-steroid-potencies/article/123847/.
5	Ala-Scalp prescribing information. Derm Ventures LLC. June 2020.
6	Amcinonide prescribing information. Taro Pharmaceuticals USA, Inc. January 2024.
7	ApexiCon E prescribing information. ANI Pharmaceuticals, Inc. September 2021.
8	Betamethasone dipropionate augmented gel prescribing information. Taro Pharmaceuticals U.S.A., Inc. December 2019.
9	Bryhali prescribing information. Bausch Health US, LLC. June 2020.
10	Capex prescribing information. Galderma Laboratories, LP. December 2015.
11	Clobex prescribing information. Galderma Laboratories, L.P. February 2023.

Number	Reference
12	Cloderm prescribing information. EPI Health, LLC. November 2022.
13	Cordran cream/ointment prescribing information. Almirall, LLC. July 2019.
14	Cordran tape prescribing information. Allergan, Inc. July 2019.
15	Fluticasone lotion prescribing information. Glenmark Pharmaceuticals Inc., USA. February 2020.
16	Derma-Smoothe prescribing information. Royal Pharmaceuticals. January 2022.
17	Desonide prescribing information. Cintex Services, LLC. July 2020.
18	DesOwen prescribing information. Galderma Laboratories, LP. April 2017.
19	Reference no longer used.
20	Diprolene prescribing information. Merck Sharp & Dohme Corp. February 2022.
21	Fluocinonide gel prescribing information. Taro Pharmaceuticals U.S.A., Inc. February 2018.
22	Halog prescribing information. Sun Pharmaceutical Industries, Inc. July 2019.
23	Impeklo prescribing information. Mylan Specialty L.P. May 2020.
24	Impoyz prescribing information. Primus Pharmaceuticals, Inc. April 2021.
25	Kenalog spray prescribing information. Sun Pharmaceuticals Industries, Inc. May 2018.
26	Lexette prescribing information. Mayne Pharma. August 2021.
27	Locoid prescribing information. Onset Dermatologics, LLC. March 2021.
28	Locoid Lipocream prescribing information. Onset Dermatologics, LLC. March 2021.
29	Luxiq prescribing information. Mylan Pharmaceuticals, Inc. April 2018.
30	Olux prescribing information. Mylan Pharmaceuticals Inc. April 2018.

Number	Reference
31	Olux-E prescribing information. Mylan Pharmaceuticals Inc. May 2018.
32	Pandel prescribing information. ANI Pharmaceuticals Inc. September 2021.
33	Prednicarbate prescribing information. Fougera Pharmaceuticals Inc. December 2021.
34	Diflorasone prescribing information. Taro Pharmaceuticals U.S.A., Inc. May 2018.
35	Sernivo prescribing information. Encore Dermatology Inc. March 2020.
36	Synalar prescribing information. Medimetriks Pharmaceuticals, Inc. July 2024.
37	Reference no longer used.
38	Texacort prescribing information. Mission Pharmacal Company. January 2024.
39	Topicort prescribing information. Taro Pharmaceuticals USA, Inc. September 2021.
40	Ultravate prescribing information. Sun Pharmaceutical Industries, Inc. September 2020.
41	Vanos prescribing information. Valeant Pharmaceuticals North America LLC. May 2017.
42	Verdeso prescribing information. Almirall LLC. April 2019.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support therapy with a higher dose for the requested indication **OR**

Module	Clinical Criteria for Approval
	B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. Information has been provided to support therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Topical Doxepin

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Prudoxin® (doxepin) 5% cream*	Short-term (up to 8 days) management of moderate pruritus in adult patients with atopic dermatitis or lichen simplex chronicus	* Generic available	2
Zonalon® (doxepin) 5% cream*	Short-term (up to 8 days) management of moderate pruritus in adult patients with atopic dermatitis or lichen simplex chronicus	* Generic available	3

CLINICAL RATIONALE

Atopic Dermatitis	Atopic dermatitis is a chronic, pruritic, inflammatory skin disease. Clinical features include skin dryness, erythema, oozing and crusting, and lichenification. Pruritus is responsible for much of the disease burden for patients. The goals of treatment are to reduce symptoms of pruritus and dermatitis, prevent exacerbations, and minimize therapeutic risks.(4) Initial nonpharmacological therapy for atopic dermatitis, as recommended by American Academy of Dermatology (AAD) guidelines, is use of moisturizing agents. Moisturizers are the cornerstone of atopic dermatitis therapy as an important component of maintenance treatment and for the prevention of flares. Recommended topical therapy for atopic dermatitis, indicated when nonpharmacologic interventions have failed, includes topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI).(6,7) Proactive, once to twice weekly application of mid-potency TCS for up to 40 weeks has not demonstrated adverse events in clinical trials. AAD notes that mid-to higher-potency topical corticosteroids are appropriate for short courses to gain rapid control of symptoms, but long-term management should use the least-potent corticosteroid that is effective. TCIs (e.g., pimecrolimus, tacrolimus) are recommended by the AAD as second-line therapy, and are particularly useful in selected clinical situations such as recalcitrance to steroids; for sensitive areas (face, anogenital, skin folds); for steroid-induced

	atrophy; and when there is long-term uninterrupted topical steroid use.(6) Prescribing information for Elidel (pimecrolimus) cream and Protopic (tacrolimus) ointment indicate evaluation after 6 weeks if signs and symptoms of atopic dermatitis persist.(9,10) While topical doxepin does provide short-term decrease in pruritus, it is not recommended for atopic dermatitis by the AAD guidelines due to the risk of absorption, contact dermatitis, and noting that studies have shown no significant reduction in disease severity or control.(6)
Lichen Simplex Chronicus	Lichen simplex chronicus (LSC) is a common form of chronic neurodermatitis that presents as localized dry, patchy areas of skin that are scaly and thick. The plaques form as a result of constant and repeated scratching and/or rubbing of specific areas. The root of the disorder may be both a primary symptom reflective of a psychological component, or secondary to other cutaneous issues such as eczema or psoriasis. The treatment of LSC centers on breaking the itch-scratch cycle. Reducing inflammation is another cornerstone to treatment. As LSC is usually localized, topical agents are often used with high-potency topical corticosteroids considered first-line for treatment.(1,8)
Safety	Prudoxin and Zonalon are contraindicated in the following:(2,3) • Patients with untreated narrow angle glaucoma or a tendency to urinary retention • Individuals who have shown previous sensitivity to any of its components

REFERENCES

Number	Reference
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2	Prudoxin prescribing information. Mylan Pharmaceuticals, Inc. June 2017.
3	Zonalon prescribing information. Mylan Pharmaceuticals, Inc. June 2017.

Number	Reference
4	Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis. *Journal of the American Academy of Dermatology*. 2014;70(2):338-351. doi:10.1016/j.jaad.2013.10.010
5	Reference no longer used
6	Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis. *Journal of the American Academy of Dermatology*. 2014;71(1):116-132. doi:10.1016/j.jaad.2014.03.023
7	Eichenfield LF, Ahluwalia J, Waldman A, Borok J, Udkoff J, Boguniewicz M. Current guidelines for the evaluation and management of atopic dermatitis: A comparison of the Joint Task Force Practice Parameter and American Academy of Dermatology guidelines. *The Journal of Allergy and Clinical Immunology/Journal of Allergy and Clinical Immunology/The Journal of Allergy and Clinical Immunology*. 2017;139(4):S49-S57. doi:10.1016/j.jaci.2017.01.009
8	Charifa A, Badri T, Harris BW. Lichen simplex chronicus. StatPearls - NCBI Bookshelf. Published August 7, 2023. https://www.ncbi.nlm.nih.gov/books/NBK499991/
9	Elidel prescribing information. Bausch Health Companies Inc. September 2020.
10	Protopic prescribing information. Leo Pharma Inc. June 2022.

ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
90220015103710	Prudoxin ; Zonalon	Doxepin HCl Cream 5%	5 %	Quantity Limit is cumulative across agents			

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of moderate pruritus associated with atopic dermatitis **AND** ONE of the following: 1. The patient has tried and had an inadequate response to BOTH a topical corticosteroid used for a minimum of 4 weeks AND a topical calcineurin inhibitor used for a minimum of 6 weeks **OR** 2. The patient has an intolerance or hypersensitivity to a topical corticosteroid AND a topical calcineurin inhibitor **OR** 3. The patient has an FDA labeled contraindication to ALL topical corticosteroids AND topical calcineurin inhibitors **OR** B. The patient has a diagnosis of moderate pruritus associated with lichen simplex chronicus **AND** ONE of the following: 1. The patient has tried and had an inadequate response to ONE topical corticosteroid **OR** 2. The patient has an intolerance or hypersensitivity to ONE topical corticosteroid **OR** 3. The patient has an FDA labeled contraindication to ALL topical corticosteroids **OR** C. The patient has another FDA labeled indication for the requested agent and route of administration **OR** D. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
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2. If the patient has an FDA labeled indication, then ONE of the following:
   A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**
   B. There is support for using the requested agent for the patient's age for the requested indication **AND**
3. If the request is for one of the following brand agents with an available generic (listed below), then ONE of the following:

<table>
<tr><th>Brand</th><th>Generic</th></tr>
<tr><td>Prudoxin cream
Zonalon cream</td><td>doxepin hydrochloride cream 5%</td></tr>
</table>

   A. The patient has an intolerance or hypersensitivity to the generic that is not expected to occur with the brand agent **OR**
   B. The patient has an FDA labeled contraindication to the generic that is not expected to occur with the brand agent **OR**
   C. There is support for the use of the requested brand agent over the generic **AND**
4. The patient will NOT be using the requested agent in combination with another topical doxepin agent for the requested indication **AND**
5. The patient has NOT already received 8 days of therapy with a topical doxepin agent for the current course of therapy **AND**
6. The patient does NOT have any FDA labeled contraindications to the requested agent

Compendia Allowed: AHFS or DrugDex 1 or 2a level of evidence

Length of Approval: pruritus associated with atopic dermatitis or lichen simplex chronicus - 1 month; or all other requests - 12 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
</td></tr>
</table>

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR**

Module	Clinical Criteria for Approval
	2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Topical Estrogen

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
ALORA® (estradiol) Transdermal system*	Treatment of moderate to severe vasomotor symptoms associated with the menopause Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause • Limitation of use: When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, first consider the use of topical vaginal products. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure Prevention of postmenopausal osteoporosis • Limitation of use: When prescribing solely for the prevention of postmenopausal osteoporosis, only consider therapy for women at significant risk of osteoporosis. First consider the use of non-estrogen medications.	*generic available	3
Climara® (estradiol) Transdermal system*	Treatment of moderate to severe vasomotor symptoms due to menopause Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause • Limitation of use: When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due	*generic available	4

Agent(s)	FDA Indication(s)	Notes	Ref#
	to menopause, first consider the use of topical vaginal products. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure Prevention of postmenopausal osteoporosis • Limitation of use: When prescribing solely for the prevention of postmenopausal osteoporosis, first consider the use of non-estrogen medications. Consider estrogen therapy only for women at significant risk of osteoporosis.		
Climara Pro® (estradiol/levonorgestrel) Transdermal System	Treatment of moderate to severe vasomotor symptoms due to menopause in women with a uterus Prevention of postmenopausal osteoporosis in women with a uterus • Limitation of use: When prescribing solely for the prevention of postmenopausal osteoporosis, first consider the use of non-estrogen medications. Consider estrogen therapy only for women at significant risk of osteoporosis.		5
CombiPatch® (estradiol/norethindrone) Transdermal System	Treatment in women with a uterus for: • Moderate to severe vasomotor symptoms due to menopause • Moderate to severe symptoms of vulvar and vaginal atrophy due to menopause • Hypoestrogenism due to hypogonadism, castration, or primary ovarian failure		6

Agent(s)	FDA Indication(s)	Notes	Ref#
Divigel® (estradiol) Gel*	Treatment of moderate to severe vasomotor symptoms due to menopause	*generic available	7
Elestrin® (estradiol) Topical Gel	Treatment of moderate to severe vasomotor symptoms due to menopause		8
ESTRACE® (estradiol) Vaginal Cream*	Treatment of moderate to severe symptoms of vulvar and vagial atrophy due to menopause	*generic available	17
Estring® (estradiol) Vaginal Ring	Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause		9
EstroGel® (estradiol) Topical Gel*	Treatment of moderate to severe vasomotor symptoms due to menopause Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause • Limitation of Use: When prescribing solely for the treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, first consider the use of topical vaginal products.	*generic available	10
Evamist® (estradiol) Transdermal Spray	Treatment of moderate to severe vasomotor symptoms due to menopause		11

Agent(s)	FDA Indication(s)	Notes	Ref#
Femring® (estradiol) Vaginal Ring	Treatment of moderate to severe vasomotor symptoms due to menopause Treatment of moderate to severe vulvar and vaginal atrophy due to menopause		12
Imvexxy® (estradiol) Vaginal Insert	Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause		13
MENOSTAR® (estradiol) Transdermal System	Prevention of postmenopausal osteoporosis Limitation of use: When prescribing solely for the prevention of postmenopausal osteoporosis, first consider the use of non-estrogen medication. Consider estrogen therapy only for women at significant risk of osteoporosis.		14
Minivelle® (estradiol) Transdermal System*	Treatment of moderate to severe vasomotor symptoms due to menopause Prevention of postmenopausal osteoporosis • Limitation of Use: When prescribing solely for the prevention of postmenopausal osteoporosis, first consider the use of non-estrogen medications. Consider estrogen therapy only for women at significant risk of osteoporosis.	*generic available	15
Vivelle-Dot® (estradiol) Transdermal System*	Treatment of moderate to severe vasomotor symptoms due to menopause Treatment of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause • Limitation of Use: When prescribing solely for the treatment of symptoms of vulvar and	*generic available	16

Agent(s)	FDA Indication(s)	Notes	Ref#
	vaginal atrophy, topical vaginal products should be considered. Treatment of hypoestrogenism due to hypogonadism, castration, or primary ovarian failure Prevention of postmenopausal osteoporosis • Limitation of Use: When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.		

CLINICAL RATIONALE

Overview	Menopause, defined as one year without menses, typically occurs around the age of 50 in most women and is due to the ovary's loss of estrogen production. Estrogen deficiency can often be asymptomatic, but can be associated with vasomotor symptoms (e.g., hot flashes, sweating, insomnia, vaginal dryness). Estrogen therapy, with or without progestin, is considered the most effective therapy for menopausal vasomotor symptoms. The American Association of Clinical Endocrinologists (AACE) recommend transdermal estrogen therapy to avoid the risk of first-pass effect and potentially reduce the risk of thromboembolic events. Transvaginal estrogen may be considered to provide topical effects with less systemic absorption. AACE also recommend that hormone therapy (HT) should be used at the lowest dose possible, the dose should be decreased as the patient ages, and should be used for the shortest duration necessary to control menopausal symptoms.(1) Estrogens are also recommended as adjunct therapy to treat gender dysphoric/gender incongruence. The Endocrine Society recommends the use of oral, transdermal, and injectable estrogen. Transdermal estrogen should be used at doses between 0.025-0.2 mg/day.(2)

Safety	Topical estradiol has a boxed warning due to endometrial cancer, cardiovascular disorders, probable dementia, and breast cancer. See full prescribing information for complete boxed warning.(3-17) Estrogen-Alone Therapy • There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens • Estrogen-alone therapy should not be used for the prevention of cardiovascular disease or dementia • The Women's Health Initiative (WHI) estrogen-alone substudy reported increased risks of stroke and deep vein thrombosis (DVT) • The WHI Memory Study (WHIMS) estrogen-alone ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age or older Estrogen Plus Progestin Therapy • Estrogen plus progestin therapy should not be used for the prevention of cardiovascular disease or dementia • The WHI estrogen plus progestin substudy reported increased risks of stroke, DVT, pulmonary embolism (PE), and myocardial infarction (MI) • The WHI estrogen plus progestin substudy reported increased risks of invasive breast cancer • The WHIMS estrogen plus progestin ancillary study of WHI reported an increased risk of probable dementia in postmenopausal women 65 years of age and older Evamist also has a boxed warning due to unintentional secondary exposure.(11) • Breast budding, breast masses, and gynecomastia have been reported in children following unintentional secondary exposure to Evamist Topical estradiol is contraindicated in patients with:(3-17) • Undiagnosed abnormal genital bleeding • Breast cancer or history of breast cancer • Estrogen-dependent neoplasia • Active DVT, PE, or a history of these conditions • Active arterial thromboembolic disease (e.g., stroke and MI) or a history of these conditions

	• Known anaphylactic reaction, angioedema, or hypersensitivity to the inactive or active ingredients in the product • Hepatic impairment or disease • Protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders CombiPatch, Estrace, Estring, Evamist, and Femring are also contraindication in patients with known or suspected pregnancy.(6,9,11,12,17)

REFERENCES

Number	Reference
1	Rhoda H. Cobin and Neil F. Goodman (2017) American Association of Clinical Endocrinologists and American College of Endocrinology Position Statement on Menopause–2017 Update. Endocrine Practice: July 2017, Vol. 23, No. 7, pp. 869-881.
2	Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017;102:3869–3903.
3	Alora prescribing information. Allergan USA, Inc. March 2020.
4	Climara prescribing information. Bayer HealthCare Pharmaceuticals, Inc. December 2023.
5	Climara Pro prescribing information. Bayer HealthCare Pharmaceuticals, Inc. December 2023.
6	CombiPatch prescribing information. Noven Pharmaceuticals, Inc. February 2024.
7	Divigel prescribing information. Vertical Pharmaceuticals, Inc. November 2023.
8	Elestrin prescribing information. MEDA Pharmaceuticals. December 2023.
9	Estring prescribing information. Pharmacia & Upjohn Company, LLC. December 2021.
10	Estrogel prescribing information. Ascend Pharmaceuticals, LLC. March 2024.
11	Evamist prescribing information. Padagis US, LLC. December 2023.

Number	Reference
12	Femring prescribing information. Millicent Pharma Limited. November 2023.
13	Imvexxy prescribing information. Therapeutics MD, Inc. February 2024.
14	Menostar prescribing information. Bayer HealthCare Pharmaceuticals, Inc. December 2023.
15	Minivelle prescribing information. Noven Pharmaceuticals, Inc. February 2024.
16	Vivelle Dot prescribing information. Novartis Pharmaceuticals Corporation. November 2023.
17	Estrace Cream prescribing information. Allergan USA, Inc. December 2022.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The patient has a diagnosis of gender dysphoria/gender incongruent **AND** 2. The requested agent is ONE of the following: A. Alora (estradiol) B. Climara (estradiol) C. Divigel (estradiol) D. Elestrin (estradiol) E. Estrogel (estradiol) F. Evamist (estradiol) G. Menostar (estradiol) H. Minivelle (estradiol) I. Vivelle Dot (estradiol) **OR** B. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** C. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** D. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Topical Lidocaine

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
lidocaine topical jelly 2% Topical jelly*	Prevention and control of pain in procedures involving the male and female urethra, for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal)	* generic available	7
lidocaine topical solution 4% Solution*	Topical anesthesia of accessible mucous membranes of the oral and nasal cavities and proximal portions of the digestive tract	* generic available	6
lidocaine topical ointment 5% Ointment*	Anesthesia of accessible mucous membranes of the oropharynx Anesthetic lubricant for intubation Temporary relief of pain associated with minor burns, including sunburn, abrasions of the skin, and insect bites	* generic available	3
Lidoderm® (lidocaine patch 5%) Transdermal patch*	Relief of pain associated with post-herpetic neuralgia. It should be applied only to intact skin.	* generic available	1
Pliaglis® (lidocaine 7%/tetracaine 7% cream) Cream	Use on intact skin in adults to provide topical local analgesia for superficial dermatological procedures such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal		9
Synera®	Use on intact skin to provide local dermal analgesia for superficial venous access and superficial dermatological		5

Agent(s)	FDA Indication(s)	Notes	Ref#
(lidocaine 70 mg/tetracaine 70 mg patch) Topical patch	procedures such as excision, electrodessication, and shave biopsy of skin lesions		
ZTlido® (lidocaine topical system 1.8%) Transdermal system	Relief of pain associated with post-herpetic neuralgia (PHN)		4

CLINICAL RATIONALE

Clinical Rationale	Moderate to severe cancer pain is treated with opioids; however, opioids alone may not provide optimal analgesia. When a specific cancer pain syndrome is suspected or documented, additional interventions may be targeted to that pain syndrome. Cancer-related neuropathic pain is common and can be related to the cancer itself or the acute or chronic effects of cancer treatment. Adjuvant analgesics (e.g., antidepressants, anticonvulsants, corticosteroids, topical anesthetic agents) are particularly important in treating neuropathic pain. Topical local anesthetic agents can be useful in preventing procedural pain and in relieving some types of cancer-related neuropathic pain. They act locally and are also thought to have some central inhibitory effect on pain. They may be used in combination with an opioid, antidepressant, and/or an anticonvulsant. Both the gel and patch forms of lidocaine have been shown to reduce the pain of postherpetic neuropathy and cancer-related pain.(2) Certain treatments for cancer can cause pain in the mouth, pharynx, and esophagus. Therapeutic approaches include cryotherapy, gabapentin in combination with opioid or non-opioid analgesics, and oral care protocols such as good oral hygiene and prophylactic mouth rinses. Local anesthetics may be used to treat mucositis either as component of a mouth rinse or separately in a topical solution or topical gel formulation.(2,11) Topical lidocaine products for use as a topical anesthetic are available over-the-counter.

	The 95th percentile weight for adult females aged 20 and over is 119.6 kilograms (kg) (263.8 pounds lbs) and 130.3 kg (287.2 lbs) for adult males aged 20 and over.(10)
Safety	The safety and effectiveness of lidocaine depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. The lowest dosage that results in effective anesthesia should be used to avoid high plasma levels and serious adverse effects. Repeated doses of lidocaine may cause significant increases in blood levels with each repeated dose because of slow accumulation of the drug or its metabolites.(1,3-7,9) When lidocaine patch is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations (additive effect) must be considered. All lidocaine topical products have a contraindication of known history of sensitivity to local anesthetics of the amide type, or to any other component of the product. Pliaglis and Synera have an additional contraindication of para-aminobenzoic acid (PABA) hypersensitivity.(1,3-7,9)

REFERENCES

Number	Reference
1	Lidoderm prescribing information. Endo Pharmaceuticals Inc. November 2022.
2	National Comprehensive Cancer Network (NCCN) Guidelines in Oncology: Adult Cancer Pain Version 2.2024
3	lidocaine 5% ointment prescribing information. Atlantic Biologicals Corp. January 2021.
4	ZTilodo prescribing information. Scilex Pharmaceuticals Inc. April 2021.
5	Synera prescribing information. Galen US Inc. November 2018.
6	lidocaine 4% solution prescribing information. Hikma Pharmaceuticals USA Inc. December 2023.
7	lidocaine 2% jelly prescribing information. Sagent Pharmaceuticals. January 2022.
8	Reference no longer used.

Number	Reference
9	Pliaglis prescribing information. Taro Pharmaceuticals USA, Inc. August 2020.
10	Anthropometric Reference Data for Children and Adults: United States, 2015–2018. Vital Health Statistics Series 3, Number 46, January 2021. US Department of Health and Human Services – Centers for Disease Control and Prevention.
11	Bensinger W, Schubert M, Ang KK, et al. National Comprehensive Cancer Network (NCCN) Task Force Report: Prevention and Management of Mucositis in Cancer Care. J Natl Compr Canc Ne 2008;6(1):S1-S21. https://pubmed.ncbi.nlm.nih.gov/18289497/

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
lidocaine topical jelly 2%	**lidocaine topical jelly 2%** will be approved when BOTH of the following are met: 1. The requested agent will be used for ONE of the following indications: A. Prevention and control of pain in procedures involving the urethra **OR** B. Topical treatment of painful urethritis **OR** C. Anesthetic lubricant for endotracheal intubation (oral and nasal) **OR** D. Mucositis associated with cancer treatment **OR** E. BOTH of the following: 1. The patient has ONE of the following: A. Neuropathic pain associated with cancer pain or cancer treatment **OR** B. Another FDA labeled indication for the requested agent and route of administration **OR** C. Another indication that is supported in compendia for the requested agent and route of administration **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to over-the-counter topical lidocaine **OR** B. The prescriber has provided information that indicates over-the-counter topical lidocaine is NOT clinically appropriate **AND** 2. The patient does NOT have any FDA labeled contraindications to the requested agent

Module	Clinical Criteria for Approval
	Compendia Allowed: AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
lidocaine topical ointment 5%	**lidocaine topical ointment 5%** will be approved when BOTH of the following are met: 1. The requested agent will be used for ONE of the following indications: A. Anesthesia of accessible mucous membranes of the oropharynx **OR** B. Anesthetic lubricant for intubation **OR** C. BOTH of the following: 1. The patient has ONE of the following: A. Pain associated with minor burns, including sunburn, abrasions of the skin, and insect bites **OR** B. Another FDA labeled indication for the requested agent and route of administration **OR** C. Another indication that is supported in compendia for the requested agent and route of administration **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to over-the-counter topical lidocaine **OR** B. The prescriber has provided information that indicates over-the-counter topical lidocaine is NOT clinically appropriate **AND** 2. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
lidocaine topical solution 4%	**lidocaine topical solution 4%** will be approved when BOTH of the following are met: 1. The requested agent will be used for ONE of the following indications: A. Topical anesthesia of accessible mucous membranes of the oral and nasal cavities and proximal portions of the digestive tract **OR** B. Mucositis associated with cancer treatment **OR** C. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The patient has ONE of the following: A. Another FDA labeled indication for the requested agent and route of administration **OR** B. Another indication that is supported in compendia for the requested agent and route of administration **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to over-the-counter topical lidocaine **OR** B. The prescriber has provided information that indicates over-the-counter topical lidocaine is NOT clinically appropriate **AND** 2. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
Lidoderm (lidocaine patch 5%) and ZTlido (lidocaine topical system 1.8%)	**Lidoderm (lidocaine patch 5%) and ZTlido (lidocaine topical system 1.8%)** will be approved when ALL of the following are met: 1. The requested agent will be used for ONE of the following indications: A. Pain associated with post-herpetic neuralgia (PHN) **OR** B. Neuropathic pain associated with cancer or cancer treatment **OR** C. Another FDA labeled indication for the requested agent and route of administration **OR** D. Another indication that is supported in compendia for the requested agent and route of administration **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to over-the-counter topical lidocaine **OR** B. The prescriber has provided information that indicates over-the-counter topical lidocaine is NOT clinically appropriate **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 12 months

Module	Clinical Criteria for Approval
	NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
Pliaglis (lidocaine 7%/tetracaine cream 7%)	**Pliaglis (lidocaine 7%/tetracaine cream 7%)** will be approved when BOTH of the following are met: 1. The requested agent will be used for ONE of the following indications: A. Analgesia for superficial dermatological procedures such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal **OR** B. BOTH of the following: 1. The patient has ONE of the following: A. Another FDA labeled indication for the requested agent and route of administration **OR** B. Another indication that is supported in compendia for the requested agent and route of administration **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to over-the-counter topical lidocaine **OR** B. The prescriber has provided information that indicates over-the-counter topical lidocaine is NOT clinically appropriate **AND** 2. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
Synera (lidocaine 70 mg/tetracaine 70 mg patch)	**Synera (lidocaine 70 mg/tetracaine 70 mg patch)** will be approved when BOTH of the following are met: 1. The requested agent will be used for ONE of the following indications: A. Local dermal analgesia for superficial venous access **OR** B. Local dermal analgesia for superficial dermatological procedures such as excision, electrodessication, and shave biopsy of skin lesions **OR** C. BOTH of the following: 1. The patient has ONE of the following: A. Another FDA approved indication for the requested agent and route of administration **OR**

Module	Clinical Criteria for Approval
	B. Another indication that is supported in compendia for the requested agent and route of administration **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to over-the-counter topical lidocaine **OR** B. The prescriber has provided information that indicates over-the-counter topical lidocaine is not clinically appropriate **AND** 2. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Topical NSAID

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Flector®, Diclofenac epolamine Topical patch	Topical treatment of acute pain due to minor strains, sprains, and contusions in adults and pediatric patients 6 years and older.		1
Licart® (diclofenac epolamine) Topical system	Topical treatment of acute pain due to minor strains, sprains, and contusions		10
Pennsaid® (diclofenac sodium)* 1.5% Topical solution 2% Topical solution	Treatment of the pain of osteoarthritis of the knee(s)	*generic available	2,7

CLINICAL RATIONALE

Acute Pain	The American College of Physicians (ACP) and American Academy of Family Physicians (AAFP) recommend that clinicians treat patients with acute pain from non–low back, musculoskeletal injuries with topical nonsteroidal anti-inflammatory drugs (NSAIDs) with or without menthol gel as first-line therapy to reduce or relieve symptoms, including pain; improve physical function; and improve the patient's treatment satisfaction. ACP and AAFP suggest that clinicians treat patients with acute pain from non–low back, musculoskeletal injuries with oral NSAIDs to reduce or relieve symptoms, including pain, and to improve physical function, or with oral acetaminophen to reduce pain.(3)
Osteoarthritis (OA)	The American Academy of Orthopedic Surgeons recommended the following: • For the management of knee OA:(8)

	○ NSAIDs (oral or topical) or tramadol are recommended for patients with symptomatic OA of the knee. (Strong recommendation; high level evidence) ○ The panel was unable to recommend for or against the use of acetaminophen, opioids, or pain patches for patients with symptomatic OA of the knee. (Inconclusive recommendation) • For the management of hip OA:(9) ○ NSAIDs improve short-term pain, function, or both The American College of Rheumatology and the Arthritis Foundation states the following for the management of OA in the hand, hip, or knee:(4) • Usual care includes the use of oral NSAIDs and/or acetaminophen • Oral NSAIDs are strongly recommended for knee, hip, and/or hand OA • Topical NSAIDs are strongly recommended for knee OA and conditionally recommended for hand OA • Topical NSAIDs should be considered prior to use of oral NSAIDs to limit systemic exposure A current review suggests topical NSAIDs are as effective as oral NSAIDs and generally safer, but only effective for OA of more superficial joints such as hands and knees.(5) For multiple or deep arthritic joints, oral NSAIDs are easier to use and more efficacious. The American Geriatric Society recommendeds that the chronic use of all NSAIDs, including high dose aspirin, should be avoided because of the risk of gastrointestinal bleeding. High-risk groups include: age above 75 years, corticosteroid use, current use of anticoagulants or antiplatelet agents.(6)
Safety	Flector, Licart, Pennsaid, and Voltaren gel contain the following box warnings:(1-3,7,10) • Cardiovascular risk ○ Non-steroidal anti-inflammatory drugs (NSAIDs) may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. ○ NSAIDs are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery. • Gastrointestinal Risk ○ NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of

	the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events. Flector and Licart carry the following contraindications: • Known hypersensitivity to diclofenac or any components of the product • History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs • In the setting of CABG surgery • For use on non-intact or damaged skin Pennsaid and Voltaren gel carry the following contraindications: • Known hypersensitivity to diclofenac or any components of the product • History of asthma, urticaria, or allergic-type reactions after taking aspirin or other NSAIDs • In the setting of coronary artery bypass graft (CABG) surgery

REFERENCES

Number	Reference
1	Flector prescribing information. Pfizer, Inc. April 2021.
2	Diclofenac 1.5% prescribing information. SOLA Pharmaceuticals, LLC. June 2021.
3	Qaseem A, McLean RM, O'Gurek D, Batur P, Lin K, Kansagara DL. Nonpharmacologic and pharmacologic management of Acute Pain from Non–Low Back, Musculoskeletal Injuries in Adults: a clinical guideline from the American College of Physicians and American Academy of Family Physicians. Annals of Internal Medicine. 2020;173(9):739-748. doi:10.7326/m19-3602.
4	Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis & Rheumatology. 2020; 72(2):220-233.
5	Reference no longer used.

Number	Reference
6	Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A Comprehensive Review of Non-Steroidal Anti-Inflammatory Drug Use in The Elderly. Aging Dis. 2018 Feb 1;9(1):143-150. doi: 10.14336/AD.2017.0306.
7	Pennsaid (2%) prescribing information. Horizon USA, Inc. Jan 2022.
8	American Academy of Orthopedic Surgeons. Management of Osteoarthritis of the Knee (Non-Arthroplasty). August 2021. https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-knee/oak3cpg.pdf
9	American Academy of Orthopedic Surgeons. Management of Osteoarthritis of the Hip Evidence-based Clinical Practice Guideline. March, 2023. Available at: https://www.aaos.org/globalassets/quality-and-practice-resources/osteoarthritis-of-the-hip/oah-cpg.pdf.
10	Licart prescribing information. IBSA INST BIO. April 2021.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Topiramate ER

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Qudexy XR® (topiramate ER)* Capsules	Epilepsy: initial monotherapy for the treatment of partial-onset or primary generalized tonic-clonic seizures in patients 2 years of age and older; adjunctive therapy for the treatment of partial-onset seizures, primary generalized tonic-clonic seizures, or seizures associated with Lennox-Gastaut Syndrome in patients 2 years of age or older Preventative treatment of migraine in patients 12 years of age and older	*generic available	1
Trokendi XR® (topiramate ER)* Capsules	Epilepsy: initial monotherapy for the treatment of partial-onset or primary generalized tonic-clonic seizures in patients 6 years of age and older; adjunctive therapy for the treatment of partial-onset, primary generalized tonic-clonic seizures, or seizures associated with Lennox Gastaut syndrome in patients 6 years of age and older Preventative treatment of migraine in patients 12 years of age and older	*generic available	2

CLINICAL RATIONALE

Safety	Qudexy XR has no FDA labeled contraindications for use.(1) Trokendi XR is contraindicated in patients with recent alcohol use (i.e., within 6 hours prior to and 6 hours after Trokendi XR use).(2)

REFERENCES

Number	Reference
1	Qudexy XR prescribing information. Upsher-Smith Laboratories, LLC. December 2022.
2	Trokendi XR prescribing information. Supernus Pharmaceuticals Inc. October 2022.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has been treated with an anti-seizure medication that is not topiramate **OR** B. The patient has ONE of the following diagnoses: 1. Partial onset seizures **OR** 2. Primary generalized tonic-clonic seizures **OR** 3. Lennox-Gastaut Syndrome **OR** 4. Migraine **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. The prescriber has provided information in support of using the requested agent for the patient's age for the requested indication **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met:

Module	Clinical Criteria for Approval
	1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process **AND** 2. ONE of the following: A. The patient has a medication history of use of an anti-seizure medication that is not topiramate **OR** B. The patient has had clinical benefit with the requested agent **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** C. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Triptans

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
almotriptan Tablet	Acute treatment of migraine attacks in adults with a history of migraine with or without aura Acute treatment of migraine headache pain in adolescents age 12 to 17 years with a history of migraine with or without aura, and who have migraine attacks usually lasting 4 hours or more Important limitations: • Use only after a clear diagnosis of migraine has been established • In adolescents age 12 to 17 years, efficacy of almotriptan tablets on migraine-associated symptoms was not established • Not intended for the prophylactic therapy of migraine • Not indicated for the treatment of cluster headache		
Amerge® (naratriptan)* Tablet	Acute treatment of migraine attacks with or without aura in adults Limitations of Use: • Use only if a clear diagnosis of migraine has been established • Not indicated for the prophylactic therapy of migraine attacks • Not indicated for the treatment of cluster headache	*generic available	1

Agent(s)	FDA Indication(s)	Notes	Ref#
Frova® (frovatriptan)* Tablet	Acute treatment of migraine attacks with or without aura in adults Limitations of Use: • Use only if a clear diagnosis of migraine has been established • Not indicated for the prophylactic therapy of migraine attacks • Not indicated for the treatment of cluster headache	*generic available	3
IMITREX® (sumatriptan)* Nasal spray	Acute treatment of migraine with or without aura in adults Limitations of Use: • Use only if a clear diagnosis of migraine headache has been established • Not indicated for the prophylactic therapy of migraine attacks • Not indicated for the treatment of cluster headache	*generic available	5
IMITREX® (sumatriptan)* Subcutaneous injection	Acute treatment of migraine with or without aura in adults Acute treatment, cluster headache episodes in adults Limitations of Use: • Use only if a clear diagnosis of migraine or cluster headache has been established • Not indicated for the prophylactic therapy of migraine or cluster headache attacks	*generic available	4
IMITREX®	Acute treatment of migraine with or without aura in adults	*generic available	6

Agent(s)	FDA Indication(s)	Notes	Ref#
(sumatriptan)* Tablet	Limitations of Use: • Use only if a clear diagnosis of migraine headache has been established • Not indicated for the prophylactic therapy of migraine attacks • Not indicated for the treatment of cluster headache		
Maxalt® MLT/Maxalt® (rizatriptan)* Orally disintegrating tablet Tablet	Acute treatment of migraine with or without aura in adults and in pediatric patients 6 to 17 years old Limitations of Use: • Use only after clear diagnosis of migraine has been established • Not indicated for the prophylactic therapy of migraine • Not indicated for the treatment of cluster headache	*generic available	7
ONZETRA® Xsail® (sumatriptan) Nasal powder	Acute treatment of migraine with or without aura in adults Limitations of Use: • Use only if a clear diagnosis of migraine has been established • Not indicated for the prophylactic therapy of migraine attacks • Not indicated for the treatment of cluster headache		8
RELPAX® (eletriptan)* Tablet	Acute treatment of migraine with or without aura in adults Limitations of Use:	*generic available	9

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Use only if a clear diagnosis of migraine has been established • Not indicated for the prophylactic therapy of migraine attacks • Not indicated for the treatment of cluster headache		
Tosymra® (sumatriptan) Nasal spray	Acute treatment of migraine with or without aura in adults Limitations of Use: • Use only if a clear diagnosis of migraine has been established • Not indicated for the prophylactic therapy of migraine attacks • Not indicated for the treatment of cluster headache		11
Treximet® (sumatriptan/naproxen sodium)* Tablet	Acute treatment of migraine with or without aura in adults and pediatric patients 12 years of age and older Limitations of Use: • Use only if a clear diagnosis of migraine has been established • Not indicated for the prophylactic therapy of migraine attacks • Not indicated for the treatment of cluster headache	*generic available	12
Zembrace® SYMTOUCH® (sumatriptan) Subcutaneous injection	Acute treatment of migraine with or without aura in adults Limitations of Use: • Use only if a clear diagnosis of migraine has been established		13

Agent(s)	FDA Indication(s)	Notes	Ref#
	• Not indicated for the prophylactic therapy of migraine attacks		
Zomig® (zolmitriptan)* Nasal spray	Acute treatment of migraine with or without aura in adults and pediatric patients 12 years of age and older Limitations of Use: • Use only if a clear diagnosis of migraine has been established • Not indicated for the prophylactic therapy of migraine attacks • Not indicated for the treatment of cluster headache • Not recommended in patients with moderate to severe hepatic impairment	*generic available	15
Zomig® (zolmitriptan)* Tablet	Acute treatment of migraine with or without aura in adults and pediatric patients 12 years of age and older Limitations of Use: • Use only if a clear diagnosis of migraine has been established • Not indicated for the prophylactic therapy of migraine attacks • Not indicated for the treatment of cluster headache	*generic available	14

CLINICAL RATIONALE

Migraine and Cluster Headache Management	Migraine is a common disabling primary headache disorder with high prevalence, ranking second globally in terms of years lost to disability.(22) Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia. Migraines can present with or without aura, unilateral fully reversible visual, sensory, or other

central nervous system symptoms that usually develop gradually and are most-often followed by headache and associated migraine symptoms.(25)

The International Classification of Headache Disorders 3rd Edition (ICHD-3) Diagnostic Criteria:(25)

Indication	**Diagnostic Criteria**
Migraine without aura	A. At least five attacks fulfilling criteria B-D B. Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated) C. Headache has at least TWO of the following: 1. unilateral location 2. pulsating quality 3. moderate to severe pain intensity 4. aggravation by causing avoidance of routine physical activity D. During headache at least ONE of the following: 1. nausea and/or vomiting 2. photophobia and phonophobia E. Not better accounted for by another ICHD-3 diagnosis
Migraine with aura	A. At least two attacks fulfilling criteria B and C B. One or more of the following fully reversible aura symptoms: 1. visual 2. sensory 3. speech and/or language

		4. motor 5. brainstem 6. retinal C. At least THREE of the following: 1. at least one aura symptom spreads gradually over 5 minutes or more 2. two or more aura symptoms occur in succession 3. each individual aura symptom lasts 5-60 minutes 4. at least one aura symptom is unilateral 5. at least one aura symptom is positive 6. the aura is accompanied, or followed within 60 minutes, by headache D. Not better accounted for by another ICHD-3 diagnosis
	Chronic Migraine	A. Headache (migraine-like or tension-type-like) on greater than or equal to 15 days/month for greater than 3 months AND fulfilling B and C B. Occurring in patient who has had at least 5 attacks fulfilling 1. criteria B-D for migraine without aura (noted above) and/or 2. criteria B and C for migraine with aura (noted above) C. On greater than or equal to 8 days/month for greater than 3

		months, fulfilling any of the following: 1. criteria C and D for migraine without aura (noted above) 2. criteria B and C for migraine with aura (noted above) 3. believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative D. Not better accounted for by another ICHD-3 diagnosis
	Cluster Headache	A. At least 5 attacks fulfilling criteria B-D B. Severe to very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (untreated) C. At least one of the following: 1. At least one of the following signs or symptoms, ipsilateral to the headache a. conjunctival injection and/or lacrimation b. nasal congestion and/or rhinorrhea c. eyelid edema d. forehead and facial sweating e. miosis and/or ptosis

		2. Sense of restlessness or agitation D. Occurring with frequency between one every other day and 8 per day E. Not better accounted for by another ICHD-3 diagnosis
	Episodic Cluster Headache	A. Attacks fulfilling criteria for Cluster Headache (noted above) occurring in bouts (cluster periods) B. At least two cluster periods lasting 7 days to 1 years (untreated) and separated by pain-free remission periods of at least 3 months

The IHS notes that cluster periods usually last between 2 weeks and 3 months.(25)

Migraine prevention may be of benefit in those with the following:(20,22,30)

- Frequent or long-lasting migraine headaches (greater than 4 headaches/month or headaches lasting greater than 12 hours)
- Attacks interfere significantly with patients' daily routines despite acute treatment
- Contraindicationto acute therapies
- Failure of acute therapies
- Adverse effects with acute therapies
- Risk of medication overuse headache (MOH)
- Patient preference

The American Headache Society (AHS) and the American Academy of Neurology (AAN) suggest the following agents for the prevention of migraine:(17)

- Established as effective (Level A)
    - Antiepileptic drugs (AEDs)
        - Divalproex
        - Valproate

	▪ Topiramate ○ Beta blockers ▪ Metoprolol ▪ Propranolol ▪ Timolol ○ Triptans ▪ Frovatriptan for short term menstrually associated migraines (MAMs) prevention • Probably effective (Level B) ○ Antidepressants ▪ Amitriptyline ▪ Venlafaxine ○ Beta blockers ▪ Atenolol ▪ Nadolol ○ Triptans ▪ Naratriptan, zolmitriptan for short term MAMs prevention The 2021 American Headache Society Consensus Statement recommends the following indications for initiating treatment acute treatment with gepants and ditans agents:(30) • Prescribed by a licensed clinician • Patient is at least 18 years of age • Diagnosis of ICHD-3 migraine with aura, migraine without aura, or chronic migraine • Either of the following: ○ Contraindication to or inability to tolerate triptans ○ Inadequate response to two or more oral triptans, as determined by either of the following: ▪ Validated acute treatment patient-reported outcoming questionnaire (mTOQ, Migraine-ACT, PPMQ-R, FIS, PGIC) ▪ Clinician attestation Lasmiditan is a selective serotonin 5HT-1F receptor agonist that lacks vasoconstrictor activity. Lasmiditan is structurally different than triptans and therefore constitutes a new class of drugs called “ditans”.(30) Ditans are selective for the 5HT-1F receptor and its mechanism of action is neuronal without evidence of vasoactive effects.(26) Triptans non-specifically bind to the 5HT-1B and 5HT-1D receptors and with varying affinity bind the 5HT-1F receptors, causing direct vascular vasoconstriction. The safety, tolerability, and efficacy of co-administering lasmiditan with a triptan or a gepant has not

	been assessed.(30) Patients who do not respond to initial therapy with a triptan, may benefit from a second triptan or different therapy such as use of a gepant (ubrogepant or rimegepant) or a ditan (lasmiditan).(22)
	
	The 2021 American Headache Society Consensus Statement recommends the following indications for initiating treatment with a Calcitonin Gene-Related Peptide (CGRP) agent:(30)
	
	• Prescribed by a licensed clinician
	• Patient is at least 18 years of age
	• ONE of the following:
	  ○ Diagnosis of migraine with or without aura (4-7 monthly headache days) and both of the following:
	  ▪ Inability to tolerate (due to side effects) or inadequate response to an 8-week trial of at least two of the following:
	  • Topiramate
	  • Divalproex sodium/valproate sodium
	  • Beta blocker: metoprolol, propranolol, timolol, atenolol, nadolol
	  • Tricyclic antidepressant: amitriptyline, nortriptyline
	  • Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
	  • Other Level A or B treatment according to AAN-AHS guideline
	  ▪ At least moderate disability (Migraine Disability Assessment Questionnaire [MIDAS] greater than or equal to 11, Headache Impact Test-6 [HIT]-6 greater than 50)
	  ○ Diagnosis of migraine with or without aura (8-14 monthly headache days [MHDs]) and inability to tolerate (due to side effects) or inadequate response to an 8-week trial of at least two of the following:
	  ▪
	  • Topiramate
	  • Divalproex sodium/valproate sodium
	  • Beta blocker: metoprolol, propranolol, timolol, atenolol, nadolol
	  • Tricyclic antidepressant: amitriptyline, nortriptyline
	  • Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine
	  • Other Level A or B treatment according to AAN-AHS guideline
	  ○ Diagnosis of chronic migraine and one of the following:

	▪ Inability to tolerate (due to side effects) or inadequate response to an 8-week trial of at least two of the following: • Topiramate • Divalproex sodium/valproate sodium • Beta blocker: metoprolol, propranolol, timolol, atenolol, nadolol • Tricyclic antidepressant: amitriptyline, nortriptyline • Serotonin-norepinephrine reuptake inhibitor: venlafaxine, duloxetine • Other Level A or B treatment according to AAN-AHS guideline ▪ Inability to tolerate or inadequate response to a minimum of two quarterly injection (6 months) of onabotulinum toxin A The Medical Letter Treatment Guidelines (2023) and Institute for Clinical Systems Improvement Guideline Diagnosis and Treatment of Migraine Headache - Drugs for Migraine states that a triptan is the drug of choice for moderate to severe migraine. The short-acting oral serotonin (5-HT1B/1D) receptor agonists (triptans) sumatriptan (IMITREX, and others), almotriptan (Axert, and generics), eletriptan (RELPAX), rizatriptan (Maxalt, and generics), and zolmitriptan (Zomig, and generics) are similar in efficacy.(18,19) Onset of pain relief generally occurs 30-60 minutes after administration. The longer-acting oral triptans naratriptan (Amerge, and generics) and frovatriptan (Frova, and generics) have a slower onset of action and lower initial response rate than other triptans, but they are better tolerated. Patients with migraine who have nausea or vomiting may not be able to take an oral triptan. Intranasal triptan formulations have a more rapid onset of action than oral tablets, but their efficacy is partially dependent on GI absorption of the portion of the dose that is swallowed. Use of sumatriptan nasal powder (ONZETRA Xsail) results in a faster rise in sumatriptan plasma concentrations and higher peak concentrations than use of a similar dose of sumatriptan nasal spray, suggesting that a larger portion of the dose is absorbed intranasally with the powder. Subcutaneously administered sumatriptan relieves pain faster (in about 10 minutes) and more effectively than other triptan formulations, but it causes more adverse effects.(19) American Headache Society (AHS) (2015): The Acute Treatment of Migraine in Adults: The AHS Evidence Assessment of Migraine Pharmacotherapies: Triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan [oral, nasal spray, injectable, transcutaneous patch], zolmitriptan [oral and nasal spray]) are effective (Level A) and considered by AHS guidelines (2015) to be the gold standard for acute treatment of moderate to severe migraine

	headaches.(20) Dihydroergotamine is recommended for use as a second- or third-line therapy for select patients or for those with refractory migraine. Intranasal dihydroergotamine has strong evidence of effectiveness but more adverse effects than triptans because of its decreased receptor specificity.(10) An assessment of new migraine treatments by the AHS (2018; updated 2021) reaffirms previous migraine guidelines. The update lists triptans, dihydroergotamine, the oral gepants (Nurtec ODT [rimegepant] and UBRELVY [ubrogepant]), and REYVOW (lasmiditan) as effective treatment of moderate or severe acute attacks and mild to moderate attacks that respond poorly to non-specific nonsteroidal anti-inflammatory drugs (NSAIDs), non-opioid analgesics, acetaminophen, or caffeinated combinations (e.g., aspirin/acetaminophen/caffeine). The recommendation remains that prescribers must consider medication efficacy and potential medication-related adverse effects, potential adverse events, patient-specific contraindications to use with a particular medication, and drug-drug interactions when prescribing acute medications for migraine.(20,22,30) The American Academy of Neurology (AAN) 2010 Guideline: Acute and preventive pharmacologic treatment of cluster headache (CH) state that sumatriptan subcutaneous injection and zolmitriptan nasal spray first-line options for acute treatment of CH.(16,18) American Headache Society (2016): Treatment of CH: Since the publication of the 2010 AAN review, there are no new data from randomized, double-blind, controlled trials that contribute to determining the efficacy or safety for a number of acute treatments, including specifically sumatriptan and zolmitriptan. For acute treatment, sumatriptan subcutaneous, zolmitriptan nasal spray, and high flow oxygen remain the treatments with a Level A recommendation.(21) Guidelines suggest that prophylactic therapy should be started and continued for the duration of the CH period. Prophylactic pharmacological therapy includes verapamil, corticosteroids, lithium, topiramate, melatonin, gabapentin, valproic acid, ergotamine, and capsaicin. Verapamil is commonly considered the first option for prophylactic therapy in practice.(16,31,32) Corticosteroids can be used as transitional or bridging therapy until another prophylaxis agent is established.(32) Corticosteroids may be used by some practitioners for short periods of CH.(16,31) The American Academy Neurology lists the following agents as option that maybe considered or should be advised as preventative treatments: • Civamide • Suboccipital steroid injection • Melatonin • Verapamil

	• Lithium
	
	The European Headache Federation and WHO consensus article (2019) states the following:(23)
	
	• Individuals with migraine headaches should always be managed in primary care with the exception being chronic migraine, which likely requires specialist management
	• Any headache not responding satisfactorily in primary care or chronic migraine, should be referred to a specialist
	• In adults and children, regular high frequency use (greater than 2 day/week) of acute medication risks the development of MOH
	• Treatment of episodic acute migraine headaches should be approached in a step wise manner and should treat three attacks at each step before moving to the next step if needed:
	  ○ Step 1:
	  ▪ Use non-opioid analgesics, plus an antiemetic when needed
	  ○ Step 2 for adults:
	  ▪ Use triptan products
	  ▪ Triptans should not be used regularly for 10 or more days per month to avoid the risk of MOH
	  ▪ Triptan efficacy is highly variable between individuals, so patients should try different triptans and formulations. Sumatriptan subcutaneous injection should be considered when all other triptans are ineffective.
	  ▪ When vomiting is present, zolmitriptan nasal spray or sumatriptan subcutaneous injection may be preferred
	  ○ Step 2 for children and adolescents:
	  ▪ Failure of Step 1 in children should lead to specialist referral. No specific anti-migraine drugs have shown efficacy in children under 12 years of age.
	  ▪ Failure of Step 2 in adolescents (12-17 years of age), the following have shown efficacy and are approved:
	  • Sumatriptan nasal spray
	  • Zolmitriptan nasal spray
	• Episodic migraine prophylaxis:
	  ○ Indication for migraine prophylaxis include:
	  ▪ Attacks cause disability on two or more days per month, and

	▪ Acute therapy has been optimized but does not prevent this, or is poorly tolerated, or there is a risk of over-frequent use of acute therapy, even when it is effective, and ▪ Patient is willing to take daily medication ▪ Failure of acute therapy is an indication for migraine prophylaxis ▪ For children, frequent absence from school is an additional indication for prophylaxis ○ Migraine prophylaxis agents may take 2-3 months to show efficacy ○ Children requiring prophylactic medication should be referred to a specialist ○ Medications which are effective in adult prophylaxis of episodic migraine include: ▪ Beta blockers: • Atenolol, bisoprolol, metoprolol, propranolol ▪ Amitriptyline ▪ Topiramate ▪ Candesartan ▪ Sodium valproate ▪ Flunarizine ▪ CGRP ○ Onabotulinum toxin A is not effective in episodic migraine and not recommended ○ When prophylaxis therapy fails: ▪ May be due to subtherapeutic dosage or duration of therapy ▪ Failure of one therapy does not predict the failure of another therapy in a different class ▪ Review of the following are recommended: • Diagnosis • Adherence • Other medications, especially for MOH causes ▪ The prophylaxis therapy should be discontinued if it fails to show clear benefit ▪ If all prophylaxis therapies fail, a specialist should be referred • Chronic migraine management: ○ Chronic migraine patients should be referred to a specialist ○ Medications with efficacy in chronic migraine include: ▪ Topiramate

	▪ Onabotulinum A ▪ CGRP • Cluster Headache management: ○ Patients should be referred to a specialist ○ Acute therapies include: ▪ Triptans: • Sumatriptan subcutaneous injection • Sumatriptan nasal spray • Zolmitriptan nasal spray ▪ Oxygen ○ Transition and maintenance therapies include: ▪ Prednisone ▪ Greater occipital nerve blockade ▪ Verapamil ▪ Lithium carbonate ▪ Topiramate ○ Neuromodulation is another treatment option ○ Failure of one prophylactic therapy does not predict the failure of other therapies ○ Combination prophylaxis therapy can be considered though the potential for toxicity is high ○ Long-term prophylaxis therapy may need to be continued The European Headache Federation guideline states the following on combining migraine prophylaxis therapy:(24) • In episodic migraine, guidelines suggest to stop oral prophylaxis migraine agents before starting CGRPs, unless the patient previously had chronic migraine prior to prophylaxis. In such patients, the suggestion is to add CGRP to the ongoing oral prophylaxis therapy • In chronic migraine, guidelines suggest to add CGRP to ongoing oral prophylaxis therapy • In chronic migraine patients on onabotulinum A therapy and are receiving inadequate treatment response, guidelines suggest to stop onabotulinum A therapy before starting CGRPs • In patients with chronic migraine who are on treatment with CGRP and may benefit from additional prevention, guidelines suggest to add on oral preventative agents • In patients with medication overuse, guidelines suggest to use CGRPs before or after withdrawal of acute medications

	The clinical trials referenced in FDA labeled package inserts for the preventative CGRP agents excluded patients that had received botulinum toxin within 4 months prior to receiving the CGRP agent.(27,28,29) However the 2021 American Headache Society consensus statement states that CGRP monoclonal antibody treatment (e.g., eptinezumab-jjmr, erenumab, fremanezumab, galcanezumab) may be added to greater than or equal to one established preventative treatment, based on clinical judgement, in adults who meet the ICHD-3 criteria for the following conditions:(25,30) • Migraine with/without aura (4–7 monthly migraine days [MMDs]) with at least moderate disability (Migraine Disability Assessment greater than or equal to 11 or 6-item Headache Impact Test greater than 50) and failure of an 8-week trial of greater than or equal to 2 preventive treatments with established efficacy (e.g., topiramate, divalproex sodium, beta-blocker, tricyclic antidepressant, and others) • Migraine with/without aura (8–14 MMDs) and failure of an 8-week trial of greater than or equal to 2 established preventive treatments • Chronic migraine (greater than or equal to 15 MMDs) with any level of disability and either failure of an 8-week trial of greater than or equal to two established preventive treatments or inadequate tolerability or response to onabotulinum toxin A for two quarterly injections

Medication overuse headache (MOH)	The European Headache Federation and WHO consensus article (2019) states the following:(23)
	
	• Prevention is preferred
	• The four objectives of management are:
	  ○ Stop the overused medication
	  ○ Recovery from MOH
	  ○ Review and reassess the underlying headache disorder
	  ○ Prevent relapse while allowing acceptable use of medications
	• Comorbidities may require management

Safety	Almotriptan has the following contraindications:(2) • Ischemic heart disease, coronary artery vasospasm, or other significant underlying cardiovascular disease • Cerebrovascular syndromes (e.g., history of stroke or TIA) • Peripheral vascular disease (including ischemic bowel disease) • Uncontrolled hypertension

	• Do not use almotriptan tablets within 24 hours of an ergotamine-containing, or ergot-type medication, or of another 5-HT1 agonist, e.g., another triptan • Hemiplegic or basilar migraine • Known hypersensitivity to almotriptan tablets Eletriptan has the following contraindications:(9) • History of coronary artery disease (CAD) or coronary artery vasospasm • Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders • History of stroke, transient ischemic attack, or history or current evidence of hemiplegic or basilar migraine • Peripheral vascular disease • Ischemic bowel disease • Uncontrolled hypertension • Within 24 hours of treatment with another 5-HT1 agonist, or an ergotamine-containing medication • Hypersensitivity to RELPAX (angioedema and anaphylaxis seen) • Within at least 72 hours of treatment with the following potent CYP3A4 inhibitors: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir, or nelfinavir Frovatriptan has the following contraindications:(3) • History of coronary artery disease or coronary artery vasospasm • Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders • History of stroke, transient ischemic attack, or hemiplegic or basilar migraine • Peripheral vascular disease • Ischemic bowel disease • Uncontrolled hypertension • Recent (within 24 hours) use of treatment with another 5-HT1 agonist, or an ergotamine-containing medication • Hypersensitivity to Frova (angioedema and anaphylaxis seen) Naratriptan has the following contraindications:(1) • History of coronary artery disease or coronary artery vasospasm • Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders

	• History of stroke, transient ischemic attack, or hemiplegic or basilar migraine • Peripheral vascular disease • Ischemic bowel disease • Uncontrolled hypertension • Recent (within 24 hours) use of another 5-HT 1 agonist (e.g., another triptan) or an ergotamine-containing medication • Hypersensitivity to Amerge (angioedema and anaphylaxis seen) • Severe renal or hepatic impairment Rizatriptan has the following contraindications:(7) • History of ischemic heart disease or coronary artery vasospasm • History of stroke or transient ischemic attack • Peripheral vascular disease • Ischemic bowel disease • Uncontrolled hypertension • Recent (within 24 hours) use of another 5-HT1 agonist (e.g., another triptan), or of an ergotamine-containing medication • Hemiplegic or basilar migraine • MAO-A inhibitor used in the past 2 weeks • Hypersensitivity to rizatriptan or any of the excipients Sumatriptan subcutaneous injection, tablet, nasal spray, and nasal powder have the following contraindications:(4-6,8,11) • History of coronary artery disease or coronary artery vasospasm • Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders • History of stroke, transient ischemic attack, or hemiplegic or basilar migraine • Peripheral vascular disease • Ischemic bowel disease • Uncontrolled hypertension • Recent (within 24 hours) use of treatment with another 5-HT1 agonist, or an ergotamine-containing medication • Concurrent or recent (past 2 weeks) use of monoamine oxidase-A inhibitor Hypersensitivity to sumatriptan (angioedema and anaphylaxis seen). • Severe hepatic impairment

	Sumatriptan/naproxen sodium tablet has the following contraindications:(12) • History of coronary artery disease or coronary vasospasm • In the setting of CABG surgery • Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders • History of stroke, transient ischemic attack, or hemiplegic or basilar migraine • Peripheral vascular disease • Ischemic bowel disease • Uncontrolled hypertension • Recent (within 24 hours) use of another 5-HT1 agonist (e.g., another triptan) or of ergotamine-containing medication • Concurrent or recent (past 2 weeks) use of monoamine oxidase-A inhibitor • History of asthma, urticaria, other allergic type reactions, rhinitis, or nasal polyps syndrome after taking aspirin or other NSAID/analgesic drugs • Known hypersensitivity to sumatriptan, naproxen, or any components of Treximet (angioedema and anaphylaxis seen) • Severe hepatic impairment Sumatriptan/naproxen sodium tablet has the following boxed warning:(12) • Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use. • Treximet is contraindicated in the setting of coronary artery bypass graft (CABG) surgery • NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. Zolmitriptan has the following contraindications:(14-15) • History of coronary artery disease or coronary artery vasospasm • Symptomatic Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders

	• History of stroke, transient ischemic attack, or hemiplegic or basilar migraine • Peripheral vascular disease • Ischemic bowel disease • Uncontrolled hypertension • Recent (within 24 hours) use of treatment with another 5-HT1 agonist, or an ergotamine-containing medication • MAO-A inhibitor used in the past 2 weeks • Hypersensitivity to zolmitriptan

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3	Frova prescribing information. Endo Pharmaceuticals, Inc. August 2018.
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5	IMITREX Nasal Spray prescribing information. GlaxoSmithKline LLC. December 2017.
6	IMITREX Tablets prescribing information. GlaxoSmithKline LLC. December 2020.
7	Maxalt Tablets/Maxalt-MLT Tablets prescribing information. Organon LLC. June 2021.
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9	RELPAX Tablets prescribing information. Roerig. March 2020.
10	Mayans L, Walling A. Acute Migraine Headache: Treatment Strategies. *Am Fam Physician.* 2018; 97(4): 243-251.
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QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. ALL of the following: A. The patient has a diagnosis of migraine headache **AND** B. ONE of the following: 1. The patient is currently using migraine prophylactic medication (i.e., anticonvulsants [i.e., divalproex, valproate, topiramate], beta blockers [i.e., atenolol, metoprolol, nadolol, propranolol, timolol], antidepressants [i.e., amitriptyline, venlafaxine], candesartan, prophylactic use CGRP [i.e., Aimovig, AJOVY, Emgality, Nurtec, QULIPTA, Vyepti], onabotulinum toxin A (Botox]) **OR** 2. The patient has an intolerance or hypersensitivity to an anticonvulsant, a beta blocker, an antidepressant, candesartan, prophylactic use CGRP, or onabotulinum toxin A listed above **OR** 3. The patient has an FDA labeled contraindication to ALL anticonvulsants, beta blockers, antidepressants, candesartan, prophylactic use CGRP, or onabotulinum toxin A listed above **AND** C. Medication overuse headache has been ruled out **AND** D. The patient will NOT be using the requested agent in combination with another acute migraine therapy (e.g., triptan, 5HT-1F [REYVOW], ergotamine, acute use CGRP [e.g., Nurtec, UBRELVY, Zavzpret]) **AND** E. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **OR** 2. BOTH of the following: A. The patient has a diagnosis of cluster headache **AND** B. The requested agent is an injection or nasal spray **Length of Approval:** up to 12 months [For a diagnosis of migraine, the quantity requested up to the FDA labeled maximum dose allowed per 24 hours will be approved.]

Urea Cycle Disorders

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Buphenyl® (sodium phenylbutyrate)* Oral tablet Powder for oral, nasogastric, or gastrostomy tube administration	Adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS). All patients with neonatal-onset deficiency (complete enzymatic deficiency, presenting within the first 28 days of life). All patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy. Buphenyl must be combined with dietary protein restriction and, in some cases, essential amino acid supplementation.	* generic available	2
Olpruva™ (sodium phenylbutyrate) Oral suspension packet	Adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients weighing 20 kg or greater and with a body surface area (BSA) of 1.2 m^2 or greater, with urea cycle disorders (UCDs) involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS) Limitations of Use: Episodes of acute hyperammonemia may occur in patients while on Olpruva. Olpruva is not indicated for the treatment of acute hyperammonemia, which can be a life-threatening medical emergency that requires rapid acting interventions to reduce plasma ammonia levels.		8

Agent(s)	FDA Indication(s)	Notes	Ref#
Pheburane® (sodium phenylbutyrate) Oral pellets	Adjunctive therapy to standard of care, which includes dietary management, for the chronic management of adult and pediatric patients with urea cycle disorders (UCDs), involving deficiencies of carbamylphosphate synthetase (CPS), ornithine transcarbamylase (OTC), or argininosuccinic acid synthetase (AS)		7
Ravicti® (glycerol phenylbutyrate) Oral liquid	Chronic management of patients with urea cycle disorders (UCDs) who cannot be managed by dietary protein restriction and/or amino acid supplementation alone. Ravicti must be used with dietary protein restriction and, in some cases, dietary supplements (e.g., essential amino acids, arginine, citrulline, protein-free calorie supplements). Limitations of Use: • Not indicated for the treatment of acute hyperammonemia in patients with UCDs because more rapidly-acting interventions are essential to reduce plasma ammonia levels. • Safety and efficacy for the treatment of N-acetylglutamate synthase (NAGS) deficiency has not been established.		1

CLINICAL RATIONALE

Urea Cycle Disorders	Urea cycle disorders (UCDs) are rare genetically inherited metabolic deficiencies that result from defects in the metabolism of waste nitrogen from the breakdown of protein and other nitrogen-containing molecules. Severe deficiency, or total absence, of any of the enzymes in the urea cycle (carbamoyl phosphate synthetase I [CPS1], ornithine transcarbamylase [OTC], argininosuccinic acid synthetase [ASS1], argininosuccinic acid lyase [ASL], arginase [ARG1]) or the cofactor producer (N-acetyl glutamate synthetase [NAGS]) results in the accumulation of ammonia (hyperammonemia) during the first few days of life. In severe disease, infants rapidly develop cerebral edema and signs of lethargy, anorexia, hyper- or hypoventilation, hypothermia, seizures, neurologic posturing,

	and coma, whereas milder disease and the associated accumulation of ammonia may be triggered by illness or stress.(3,4,5) The most important diagnostic step in UCDs is clinical suspicion of hyperammonemia. Laboratory data useful in the diagnosis of UCD includes, but is not limited to, plasma ammonia, anion gap, and plasma glucose. A normal anion gap and normal blood glucose in the presence of a plasma ammonia concentration of 150 micomol/L (greater than 260 micrograms/dL) or higher in neonates and greater than 100 micromol/L (175 micrograms/dL) in older children and adults is indicative of UCD. The diagnosis of a specific UCD can be confirmed by genetic testing. Specifically, NAGS, OTC, and CPSI deficiencies can be confirmed by liver biopsy.(3,4,5) Pharmacologic therapy for acute hyperammonemia consists of initial IV administration of a combination preparation of sodium phenylacetate and sodium benzoate, ideally while the dialysis is being arranged and the diagnostic workup is under way. If chronic therapy is warranted, the patient can then be switched to nitrogen scavengers such as sodium phenylbutyrate, glycerol phenylbutyrate, and carglumic acid.(4,5,6) Sodium phenylbutyrate (Buphenyl) and glycerol phenylbutyrate (Ravicti) are metabolized to phenylacetate. Phenylacetate is a metabolically-active compound that conjugates with glutamine to form phenylacetylglutamine, which is then excreted by the kidneys. On a molar basis it is comparable to urea, which makes it an alternate vehicle for excreting waste nitrogen.(1,2) Long term management options to prevent hyperammonemia includes dietary modification and nutritional oversight (e.g., protein restriction, limitation of alcohol intake, essential amino acid supplementation if clinically appropriate).(4-6) Not all adult patients who recover from a hyperammonemic episode require chronic nitrogen scavengers, but they ought to be considered since many of these patients can become more brittle as time goes on.(4,5)
Safety	Buphenyl (sodium phenylbutyrate) is contraindicated for management of acute hyperammonemia, which is a medical emergency.(2) Pheburane and Olpruva (sodium phenylbutyrate) have no noted contraindications.(7,8) Ravicti (glycerol phenylbutyrate) is contraindicated in patients with known hypersensitivity to phenylbutyrate.(1)

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has a diagnosis of hyperammonemia AND ALL of the following: A. The patient has elevated ammonia levels according to the patient's age [Neonate: plasma ammonia level 150 micromol/L (greater than 260 micrograms/dL) or higher; Older child or adult: plasma ammonia level greater than 100 micromol/L (175 micrograms/dL)] **AND**

Module	Clinical Criteria for Approval
	B. The patient has a normal anion gap **AND** C. The patient has a normal blood glucose level **AND** 2. The patient has a diagnosis of ONE of the following urea cycle disorders confirmed by enzyme analysis OR genetic testing: a. carbamoyl phosphate synthetase I deficiency [CPSID] b. ornithine transcarbamylase deficiency [OTCD] c. argininosuccinic acid synthetase deficiency [ASSD] d. argininosuccinic acid lyase deficiency [ASLD] e. arginase deficiency [ARG1D] **AND** 3. The requested agent will NOT be used as treatment of acute hyperammonemia **AND** 4. The patient is unable to maintain a plasma ammonia level within the normal range with the use of a protein restricted diet and, when clinically appropriate, essential amino acid supplementation **AND** 5. The patient will be using the requested agent as adjunctive therapy to dietary protein restriction **AND** 6. ONE of the following: A. If the requested agent is Buphenyl or Olpruva, then ONE of the following: 1. The patient has an intolerance or hypersensitivity to generic sodium phenylbutyrate that is not expected to occur with the brand agent **OR** 2. The patient has an FDA labeled contraindication to generic sodium phenylbutyrate that is not expected to occur with the brand agent **OR** 3. There is support for the use of the requested brand agent over generic sodium phenylbutyrate **OR** B. If the requested agent is Ravicti, ONE of the following: 1. The patient has tried and had an inadequate response to generic sodium phenylbutyrate AND Pheburane **OR** 2. The patient has an intolerance or hypersensitivity to generic sodium phenylbutyrate AND Pheburane **OR** 3. The patient has an FDA labeled contraindication to generic sodium phenylbutyrate AND Pheburane **OR** 4. There is support for the use of the requested brand agent over generic sodium phenylbutyrate AND Pheburane **AND** 7. The prescriber is a specialist in the area of the patient's diagnosis (e.g., metabolic disorders) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 8. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 9. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months

Module	Clinical Criteria for Approval
	Renewal Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent (e.g., plasma ammonia level within the normal range) **AND** 3. The requested agent will NOT be used as treatment of acute hyperammonemia **AND** 4. The patient will be using the requested agent as adjunctive therapy to dietary protein restriction **AND** 5. ONE of the following: A. If the requested agent is Buphenyl or Olpruva, then ONE of the following: 1. The patient has an intolerance or hypersensitivity to generic sodium phenylbutyrate that is not expected to occur with the brand agent **OR** 2. The patient has an FDA labeled contraindication to generic sodium phenylbutyrate that is not expected to occur with the brand agent **OR** 3. There is support for the use of the requested brand agent over generic sodium phenylbutyrate **OR** B. If the requested agent is Ravicti, ONE of the following: 1. The patient has tried and had an inadequate response to generic sodium phenylbutyrate AND Pheburane **OR** 2. The patient has an intolerance or hypersensitivity to generic sodium phenylbutyrate AND Pheburane **OR** 3. The patient has an FDA labeled contraindication to generic sodium phenylbutyrate AND Pheburane **OR** 4. There is support for the use of the requested brand agent over generic sodium phenylbutyrate AND Pheburane **AND** 6. The prescriber is a specialist in the area of the patient's diagnosis (e.g., metabolic disorders) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 7. The patient does NOT have any FDA labeled contraindications to the requested agent **AND** 8. The requested quantity (dose) is within FDA labeled dosing for the requested indication **Length of Approval:** 12 months

Verquvo

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Verquvo® (vericiguat) Tablets	Reduce the risk of cardiovascular death and heart failure (HF) hospitalization following a hospitalization for HF or need for outpatient IV diuretics, in adults with symptomatic chronic HF and ejection fraction less than 45%		1

CLINICAL RATIONALE

Heart Failure	Heart failure (HF) is a complex clinical syndrome with symptoms and signs that result from any structural or functional impairment of ventricular filling or ejection of blood. The American Heart Association/American College of Cardiology (AHA/ACC) stages of heart failure emphasize the development and progression of disease, and advanced stages and progression are associated with reduced survival. The New York Heart Association (NYHA) classification is used to characterize symptoms and functional capacity of patients with symptomatic (NYHA Class II-IV) HF or advanced HF. In HF, NYHA functional class I includes patients with no limitations in physical activity resulting from their HF. NYHA class II includes patients who are comfortable at rest but have slight symptoms resulting from HF (dyspnea, fatigue, lightheadedness) with ordinary activity. NYHA class III includes patients who are comfortable at rest but have symptoms of HF with less than ordinary activity. NYHA class IV includes patients who are unable to carry out any physical activity without symptoms and have symptoms at rest. It is a subjective assessment by a clinician and can change over time. Although reproducibility and validity can be limited, the NYHA functional classification is an independent predictor of mortality, and it is widely used in clinical practice to determine the eligibility of patients for treatment strategies. Because of the complexity of HF management and coordination of other health and social services required, HF care is ideally provided by multidisciplinary teams that include cardiologists, nurses, and pharmacists who specialize in HF as well as dieticians, mental health clinicians, social workers, primary care clinicians, and additional specialists.(2)

Left ventricular ejection fraction (LVEF) is considered important in the classification of patients with HF because of differing prognosis and response to treatments and because most clinical trials select patients based on ejection fraction (EF). The classification of HF by LVEF is as follows:(2)

Type of HF According to LVEF	LVEF Criteria
HFrEF (HF with reduced EF)	Less than or equal to 40%
HFimpEF (HF with improved EF)	Previous LVEF less than or equal to 40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	41-49% Evidence of spontaneous or provokable increased LV filling pressures
HFpEF (HF with preserved EF)	Greater than or equal to 50% Evidence of spontaneous or provokable increased LV filling pressures

Medication recommendations for HFmrEF (LVEF 41-49%) give a class of recommendation (COR) of 1 (strong) to diuretics, as needed followed by a COR of 2a (moderate) to sodium-glucose cotransporter 2 inhibitor (SGLT2i). EMPEROR-Preserved trial showed a significant benefit of empagliflozin in patients with symptomatic HF with LVEF >40%. There are no prospective randomized controlled trials for patients specifically with HFmrEF (LVEF, 41%–49%). All data for HFmrEF are from post hoc or subsets of analyses from previous HF trials with patients now classified as HFmrEF. LVEF is a spectrum, and among patients with LVEF 41% to 49%, patients with LVEF on the lower end of this spectrum appear to respond to medical therapies similarly to patients with HFrEF. Thus, it may be reasonable to treat these patients with guideline-directed medical therapy (GDMT) used for treatment of HFrEF (beta blockers; mineralocorticoid receptor antagonist [MRA]; angiotensin receptor-neprilysin inhibitor [ARNi], angiotensin-converting enzyme inhibitor [ACEi], or angiotensin receptor blocker [ARB]). A COR of 2b (weak) is assigned to these medications which are also used for HFrEF (beta blockers, MRA, ARNi, ACEi, ARB).(2)

Efficacy	Vericiguat is a stimulator of soluble guanylate cyclase (sGC), an enzyme in the nitric oxide (NO) signaling pathway. When NO binds to sGC, the enzyme catalyzes the synthesis of intracellular cyclic guanosine monophosphate (cGMP) a second messenger that plays a role in the regulation of vascular tone, cardiac contractility, and cardiac remodeling. Heart failure is associated with impaired synthesis of NO and decreased activity of sGC, which may contribute to myocardial and vascular dysfunction. By directly stimulating sGC, both independently and synergistically with NO, vericiguat increases levels of intracellular cGMP, leading to smooth muscle relaxation and vasodilation. Vericiguat also demonstrated a dose-dependent reduction in N-terminal-prohormone B natriuretic peptide (NT-proBNP), a biomarker in heart failure.(1) Verquvo gained FDA approval through the VICTORIA trial. This was a randomized, parallel-group, placebo-controlled, double-blind, multicenter trial that enrolled 5,050 adult patients with symptomatic chronic heart failure (New York Heart Association class II-IV) that also had a left ventricular ejection fraction (LVEF) of less than 45%, following a worsening heart failure event. A worsening heart failure event was defined as a heart failure hospitalization within 6 months before randomization or use of outpatient intravenous diuretics for heart failure within 3 months before randomization. At baseline, 93% of patients were on a beta blocker, 73% of patients were on an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), 70% of patients were on a mineralocorticoid receptor antagonist (MRA), 15% of patients were on a combination of an angiotensin receptor and neprilysin inhibitor (ARNI), 28% of patients had an implantable cardiac defibrillator, and 15% had a biventricular pacemaker. Ninety-one percent of patients were treated with 2 or more heart failure medications (beta blocker, any renin-angiotensin system [RAS] inhibitor or MRA) and 60% of patients were treated with all 3. At baseline, 6% of patients were on ivabradine and 3% of patients were on a sodium glucose co-transporter 2 (SGLT2) inhibitor. Patients in both the study drug and the placebo group had their doses titrated up as tolerated. The primary endpoint was a composite of time to first event of CV death or hospitalization for heart failure. The median follow-up for the primary endpoint was 11 months. Verquvo was found to be superior to placebo in reducing the risk of CV death or heart failure hospitalization based on a time-to-event analysis. Over the course of the study, there was a 4.2% annualized absolute risk reduction in CV death or heart failure hospitalization compared with placebo.(1)
Safety	Verquvo is contraindicated in patients with concomitant use of other soluble guanylate cyclase (sGC) stimulators and in patients that are pregnant.(1)

	Verquvo has a boxed warning for embryo-fetal toxicity.(1) • Do not administer VERQUVO to a pregnant female because it may cause fetal harm. • Females of reproductive potential: Exclude pregnancy before the start of treatment. To prevent pregnancy, females of reproductive potential must use effective forms of contraception during treatment and for one month after stopping treatment.

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** All target agents are eligible for continuation of therapy 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR**

Module	Clinical Criteria for Approval
	2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. The patient has a diagnosis of symptomatic chronic heart failure (NYHA Class II-IV) and ALL of the following: 1. The patient has a left ventricular ejection fraction (LVEF) less than 45% **AND** 2. ONE of the following: A. Hospitalization of heart failure within the past 6 months **OR** B. Use of outpatient IV diuretics for heart failure within the past 3 months **OR** C. The patient has another FDA labeled indication for the requested agent and route of administration **OR** D. The patient has another indication that is supported in compendia for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS or DrugDex 1 or 2a level of evidence NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Length of Approval:** 12 months **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND**

Module	Clinical Criteria for Approval
	4. The patient does NOT have any FDA labeled contraindications to the requested agent NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Length of Approval:** 12 months

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Vijoice (alpelisib)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Vijoice® (alpelisib) Tablets	Treatment of adult and pediatric patients 2 years of age and older with severe manifestations of PIK3CA-Related Overgrowth Spectrum (PROS) who require systemic therapy		1

CLINICAL RATIONALE

PIK3CA-Related Overgrowth Spectrum (PROS)	PIK3CA-related overgrowth spectrum (PROS) is a group of genetic disorders that result in overgrowth of various body parts due to mutations in the PIK3CA gene. A broad number of disorders fall into the spectrum, with some genetic and symptom overlap between the different disorders. The PIK3CA gene is involved in making a protein that helps regulate cell growth, division, and survival. Mutations to the PIK3CA gene happen spontaneously during development in the womb. There are a number of subtypes of PROS and include:(2) • CLAPO (capillary malformation of the lower lip, lymphatic malformation of the face and neck, asymmetry of face and limbs, and partial or generalized overgrowth involving one or more body segments) syndrome • Congenital lipomatous (fatty) overgrowth, vascular malformations, epidermal nevi, and scoliosis/skeletal/spinal anomalies (CLOVES) syndrome • Diffuse capillary malformation with overgrowth (DCMO) • Dysplastic megalencephaly (DMEG) • Fibroadipose hyperplasia (FAH)/fibroadipose overgrowth (FAO) • Hemihyperplasia multiple lipomatosis (HHML) syndrome • Fibro-adipose vascular anomaly (FAVA) • Facial infiltrating lipomatosis (FIL) • Hemimegalencephaly (HME) • Klippel-Trenaunay syndrome (KTS) • Lipomatosis of nerve (LON) • Macrodactyly

	• Megalencephaly-capillary malformation (MCAP) syndrome
	• Muscular hemihyperplasia (HH)
	
	PROS is caused by somatic mutations in the PIK3CA gene. There are a variety of activating mutations of the PIK3CA gene associated with each syndrome with some genetic overlap between the different syndromes. These somatic mutations occur during prenatal development and are said to be somatic mosaic mutations, where the mutations are present in only certain cells of the body affecting only certain areas of the body, leading to overgrowth in only certain body regions or asymmetrically.(2)
	
	The PIK3CA gene leads to the creation of the protein known as p110a, and mutations in this gene result in an abnormally active PI3K enzyme. With increased activity, affected cells grow and divide more rapidly, leading to abnormal bone, soft tissue and blood vessel growth. PIK3CA mutations may also cause overgrowth by influencing the effects of growth factors and hormones on nearby and distant cells. Mutations in the PIK3CA gene have been found in certain cancers of the lower GI tract, the ovaries, breasts, brain and liver. Currently, most patients with PROS do not appear to be at a significantly higher risk for cancer. The only cancer reported in PROS to date has been Wilms tumor, the most common pediatric kidney cancer in very young children.(2)
	
	Due to the phenotypic overlap and variability, the diagnosis of PROS can be complicated. Referral to a physician with expertise in the diagnosis and treatment of PROS is recommended. Biopsy of the overgrown tissue and genetic testing for PIK3CA variants are required to confirm the diagnosis of PROS.(2,3,4) The National Institute of Health (NIH) Clinical Diagnostic Criteria for PROS include the following:(3)
	
	• Required:
	  ○ Presence of somatic PIK3CA mutation*
	  ○ Congenital or early childhood onset
	  ○ Overgrowth sporadic and mosaic
	  ○ Features described in either A or B
	• A: Spectrum (two or more features)**
	  ○ Overgrowth
	  ○ Vascular malformations
	  ○ Epidermal nevus
	• B: Isolated features
	  ○ Large isolated lymphatic malformations
	  ○ Isolated macrodactyly OR overgrown splayed feet/hands, overgrown limbs

	○ Truncal adipose overgrowth ○ Hemimegalencephaly (bilateral)/dysplastic megalencephaly/focal cortical dysplasia ○ Epidermal nevus ○ Seborrheic keratoses ○ Benign lichenoid keratoses *- If no mutation identified, consider as presumptive PROS **- Typically progressive Treatment is dependent on the syndrome and symptoms present. Treatment options can include the following:(2) • Laser ablation may be used for vascular anomalies. • Surgical removal of vascular malformations may be helpful. Sclerotherapy or embolization may be performed alone or in conjunction with surgery. • Surgical removal or debulking may be an option for tissue overgrowth of limbs, digits, or soft tissue, but abnormal tissue may regrow, requiring repeated surgical interventions. • Orthopedic options may include surgical closure of growth plates in joints or shoe lifts. • Physical, occupational, and speech therapy along with special education may be warranted depending on motor and intellectual disabilities present. • Megalencephaly requires referral to a neurosurgeon for potential surgical treatments for Chiari malformations or hydrocephalus, or medications for seizures.
Efficacy	The efficacy of Vijoice was assessed in EPIK-P1 (NCT04285723), a single-arm clinical study in patients who were treated as part of an expanded access program for compassionate use. Eligible patients 2 years of age and older with PIK3CA-related overgrowth spectrum (PROS) who received Vijoice had clinical manifestations of PROS that were assessed by the treating physician as severe or life-threatening and necessitating systemic treatment and had documented evidence of mutation in the PIK3CA gene.(1) The efficacy of Vijoice was evaluated in a total of 37 patients with at least one target lesion identified on imaging performed within 24 weeks prior to receipt of the first dose of Vijoice. Ninety-two percent of patients had congenital overgrowth and 8% had early childhood-onset. The major efficacy outcome measure for the study was the proportion of patients with radiological response

	at week 24 as determined by blinded independent central review (BICR), defined as a greater than or equal to 20% reduction from baseline in the sum of measurable target lesion volume (1 to 3 lesions) confirmed by at least one subsequent imaging assessment, in the absence of a greater than or equal to 20% increase from baseline in any target lesion, progression of non-target lesions, or appearance of a new lesion. An additional efficacy outcome measure was duration of response, defined as the time from the first documented response to the date of the first documented disease progression or death due to any cause. Of the patients treated with Vijoice 10 were considered responders, and of those patients 7 sustained response for greater than or equal to 6 months and 6 sustained response for greater than or equal to 12 months.(1)
Safety	Vijoice is contraindicated in patients with severe hypersensitivity to alpelisib or any of its ingredients.(1)

REFERENCES

Number	Reference
1	Vijoice prescribing information. Novartis Pharmaceuticals Corp. November 2022.
2	National Organization for Rare Disorders (NORD) Rare Disease Database. PIK3CA-Related Overgrowth Spectrum (PROS). Accessed at: https://rarediseases.org/rare-diseases/pik3ca-related-overgrowth-spectrum/
3	Keppler-Noreuil KM, Rios JJ, Parker VER, et al. PIK3CA-Related Overgrowth Spectrum (PROS): Diagnostic and Testing Eligibility Criteria, Differential Diagnosis, and Evaluation. Am J Med Genet A. 2015 Feb;0(2):287–295.
4	Kuentz P, St-Onge J, Duffourd Y, et al. Molecular Diagnosis of PIK3CA-Related Overgrowth Spectrum (PROS) in 162 Patients and Recommendations for Genetic Testing. Genet Med. 2017 Sep;19(9):989-997.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
A. The requested agent is eligible for continuation of therapy AND ONE of the following:

<table>
<tr><th>Agents Eligible for Continuation of Therapy</th></tr>
<tr><td>Vijoice</td></tr>
</table>

1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days OR
2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed OR
B. ALL of the following:
1. The patient has a diagnosis of PIK3CA-Related Overgrowth Spectrum (PROS) confirmed by ALL of the following:
A. Presence of somatic PIK3CA mutation AND
B. Congenital or early childhood onset AND
C. Overgrowth sporadic and mosaic AND
D. ONE of the following:
1. The patient has at least TWO of the following features:
A. Overgrowth
B. Vascular malformations
C. Epidermal nevus OR
2. The patient has at least ONE of the following features:
A. Large isolated lymphatic malformations
B. Isolated macrodactyly OR overgrown splayed feet/hands, overgrown limbs
C. Truncal adipose overgrowth
D. Hemimegalencephaly (bilateral)/dysplastic megalencephaly/focal cortical dysplasia
E. Epidermal nevus
F. Seborrheic keratoses
G. Benign lichenoid keratoses AND
2. The patient has severe manifestations of PROS that requires systemic therapy AND
3. If the patient has an FDA labeled indication, then ONE of the following:
</td></tr>
</table>

Module	Clinical Criteria for Approval
	A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., experienced in PROS) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 6 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The patient has NOT had disease progression (e.g., increase in lesion number, increase in lesion volume) with the requested agent (medical records required) **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., experienced in PROS) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND**

Module	Clinical Criteria for Approval
	B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval**: up to 6 months for initial; up to 12 months for renewal

VMAT2 Inhibitors

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Austedo® (deutetrabenazine) Tablet	Treatment of adults with chorea associated with Huntington's disease Treatment of adults with tardive dyskinesia		1
Austedo XR® (deutetrabenazine er) Tablet	Treatment of adults with chorea associated with Huntington's disease Treatment of adults with tardive dyskinesia		8
Ingrezza® (valbenazine) Capsule	Treatment of adults with tardive dyskinesia Treatment of adults with chorea associated with Huntington's disease		2
Xenazine® (tetrabenazine) Tablet	Treatment of chorea associated with Huntington's disease	*generic available	3

CLINICAL RATIONALE

Huntington's Disease	Huntington's Disease (HD) is a hereditary neurodegenerative disorder caused by an expansion of a repeating cytosine-adenine-guanine (CAG) triplet series in the HTT (huntingtin) gene on chromosome 4. It is inherited in an autosomal dominant pattern with each child of an affected parent having a 50% chance of developing the disease. There is currently no cure or treatment which can halt, slow, or reverse the progression of the disease. The average length of survival after clinical diagnosis is typically 10-20 years.(6)

	Huntington's Disease manifests as a triad of motor, cognitive, and psychiatric disorders that begin gradually and progress over many years. These disorders of HD cannot be considered in isolation with disabilities in one area leading to problems in another area. The cognitive disorder is characterized by a reduction of speed and flexibility of mental processing. The psychiatric disorder is less predictable. People may suffer from depression, mania, obsessive compulsive disorder and various forms of psychosis. Almost all people with HD will experience disease-specific personality and behavioral changes that result in severe consequences to their marital, social, and economic well-being. The movement disorder includes emergence of involuntary movements (chorea) and the impairment of voluntary movements which results in reduced manual dexterity, slurred speech, swallowing difficulties, problems with balance, and falls. The most recognized motor symptom is chorea, and the clinical diagnosis of Huntington's Disease traditionally is based on the observation of this symptom. More than 90% of people affected by HD have chorea, which is characterized by involuntary movements that are often sudden, irregular, and purposeless. The movements are often more prominent in the extremities early in the disease, but may eventually include facial grimacing, eyelid elevation, neck, shoulder, trunk, and leg movements as the disease progresses. Chorea typically increases in frequency and amplitude over time and may peak about 10 years after disease onset.(6) Treating chorea is an important part of HD management and should be considered if chorea causes the patient distress or discomfort. Vesicular monoamine transporter 2 (VMAT 2) inhibitors are FDA labeled agents for treatment and are considered first-line treatment unless the patient suffers from not well-managed depression or suicidal thoughts.(4) The precise mechanism of action is unknown, but VMAT2 inhibitors are believed to exert their anti-chorea effects as a reversible depletor of monoamines (such as dopamine, serotonin, norepinephrine, and histamine) from nerve terminals. They reversibly inhibit VMAT2, a transporter that regulates monoamine uptake from the cytoplasm to the synaptic vesicle resulting in decreased uptake of monoamines and depletion of monoamine stores. (1-3,8)
Tardive dyskinesia	Tardive syndromes are persistent abnormal involuntary movement disorders caused by sustained exposure to antipsychotic medication, the most common of which are tardive dyskinesia, tardive dystonia, and tardive akathisia. They begin later in treatment than acute dystonia, akathisia, or medication-induced parkinsonism and they persist and may even increase, despite reduction in dose or discontinuation of the antipsychotic medication. Tardive dyskinesia has been reported after exposure to any of the available antipsychotic medications. It occurs at a rate of approximately 4-8% per year in adult patients treated with first

	generation antipsychotics. Evaluation of the risk of tardive dyskinesia is complicated by the fact that dyskinetic movements may be observed with a reduction in antipsychotic medication dose. Fluctuations in symptoms are also common and may be influenced by factors such as psychosocial stressors. Regular assessment of patients for tardive syndromes through clinical examination or through the use of a structured evaluative tool, such as the Abnormal Involuntary Movement Scale (AIMS), can aid in identification, clarifying the likely etiology, monitoring, and determining the effects of medication changes or treatments for tardive dyskinesia. It should be noted that there is no specific score threshold that suggests a need for intervention, although ranges of scores are noted to correspond with mild, moderate, and severe symptoms. If no other contributing etiology is identified and moderate to severe or disabling tardive dyskinesia persists, treatment with a VMAT2 inhibitor is recommended. A change in antipsychotic therapy to a lower potency medication and particularly to clozapine may be associated with a reduction in tardive dyskinesia. The potential benefits of changing medication should be considered in light of the possibility of symptom recurrence.(7)
Safety	VMAT2 inhibitors (including Austedo/Austedo XR, Ingrezza, and Xenazine) have a boxed warning due to an increased risk of depression and suicidal thoughts and behavior in patients with Huntington's disease. Anyone considering the use of VMAT2 inhibitors (including Austedo/Austedo XR, Ingrezza, and Xenazine) must balance the risks of depression and suicidal ideation and behavior with the clinical need for treatment of chorea. Closely monitor patients for the emergence or worsening of depression, suicidal ideation, or unusual changes in behavior. Inform patients, their caregivers, and families of the risk of depression and suicidal ideation and behavior and instruct them to report behaviors of concern promptly to the treating physician. Particular caution should be exercised in treating patients with a history of depression or prior suicide attempts or ideation, which are increased in frequency in patients with Huntington's disease.(1-3,8) Austedo/Austedo XR are contraindicated in patients:(1,8) • with Huntington's disease who are suicidal, or have untreated or inadequately treated depression • with hepatic impairment • taking reserpine. At least 20 days should elapse after stopping reserpine before starting Austedo/Austedo XR. • taking monoamine oxidase inhibitors (MAOIs). Austedo/Austedo XR should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI.

	• taking tetrabenazine or valbenazine Ingrezza is contraindicated in patients with a history of hypersensitivity to valbenazine or any components of Ingrezza. Rash, urticaria, and reactions consistent with angioedema (e.g., swelling of the face, lips, and mouth) have been reported.(2) Xenazine is contraindicated in patients:(3) • who are actively suicidal, or in patients with untreated or inadequately treated depression • with hepatic impairment • taking monoamine oxidase inhibitors (MAOIs). Tetrabenazine should not be used in combination with an MAOI, or within a minimum of 14 days of discontinuing therapy with an MAOI. • taking reserpine. At least 20 days should elapse after stopping reserpine before starting Xenazine. • taking deutetrabenazine or valbenazine

REFERENCES

Number	Reference
1	Austedo prescribing information. Teva Neuroscience, Inc. September 2023.
2	Ingrezza prescribing information. Neurocrine Biosciences, Inc. August 2023.
3	Xenazine Prescribing Information. Bausch Health Companies, Inc. November 2019.
4	Bachoud-Lévi AC, Ferreira JJ, Massart R, et al. International Guidelines for the treatment of Huntington's Disease. *Frontiers in Neurology*. 2019;10. doi:10.3389/fneur.2019.00710
5	Ingrezza Sprinkle prescribing information. Neurocrine Biosciences, Inc. April 2024.
6	Nance MA, Paulsen JS, Rosenblatt A, Wheelock V. A Physician's Guide to the Management of Huntington's Disease (3rd edition). Huntington's Disease Society of America. 2011. https://hdsa.org/wp-content/uploads/2015/03/PhysiciansGuide_3rd-Edition.pdf

Number	Reference
7	Keepers GA, Fochtmann LJ, Anzia JM, et al. The American Psychiatric Association Practice Guideline for the Treatment of Patients with Schizophrenia. *American Journal of Psychiatry*. 2020;177(9):868-872. doi:10.1176/appi.ajp.2020.177901
8	Austedo XR prescribing information. Teva Neuroscience, Inc. February 2023.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is Austedo/deutetrabenazine, Austedo XR/deutetrabenazine ER, or Ingrezza/valbenazine AND ONE of the following: 1. The patient has a diagnosis of tardive dyskinesia AND BOTH of the following: A. ONE of the following: 1. The patient is not taking any medications known to cause tardive dyskinesia (i.e., dopamine receptor blocking agents) **OR** 2. The prescriber has reduced the dose or discontinued any medications known to cause tardive dyskinesia **OR** 3. A reduced dose or discontinuation of any medications known to cause tardive dyskinesia is not appropriate **AND** B. The prescriber has documented the patient's baseline Abnormal Involuntary Movement Scale (AIMS) score **OR** 2. The patient has a diagnosis of chorea associated with Huntington's disease **OR** 3. The patient has another FDA labeled indication for the requested agent and route of administration **OR** 4. The patient has another indication that is supported in compendia for the requested agent and route of administration **OR** B. The requested agent is Xenazine/tetrabenazine and ONE of the following: 1. The patient has a diagnosis of chorea associated with Huntington's disease **OR** 2. The patient has another FDA labeled indication for the requested agent and route of administration **OR**

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
3. The patient has another indication that is supported in compendia for the requested agent and route of administration AND

2. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:

<table>
<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Xenazine</td><td>tetrabenazine</td></tr>
</table>

A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
C. There is support for the use of the requested brand agent over the generic equivalent AND

3. If the patient has an FDA labeled indication, then ONE of the following:
A. The patient’s age is within FDA labeling for the requested indication for the requested agent OR
B. There is support for using the requested agent for the patient’s age for the requested indication AND
4. The prescriber is a specialist in the area of the patient’s diagnosis (e.g., psychiatrist, neurologist), or the prescriber has consulted with a specialist in the area of the patient’s diagnosis AND
5. The patient will NOT be using the requested agent in combination with another agent included in this Prior Authorization program AND
6. The patient does NOT have any FDA labeled contraindications to the requested agent

Compendia Allowed: AHFS or DrugDex 1 or 2a level of evidence

Length of Approval: Tardive dyskinesia - 3 months, all other indications - 12 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Renewal Evaluation

Target Agent(s) will be approved when ALL of the following are met:
</td></tr>
</table>

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] AND
2. The prescriber is a specialist in the area of the patient's diagnosis (e.g., psychiatrist, neurologist), or the prescriber has consulted with a specialist in the area of the patient's diagnosis AND
3. ONE of the following:
   A. The patient has a diagnosis of tardive dyskinesia AND has had improvements or stabilization from baseline in their Abnormal Involuntary Movement Scale (AIMS) score OR
   B. The patient has a diagnosis other than tardive dyskinesia AND has had clinical benefit with the requested agent AND
4. If the request is for one of the following brand agents with an available generic equivalent (listed below), then ONE of the following:

<table>
<tr><th>Brand</th><th>Generic Equivalent</th></tr>
<tr><td>Xenazine</td><td>tetrabenazine</td></tr>
</table>

   A. The patient has an intolerance or hypersensitivity to the generic equivalent that is not expected to occur with the brand agent OR
   B. The patient has an FDA labeled contraindication to the generic equivalent that is not expected to occur with the brand agent OR
   C. There is support for the use of the requested brand agent over the generic equivalent AND
5. The patient will NOT be using the requested agent in combination with another agent included in this Prior Authorization program AND
6. The patient does NOT have any FDA labeled contraindications to the requested agent

Compendia Allowed: AHFS or DrugDex 1 or 2a level of evidence

Length of Approval: 12 months

NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.
</td></tr>
</table>

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Vowst (fecal microbiota spores, live-brpk)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Vowst™ (fecal microbiota spores, live-brpk caps) Capsule	To prevent the recurrence of Clostridioides difficile infection (CDI) in individuals 18 years of age and older following antibacterial treatment for recurrent CDI (rCDI). Limitation of Use: Vowst is not indicated for treatment of CDI.		1

CLINICAL RATIONALE

Clostridioides difficile infection (CDI)	Clostridioides difficile is a bacterium that can cause potentially life-threatening diarrheal illness in individuals with an unhealthy mixture of gut bacteria, known as dysbiosis, and can cause recurrent infections in nearly a third of infected individuals. Recurrent CDI (rCDI) is usually defined as an episode of CDI occurring within 8 weeks of a previous episode. rCDI may be due to relapse of the previous CDI by the same strain or reinfection by a different strain. About 15% to 30% of patients who initially respond to antimicrobial therapy experience rCDI. After the first recurrence has improved, the risk of further recurrence significantly increases. A second recurrence rate of 40% has been reported among patients with resolved first recurrence. The subsequent recurrence rate of patients who have already recurred more than twice is approximately 45% to 65%. The high recurrence rate of CDI contributes to increased health care costs. The traditional treatment of rCDI includes antibiotics, which may further exacerbate dysbiosis. Fecal microbiota transplantation (FMT) has proven to be a highly efficacious therapeutic modality to prevent recurrent CDI and increasing data support its use in severe or refractory cases.(3,4,5) The gut is estimated to contain 1000 bacterial species containing 100-fold more genes than the human genome. Viruses, bacteriophages, archaea, and fungi contribute to this microbial community, which functions as an “organ” with an immense impact on human health and disease, including host metabolism, physiology, nutrition, and immune function. Recent evidence demonstrates long-term engraftment of donor microbes into the recipients of FMT. Animal models

	and human studies indicate that manipulation of gut microbiota can affect host susceptibility to diseases such as obesity and inflammatory bowel disease (IBD).(5)
	
	Infectious Diseases Society of America (IDSA) guidelines are as follows(2):
	
	• For patients with an initial Clostridioides difficile infection (CDI) episode, we suggest using fidaxomicin rather than a standard course of vancomycin (conditional recommendation, moderate certainty of evidence).
	  ○ Comment: This recommendation places a high value in the beneficial effects and safety of fidaxomicin, but its implementation depends upon available resources. Vancomycin remains an acceptable alternative.
	• In patients with recurrent CDI episodes, we suggest fidaxomicin (standard or extended-pulsed regimen) rather than a standard course of vancomycin (conditional recommendation, low certainty evidence).
	  ○ Comment: Vancomycin in a tapered and pulsed regimen or vancomycin as a standard course are acceptable alternatives for a first CDI recurrence. For patients with multiple recurrences, vancomycin in a tapered and pulsed regimen, vancomycin followed by rifaximin, and fecal microbiota transplantation are options in addition to fidaxomicin.
	• Fecal Microbiota Transplantation (FMT): Appropriate antibiotic treatments for at least 2 recurrences (i.e., 3 CDI episodes) should be tried prior to offering FMT
	
	The 2024 American Gastroenterological Association (AGA) guidelines were updated to include recommendations for fecal microbial transplant. The AGA recommends in immunocompetent adults with rCDI, select use of fecal microbiota–based therapies upon completion of standard of care antibiotics to prevent recurrence. In mildly or moderately immunocompromised adults with rCDI, the AGA suggests select use of conventional fecal microbiota transplant. In severely immunocompromised adults, the AGA suggests against the use of any fecal microbiota–based therapies to prevent rCDI. In adults hospitalized with severe or fulminant *C difficile* not responding to standard of care antibiotics, the AGA suggests select use of conventional fecal microbiota transplant. The AGA suggests against the use of conventional fecal microbiota transplant as treatment for inflammatory bowel diseases or irritable bowel syndrome, except in the context of clinical trials.(6)
	
	Vowst contains bacterial spores; therefore, antibacterials should not be administered concurrently with Vowst.(1)

Fecal Microbiota Transplantation (FMT) Efficacy	The American Gastroenterological Association (AGA) Institute, in partnership with other professional organizations, has developed an FMT National Registry to collect clinical and patient-reported outcomes. This registry primarily aims to assess the short-term and long-term safety of FMT and other gut-related microbiota products. The current report is based on the first 259 participants enrolled in the FMT National Registry.(5) Of the 259 participants, 123 had both 1-month and 6-month follow-up within the prespecified windows. Of the 112 participants cured at 1-month and with follow-up at the 6-month point, 4 participants (4%) had developed recurrent CDI at a median of 8 weeks (range, 8–14 weeks) post FMT. Of the 11 participants failing initial FMT who were followed to 6 months, 7 (64%) were reported as cured at this later point. Treatments administered to these 7 participants included metronidazole and/or vancomycin (n = 6 [86%]) or repeat FMT (n = 1 [14%]).(5) CDI cure rates were excellent at approximately 90%, and were in line with those reported in RCTs of FMT. CDI cure could be achieved with only 1 FMT in virtually all cases with recurrence in the 6 months after successful FMT seen in only 4% of participants, occurring most often within 2 months. For those with unsuccessful FMT at 1 month, most could still achieve cure by 6 months using standard antibiotic therapy or after repeated FMT. Infectious complications after FMT appear remarkably rare, as was reported in a recent systematic review that showed infections occurred in only 2.5% of more than 1000 patients treated. Even high-risk immunocompromised patients appear to have a low risk of contracting an infection related to FMT. Understanding FMT effectiveness and safety in real-world clinical settings is important because many recurrent CDI patients are not eligible for clinical trials due to common comorbidities, such as IBD and immunocompromised status, and because interest in FMT for other indications is increasing.(5)
Vowst Efficacy	The efficacy of Vowst was evaluated in a randomized placebo-controlled multi-center study (Study 1). The primary objective was to demonstrate the reduction of Clostridioides difficile infection (CDI) recurrence. Enrolled participants were 18 years of age or older and had a confirmed diagnosis of recurrent CDI (with a total of greater than or equal to 3 episodes of CDI within 12 months). CDI episode at the study entry was defined as diarrhea (greater than or equal to 3 unformed stools per day for at least 2 consecutive days) and a positive C. difficile stool sample using a toxin assay. Participants were required to have symptom resolution, defined as <3 unformed stools in 24 hours for 2 or more consecutive days prior to randomization, following 10 to 21 days of standard-of-care antibacterial treatment with vancomycin or fidaxomicin. Participants were stratified by antibacterial received (vancomycin or fidaxomicin) and age (<65 years or greater than or equal to 65 years) and randomized 1:1 to receive a dose

	of Vowst or placebo once daily for 3 consecutive days. The primary efficacy endpoint was CDI recurrence through 8 weeks after completion of treatment. Participants were assessed for recurrence, which was defined as greater than or equal to 3 unformed stools per day for 2 consecutive days with continued diarrhea until antibacterial treatment was initiated, a positive C. difficile test on a stool sample determined by a toxin assay, and assessment by the Investigator that the clinical condition of the participant warranted antibacterial treatment. Through 8 weeks after treatment, CDI recurrence in Vowst-treated participants was lower compared to that in placebo-treated participants (12.4% compared to 39.8%). Through 12 weeks after treatment, the recurrence rates for Vowst and placebo recipients were 18.0% (16/89) and 46.2% (43/93), respectively. Through 24 weeks after treatment, recurrence rates for Vowst and placebo recipients were 21.3% (19/89) and 47.3% (44/93), respectively.(1)
Safety	Vowst has no FDA labeled contraindications for use.(1)

REFERENCES

Number	Reference
1	Vowst prescribing information. Seres Therapeutics, Inc. April 2023.
2	Johnson, S., Lavergne, V., Skinner, et.al. (2021). Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. Clinical Infectious Diseases, 73(5), e1029–e1044. https://doi.org/10.1093/cid/ciab549
3	Minkoff NZ, Aslam S, Medina M, Tanner-Smith EE, Zackular JP, Acra S, Nicholson MR, Imdad A. Fecal microbiota transplantation for the treatment of recurrent Clostridioides difficile (Clostridium difficile). Cochrane Database of Systematic Reviews 2023, Issue 4. Art. No.: CD013871. DOI: 10.1002/14651858.CD013871.pub2.
4	Song JH, Kim YS. Recurrent *Clostridium difficile* Infection: Risk Factors, Treatment, and Prevention. Gut Liver. 2019 Jan 15;13(1):16-24. doi: 10.5009/gnl18071.
5	Kelly, C. R., Yen, E. F., Grinspan, A., et.al. (2021). Fecal Microbiota Transplantation Is Highly Effective in Real-World Practice: Initial Results From the FMT National Registry. Gastroenterology, 160(1), 183-192.e3. https://doi.org/10.1053/j.gastro.2020.09.038
6	Peery AF, Kelly CR, Kao D, et al. AGA clinical practice guideline on fecal Microbiota–based therapies for select gastrointestinal diseases. Gastroenterology. 2024;166(3):409-434. doi:10.1053/j.gastro.2024.01.008

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The requested agent will be used to prevent the recurrence of Clostridioides difficile infection (CDI) **AND** 2. The patient has a diagnosis of recurrent CDI as defined by ALL of the following: A. Greater than or equal to 3 episodes of CDI in a 12 month period **AND** B. A positive C. difficile stool sample **AND** C. A CDI episode of diarrhea greater than or equal to 3 unformed stools per day for at least 2 consecutive days **AND** 3. The patient has completed a standard of care oral antibiotic regimen (e.g., vancomycin, fidaxomicin) for recurrent CDI at least 2 to 4 days before initiating treatment with the requested agent **AND** 4. The patient has had an adequate clinical response to a standard of care oral antibiotic regimen (e.g., vancomycin, fidaxomicin) as defined by less than 3 unformed stools in 24 hours for 2 or more consecutive days **AND** 5. The patient will NOT be using the requested agent in combination with any antibiotic regimen for any indication **AND** 6. If the patient has an FDA approved indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 7. The prescriber is a specialist in the area of the patient's diagnosis (e.g., infectious disease, gastroenterologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 8. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** One course per 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **Length of Approval:** One course every 12 months

Voxzogo

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Voxzogo® (vosoritide) Subcutaneous injection	Indicated to increase linear growth in pediatric patients with achondroplasia with open epiphyses. This indication is approved under accelerated approval based on an improvement in annualized growth velocity. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).		1

CLINICAL RATIONALE

Achondroplasia	Achondroplasia is the most commonly occurring abnormality of bone growth (skeletal dysplasia), occurring in approximately 1 in 15,000-35,000 live births and affects both males and females equally. This genetic disorder is caused by a mutation in the fibroblast growth factor receptor 3 (*FGFR3*) gene. Fibroblast growth factor receptors (FGFRs) belong to the tyrosine kinase family and regulate various biological processes including cell proliferation and differentiation during development, as well as tissue repair. Achondroplasia occurs as a result of a spontaneous genetic mutation in approximately 80 percent of patients. In the remaining 20 percent of cases, it is inherited from either parent and follows an autosomal dominant pattern of inheritance. The risk of passing the abnormal gene from an affected parent to an offspring is 50% for each pregnancy.(3) Like some other severe growth disorders, it is also associated with potentially serious medical complications such as foramen magnum and spinal stenosis, both of which cause increased morbidity and mortality.(2) This genetic disorder is characterized by an unusually large head (macrocephaly), short upper arms (rhizomelic dwarfism), and short stature (adult height of approximately 4 feet). Achondroplasia does not typically cause impairment or deficiencies in mental abilities. If the bones that join the head and

	neck do not compress the brainstem or upper spinal cord (craniocervical junction compression), life expectancy is near normal.(3) Growth hormone treatment has been found to be ineffective in patients with deformities of the lower limbs and to date, it has not been confirmed whether the administration of somatropin negatively affects the severity of foramen narrowing and pressure on the spinal cord, and no symptoms of acromegaly have been observed in the treated patients. A meta-analysis of recombinant human growth hormone treatment in achondroplasia based on an extensive group of patients shows that data about body disproportion in GH treatment are ambiguous.(5)
Efficacy	Voxzogo is a recombinant C-type natriuretic peptide analog that stimulates endochondral ossification, a process that is inhibited in patients with achondroplasia patients.(1) The safety and effectiveness of Voxzogo in 121 genetically confirmed patients with achondroplasia were assessed in one 52-week, multi-center, randomized, double-blind, placebo-controlled, phase 3 study - Study 1 (NCT03197766). The dosage of Voxzogo was 15 mcg/kg administered subcutaneously once daily. Baseline standing height, weight Z-score, body mass index (BMI) Z-score, and upper to lower body ratio were collected for at least 6 months prior to randomization. Subjects with limb-lengthening surgery in the prior 18 months or who planned to have limb-lengthening surgery during the study period were excluded and patients must have been ambulatory and able to stand to participate.(6) The study included a 52-week placebo-controlled treatment phase followed by an open-label treatment extension study period in which all subjects received Voxzogo. The primary efficacy endpoint was the change from baseline in annualized growth velocity (AGV) at Week 52 compared with placebo. The subjects' ages ranged from 5.1 to 14.9 years with a mean of 8.7 years. Sixty four (53%) subjects were male and 57 (47%) were female. Overall, 86 (71%) subjects were White, 23 (19%) were Asian, 5 (4%) were Black or African American, and 7 (6%) were classified as "multiple" race.(1). In children randomized to vosoritide, annualized growth velocity increased from 4.26 cm/year at baseline to 5.39 cm/year at 52 weeks and 5.52 cm/year at week 104. In children who crossed over from placebo to vosoritide in the extension study, annualized growth velocity increased from 3.81 cm/year at week 52 to 5.43 cm/year at week 104. No new adverse effects of vosoritide were detected. Longer-term studies are needed to determine whether vosoritide affects pubertal growth velocity, body segment proportionality, final adult height, or complications associated with achondroplasia. Overall, vosoritide treatment has safe and

	persistent growth-promoting effects in children with achondroplasia, and offers a precision therapy for patients impacted by this condition.(7)
Safety	Voxzogo does not have any contraindications.(1)

REFERENCES

Number	Reference
1	Voxzogo Prescribing Information. BioMarin Pharmaceutical Inc. October 2023.
2	Hogler, W., Ward, LM. New developments in the management of achondroplasia. Wien Med Wochenschr 170, 104–111 (2020). https://doi.org/10.1007/s10354-020-00741-6
3	Achondroplasia. NORD. https://rarediseases.org/rare-diseases/achondroplasia
4	Kubota T, Adachi M, Kitaoka T, et al. Clinical Practice Guidelines for Achondroplasia. Clin Pediatr Endocrinol. 2020;29(1):25-42. doi:10.1297/cpe.29.25
5	Wrobel W, Pach E, Ben-Skowronek I. Advantages and Disadvantages of Different Treatment Methods in Achondroplasia: A Review. International Journal of Molecular Sciences. 2021; 22(11):5573. https://doi.org/10.3390/ijms22115573
6	A Study to Evaluate the Efficacy and Safety of BMN 111 in Children With Achondroplasia. BioMarin Pharmaceutical. Available at: https://clinicaltrials.gov/ct2/show/NCT03197766
7	Savarirayan R, Tofts L, Irving M, et al. Safe and persistent growth-promoting effects of vosoritide in children with achondroplasia: 2-year results from an open-label, phase 3 extension study. Genet Med. 2021;23(12):2443-2447. doi:10.1038/s41436-021-01287-7.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following:

Module	Clinical Criteria for Approval
	A. ALL of the following: 1. The patient has a diagnosis of achondroplasia as confirmed by ONE of the following (medical records required): A. Genetic testing **OR** B. Radiographic findings **AND** 2. The requested agent will be used to increase linear growth **AND** 3. The patient has open epiphyses **OR** B. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient will NOT be using the requested agent in combination with another growth hormone agent for the requested indication **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has open epiphyses **AND** 3. The patient has had clinical benefit with the requested agent **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., endocrinologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient will NOT be using the requested agent in combination with another growth hormone agent for the requested indication **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent

Module	Clinical Criteria for Approval
	Length of Approval: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Vtama (tapinarof)

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
VTAMA® (tapinarof) Cream	Topical treatment of plaque psoriasis in adults		1

CLINICAL RATIONALE

Psoriasis (PS)	Psoriasis (PS) is a chronic inflammatory skin and systemic disorder. It is a complex disease that affects the skin and joints and is associated with numerous comorbidities, including obesity and inflammatory bowel disease. Psoriasis vulgaris, or plaque psoriasis, is a cutaneous form that often presents with pink plaques with silvery scale on the scalp, elbows, knees, or presacral region, but any area of the skin may be involved.(3,4) Plaque psoriasis is the most common form (affecting 90% of adults with psoriasis), but others include guttate, erythrodermic, pustular, inverse, nail, and psoriatic arthritis. PS is clinically diagnosed based on the presence of cutaneous and systemic symptoms, and treatment is similar for most forms but is guided by the body surface area (BSA) involved.(6) The American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) categorize psoriasis severity as mild (less than 3% of body surface area [BSA]), moderate (3% to 10% of BSA), or severe (greater than 10% of BSA). The AAD/NPF guidelines also note that psoriasis can be considered severe irrespective of BSA when it occurs in select locations (e.g., hands, feet, scalp, face, or genital area) or when it causes intractable pruritus.(2) Topical therapies are most commonly used to treat mild to moderate PS, but they may be used in combination with phototherapy, systemic, or biologic therapies for the treatment of moderate to severe PS.(2) Topical therapies alone

	can be sufficient for managing limited disease and also have fewer significant adverse effects compared to systemic treatment options.(3) Topical corticosteroids (TCS) have high efficacy and good safety for the treatment of PS, especially localized disease.(2) TCS have shown to be the most effective topical treatment for psoriasis plaques.(7) Moderate to high potency TCS are generally recommended as initial therapy, but very high (super) potency TCS may be required for thick, chronic plaques. Lower potency TCS should be used to treat PS on the face or intertriginous areas, or areas that are susceptible to skin atrophy and adverse effects.(2) It is important to consider the anatomical site, BSA of application, patient age, and severity of the disease when choosing a steroid potency and vehicle.(2,5) Studies have shown that different potency TCS were effective and safe at 2 to 4 weeks in the treatment of mild to severe plaque psoriasis. To decrease the risk of corticosteroid adverse effects, TCS may be used short term (e.g., 2 to 4 weeks) to treat flares, while vitamin D analogues, topical retinoids, and calcineurin inhibitors can be used as maintenance treatment.(2) Topical calcineurin inhibitors (TCIs), such as tacrolimus and pimecrolimus, are often used in the treatment of psoriasis.(2) The use of TCIs can lead to the avoidance of adverse effects secondary to long term TCS use, and can be beneficial for prolonged treatment of areas of thinner skin, the face, and intertriginous areas.(2,7) Vitamin D analogues (e.g., calcipotriene and calcitriol) have been shown to be safe and effective for the treatment of mild to moderate PS.(2) Vitamin D analogues may be used as monotherapy, but combination therapy with a TCS has shown superior efficacy.(2,7) Calcipotriene ointment combined with topical tacrolimus is also more efficacious than tacrolimus alone.(2) Tazarotene is a topical retinoid that is recommended for the treatment of mild to moderate PS. Tazarotene has been shown to be efficacious as monotherapy, but adding a TCS as combination therapy increases efficacy. The combination use with a medium to high potency TCS has been shown to increase the duration of treatment effect and the time of remission. Tazarotene can also be beneficial for the treatment of palmar-plantar psoriasis and nail psoriasis. Studies have shown topical tazarotene has similar efficacy to fluocinonide cream, crude coal tar 5% ointment, and calcipotriene 0.005% ointment.(2) Other topical medications that can be used for the treatment of PS include salicylic acid and coal tar, and both are recommended for the treatment of mild to moderate psoriasis.(2) Salicylic acid is an effective treatment as monotherapy,

	or it can be combined with a TCS or TCI to increase efficacy and the penetration of the combined agent.(2,7) Coal tar may be combined with phototherapy to reduce the time of clearance and improve therapeutic outcomes compared to phototherapy alone. Topical anthralin is also an effective treatment for mild to moderate psoriasis.(2) For the treatment of PS in the pediatric patient population, topical corticosteroids are the mainstay option based on extensive clinical experience that supports efficacy. Topical calcineurin inhibitors are also a treatment option and may be preferred for psoriasis of the face, genitalia, and body folds. Vitamin D analogues are recommended as a treatment option for childhood plaque psoriasis and are considered safe, effective, and generally well tolerated. Vitamin D analogues are frequently used in combination with TCS. Other topical therapies that may be used for the treatment of pediatric psoriasis include tazarotene, anthralin, and coal tar.(5)
Efficacy	Two multicenter, randomized, double-blind, vehicle-controlled trials were conducted to evaluate the safety and efficacy of VTAMA cream for the treatment of adults with plaque psoriasis (PSOARING 1 [NCT03956355] and PSOARING 2 [NCT03983980]). These trials were conducted in a total of 1025 subjects randomized 2:1 to VTAMA cream or vehicle cream applied once daily for 12 weeks to any lesion regardless of anatomic location. Baseline disease severity was graded using the 5-point Physician's Global Assessment (PGA). The majority of subjects had "Moderate" disease (82%), while 10% had "Mild" disease, and 8% had "Severe" disease at baseline. The extent of disease involvement assessed by mean body surface area (BSA), excluding the scalp, palms, and soles, was 8% (range 3 to 20%).(1) The primary efficacy endpoint in both studies was the proportion of subjects who achieved treatment success, defined as a PGA score of "Clear" (0) or "Almost Clear" (1) and at least a 2-grade improvement from baseline. At week 12, patients treated with VTAMA achieved treatment success at a 29% greater rate than placebo in PSOARING 1 and at a 34% greater rate than placebo in PSOARING 2. Following 12 weeks of treatment, 73 subjects randomized to VTAMA achieved complete disease clearance (PGA 0) and had VTAMA withdrawn. These subjects were followed for up to 40 additional weeks with a median time to first worsening (PGA greater than or equal to 2 ["Mild"]) of 114 days (95% CI: 85, 142).(1)
Safety	VTAMA does not have any FDA labeled contraindications for use.(1)

REFERENCES

Number	Reference
1	VTAMA prescribing information. Dermavent Sciences Inc. December 2023.
2	Elmets CA, Korman NJ, Prater EF, et al. Joint AAD–NPF Guidelines of care for the management and treatment of psoriasis with topical therapy and alternative medicine modalities for psoriasis severity measures. *Journal of the American Academy of Dermatology*. 2021;84(2):432-470. doi:10.1016/j.jaad.2020.07.087
3	Menter A, Gelfand JM, Connor C, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management of psoriasis with systemic nonbiologic therapies. *Journal of the American Academy of Dermatology*. 2020;82(6):1445-1486. doi:10.1016/j.jaad.2020.02.044
4	Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *Journal of the American Academy of Dermatology*. 2019;80(4):1029-1072. doi:10.1016/j.jaad.2018.11.057
5	Menter A, Cordoro KM, Davis DMR, et al. Joint American Academy of Dermatology–National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis in pediatric patients. *Journal of the American Academy of Dermatology*. 2020;82(1):161-201. doi:10.1016/j.jaad.2019.08.049
6	Garner KK, Hoy KDS, Carpenter AM. Psoriasis: Recognition and Management Strategies. *Am Fam Physician*. 2023;108(6):562-573.
7	Shreiber AM, Friery E. Psoriasis: Update on topical therapy from the American Academy of Dermatology. *Am Fam Physician*. 2022;105(5):558-560.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following A. The patient has a diagnosis of plaque psoriasis AND ALL of the following: 1. The patient's affected body surface area (BSA) is less than or equal to 20% **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to a topical corticosteroid used in the treatment of plaque psoriasis after at least a 2-week duration of therapy **OR** B. The patient has an intolerance or hypersensitivity to therapy with a topical corticosteroid used in the treatment of plaque psoriasis **OR** C. The patient has an FDA labeled contraindication to ALL topical corticosteroids used in the treatment of plaque psoriasis **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response to another topical psoriasis agent with a different mechanism of action (e.g., vitamin D analogs, calcineurin inhibitors, tazarotene) **OR** B. The patient has an intolerance or hypersensitivity to another topical psoriasis agent with a different mechanism of action **OR** C. The patient has an FDA labeled contraindication to ALL other topical psoriasis agents with a different mechanism of action **OR** B. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., dermatologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months

Module	Clinical Criteria for Approval
	Renewal Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., dermatologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months

Weight Management

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#

Saxenda®
 	
(liraglutide)
 	
Subcutaneous injection solution
	Adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in:
	
	• Adults with an initial body mass index (BMI) of:
	  ○ 30 kg/m^2 or greater (obese), or
	  ○ 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia)
	• Pediatric patients aged 12 years or older with:
	  ○ Body weight above 60 kg, and
	  ○ An initial BMI corresponding to greater than 30 kg/m^2 for adults (obese) by international cut-offs (Cole Criteria)
	
	Limitations of Use:
	
	• Contains liraglutide and should not be coadministered with other liraglutide-containing products or with any other GLP-1 receptor agonist
	• The safety and effectiveness in pediatric patients with type 2 diabetes have not been established
	• The safety and efficacy of Saxenda in combination with other products intended for weight loss have not been established
			1

Wegovy® (semaglutide) Subcutaneous injection solution	In combination with a reduced calorie diet and increased physical activity: • To reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with		2

Agent(s)	FDA Indication(s)	Notes	Ref#

	established cardiovascular disease and either obesity or overweight
	• To reduce excess body weight and maintain weight reduction long term in:
	  ○ Adults and pediatric patients aged 12 years and older with obesity
	  ○ Adults overweight in the presence of at least one weight-related comorbid condition
	
	Limitations of Use: Coadministration with other semaglutide-containing products or with any other GLP-1 receptor agonist is not recommended		

Zepbound® (tirzepatide) Subcutaneous injection solution Vial	As an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of: • 30 kg/m2 or greater (obesity) or • 27 kg/m2 or greater (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidemia, type 2 diabetes mellitus, obstructive sleep apnea or cardiovascular disease). Limitations of Use: • Coadministration with other tirzepatide-containing products or any GLP-1 receptor agonist is not recommended. • The safety and efficacy of coadministration with other products for weight management have not been established. • Zepbound has not been studied in patients with a history of pancreatitis.		3

CLINICAL RATIONALE

Obesity	Obesity rates have increased sharply over the last 30 years, creating a global public health crisis. The National Health and Nutrition Examination Surveys show

	that nearly 2 of 3 US adults are overweight or obese, and 1 of 3 adults are obese. Adults with body mass index (BMI) 25-29.9 kg/m^2 are considered overweight; those with BMI greater than or equal to 30 kg/m^2 are considered obese.(5) Weight loss is difficult for most people and weight loss medications help reinforce behavioral strategies to lose weight. Medications for weight loss do not work on their own. Numerous guidelines recommend the addition of weight loss medications only in conjunction with lifestyle and behavioral modifications.(4,5,6,11)
	
	GLP-1 is an endogenous incretin hormone produced by L cells within the intestinal mucosa in response to the intake of nutrients. GLP-1 receptors are expressed in multiple organs, including pancreas, gastrointestinal (GI) tract, heart, brain, kidney, lung, and thyroid. This ubiquitous expression of GLP-1 receptors could be the reason for its pleiotropic benefits for T2DM, weight loss, and cardio protection. GLP-1 has numerous metabolic effects, including but not limited to, glucose-dependent stimulation of insulin secretion, delayed gastric emptying, inhibition of food intake, and modulation of β-cell proliferation. Semaglutide was approved for the management of obesity in 2021. Having a dose–response effect on weight loss, semaglutide was approved at doses higher than indicated for T2DM. GLP-1 RAs do not have the same neuropsychiatric adverse effects as other FDA-approved drugs on the market. Other benefits include inherent glucoregulatory properties and cardio protection in select populations.(11)
	
	The American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity recommends the following:(5)
	
	• The principal outcome and therapeutic target in the treatment of obesity should be to improve the health of the patient by preventing or treating weight related complications using weight loss, not the loss of body weight per se
	• For overweight (BMI 25-29.9 kg/m^2) or obese (BMI greater than or equal to 30 kg/m^2) patients, evaluate for adiposity related complications (e.g., type 2 diabetes, dyslipidemia, hypertension, cardiovascular disease, obstructive sleep apnea).
	• Pharmaceutical therapy should only be used as adjunct to lifestyle modifications and depends on the staging of obesity:
	  ○ Overweight Stage 0 (BMI 25-29.9 kg/m^2 or 23-24.9 kg/m^2 in certain ethnicities* with no complications)
	  ▪ Lifestyle therapy – reduced-calorie healthy meal plan/physical activity/behavioral interventions

	○ Obesity Stage 0 (BMI greater than or equal to 30 kg/m^2 or greater than or equal to 25 kg/m^2 in certain ethnicities* with no complications) ▪ Lifestyle therapy – reduced-calorie healthy meal plan/physical activity/behavioral intervention ▪ Weight loss medications – consider if lifestyle therapy fails to prevent progressive weight gain (BMI greater than or equal to 27 kg/m^2) ○ Obesity Stage 1 (BMI greater than or equal to 25 kg/m^2 or greater than or equal to 23 kg/m^2 in certain ethnicities* with greater than or equal to 1 mild/moderate complications) ▪ Lifestyle therapy – reduced-calorie healthy meal plan/physical activity/behavioral interventions ▪ Weight loss medications – consider if lifestyle therapy fails to achieve therapeutic target or initiate concurrently with lifestyle therapy (BMI greater than or equal to 27 kg/m^2) ○ Obesity Stage 2 (BMI greater than or equal to 25 kg/m^2 or greater than or equal to 23 kg/m^2 in certain ethnicities* with greater than or equal to 1 severe complications): ▪ Lifestyle therapy – reduced-calorie healthy meal plan/physical activity/behavioral interventions ▪ Weight loss medication – initiate concurrently with lifestyle therapy (BMI greater than or equal to 27 kg/m^2) ▪ Consider bariatric surgery (BMI greater than or equal to 35 kg/m^2) *Certain ethnicities (A BMI cutoff point value of greater than or equal to 23 kg/m^2 should be used in the screening and confirmation of excess adiposity in South Asian, Southeast Asian, and East Asian adults) The Endocrine Society clinical practice guidelines suggests medications approved for chronic weight management can be useful adjuncts to lifestyle change for patients who have been unsuccessful with diet and exercise alone. They recommend adherence to American Heart Association Guidelines (2013) [see below] which include advice for assessment and treatment with diet and exercise, as well as bariatric surgery for appropriate candidates.(4) • Diet, exercise, and behavioral modification should be included in all overweight and obesity management approaches for BMI greater than or equal to 25 kg/m^2 and other tools [e.g., pharmacotherapy (if BMI greater than or equal to 27 kg/m^2 with comorbidity or BMI greater than 30 kg/m^2) and bariatric surgery (BMI greater than or equal to 35

	kg/m^2 with comorbidity or BMI greater than 40 kg/m^2)] should be used as adjuncts to behavioral modification to reduce food intake and increase physical activity when possible. Patients who have a history of being unable to successfully lose and maintain weight and who meet label indications are candidates for weight loss medications. • Assessment of efficacy and safety of prescribed weight loss medications should be performed at least monthly for the first 3 months, then at least every 3 months thereafter. • Clinicians are recommended to perform annual and symptom-based screening for major obesity related chronic conditions in all adult patients with a BMI greater than or equal to 30 kg/m^2, including diabetes, cardiovascular disease, hypertension, hyperlipidemia, obstructive sleep apnea, non-alcoholic fatty liver disease, osteoarthritis, and major depression. • Prescribers should identify chronic medications, for concomitant medical conditions, that contribute to weight gain, and prescribe drugs that are weight neutral or that will promote weight loss when possible. • If a patient's response to a weight loss medication is deemed effective (weight loss greater than or equal to 5% of body weight at 3 months) and safe, it is recommended that the medication be continued. If deemed ineffective (weight loss less than 5% at 3 months) or if there are safety or tolerability issues at any time, the medication should be discontinued and alternative medications or referral for alternative treatment approaches instead considered. The American Heart Association/American College of Cardiology/Obesity Society Guideline (2013) suggests if weight and lifestyle history indicates the patient has never participated in a comprehensive lifestyle intervention program as defined in the guidelines (i.e., trained interventionist or nutritional professional supervision of diet, exercise, and behavior therapy), it is recommended that the patient undertake such a program before addition of adjunctive therapies (e.g., pharmacotherapy), since a substantial proportion of patients will lose sufficient weight to improve health with comprehensive lifestyle management alone. If a patient has been unable to lose weight or sustain weight loss with comprehensive lifestyle intervention and has BMI greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 with greater than or equal to 1 obesity-associated comorbid condition(s), adjunctive therapy may be considered. The expert panel did not review comprehensive evidence on pharmacotherapy for weight loss. Medications should be FDA approved and clinicians should be knowledgeable about the product label. The provider should weigh potential risks of the medication vs. potential benefits of successful weight loss for the individual patient. If the patient is currently taking an obesity medication but has

	not lost at least 5% of initial body weight after 12 weeks on a maximal dose of the medication, the provider should reassess the risk-to-benefit ratio of that medication for the patient and consider discontinuation of that drug.(6) The American Gastroenterological Association (AGA) clinical practice guidelines (2022) strongly recommended the use of pharmacotherapy in addition to lifestyle intervention in adults with overweight and obesity (body mass index 30 kg/m^2 or greater, or 27 kg/m^2 or greater with weight-related complications) who have an inadequate response to lifestyle interventions. The panel suggested the use of semaglutide 2.4 mg, liraglutide 3.0 mg, phentermine-topiramate ER, and naltrexone-bupropion ER (based on moderate certainty evidence), and phentermine and diethylpropion (based on low certainty evidence), for long-term management of overweight and obesity. The guideline panel suggested against the use of orlistat. The panel identified the use of Gelesis100 oral superabsorbent hydrogel as a knowledge gap.(11)
Pediatric Obesity	Pediatric obesity has become an epidemic and international problem. In the United States, the prevalence of obesity in children has risen from 5% in 1970 to 17% in 2004. Genetics and environment are the underlying causes of the increase in pediatric obesity. Obese children and adolescents are at risk of developing the same comorbid conditions as obese and overweight adults. Obesity and overweight in children are defined on percentages specific for age and gender defined BMI values. The American Academy of Pediatrics (AAP) define obesity as a BMI greater than or equal to 95th percentile or a BMI greater than or equal to 30 kg/m^2, whichever is lower, and overweight as a BMI within 85th to 94th percentile for children and adolescents 2 years of age and older.(9,10) The AAP recommends that clinicians should assess medical and behavioral risks in any child with a BMI above the 85th percentile before initiating any intervention.(9,10) The Endocrine Society Pediatric Obesity Treatment Guidelines also recommend that clinicians should evaluate for potential comorbidities in children and adolescents with a BMI greater than or equal to 85th percentile.(8) The 2023 AAP guidelines recommend the use of weight loss agents in conjunction with lifestyle and behavioral changes. Pediatricians and other primary healthcare providers should treat children and adolescents for overweight with comorbidities (BMI greater than or equal to 85th percentile; comorbidities such as dyslipidemia, prediabetes, Type 2 diabetes, fatty liver disease, hypertension) and obesity (BMI greater than or equal to 95th percentile).(10)

	The 2017 Endocrine Society guidelines only recommend the use of FDA approved pharmacotherapy in pediatric patients as adjunctive therapy to lifestyle modifications of the highest intensity available and only by clinicians that are experienced in the use of anti-obesity agents.(8) • Suggest pharmacotherapy in children or adolescents with obesity (greater than or equal to 95th percentile for age and gender) only after a formal program of intense lifestyle modifications has failed to limit weight gain or to ameliorate comorbidities. • Recommend against using obesity agents in children and adolescents less than 16 years of age who are overweight, but not obese, except in the context of clinical trials. • Anti-obesity agents should be discontinued, and patients reevaluated if the patient does not have a greater than 4% BMI reduction after 12 weeks at the medication's full dosage. • Discourages prescribing weight loss medications off-label to pediatric patients less than 16 years of age.

Cardiovascular	Wegovy (semaglutide) was studied to determine its effect relative to placebo on major adverse cardiovascular events (MACE) when added to current standard of care, which included management of cardiovascular risk factors and individualized healthy lifestyle counseling (including diet and physical activity), in patients who are overweight or with obesity, and without diabetes. The primary endpoint, MACE, was the time to first occurrence of a three-part composite outcome which included cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. Inclusion requirements of the trial included:(12)
	
	• Patients who have established cardiovascular disease (CVD) as determined by having at least one of the following:
	  ○ Prior myocardial infarction
	  ○ Prior stroke (ischemic or hemorrhagic stroke)
	  ○ Symptomatic peripheral arterial disease (intermittent claudication with ankle-brachial index <0.85 (at rest), peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease)
	• Patients with a BMI greater than or equal to 27 kg/m^2
	• Patients 45 years of age or over
	
	Guidelines recommend that patients work towards a goal of tobacco cessation and avoiding tobacco exposure, managing hypertension to goal, and managing

	lipid levels to goal as risk reduction measures for CVD secondary prevention.(13,14,15)
Metabolic dysfunction-associated steatotic liver disease (MASLD)/Metabolic dysfunction-associated steatohepatitis (MASH)	Metabolic dysfunction-associated steatotic liver disease (MASLD), previously termed non-alcoholic fatty liver disease (NAFLD), is defined as steatotic liver disease (SLD) in the presence of one or more cardiometabolic risk factor(s) and the absence of harmful alcohol intake. SLD occurs when your body begins storing fat in your liver. While some fat in your liver is normal, when more than 5 to 10% of the liver's weight is fat, it is classified as steatosis. MASLD and ALD (alcohol intake >50 g/day for females and >60 g/day for males) comprise the most common causes of SLD. A new category, requiring further characterization, termed MetALD, describes those with MASLD who consume greater amounts of alcohol (20-50 g/day for females and 30-60 g/day for males, respectively), but do not meet the criteria for ALD. The history of alcohol consumption is an important factor as the current drinking pattern may not necessarily reflect previous drinking behavior. Importantly, despite sharing the same prevalence of cardiometabolic risk factors, MetALD is associated with a higher risk of all-cause mortality, underpinning MetALD as a distinct subclass of SLD with poorer prognosis. Therefore, diagnostic and treatment recommendations provided for MASLD cannot be extended to the MetALD population.(19,22,27,28) The spectrum of MASLD includes steatosis, metabolic dysfunction-associated steatohepatitis (MASH, previously NASH), fibrosis, cirrhosis and MASH-related hepatocellular carcinoma (HCC). With MASH, fat buildup progresses to inflammation, then tissue damage and scarring (fibrosis). Metabolic dysfunction-associated steatohepatitis (MASH) is inflammation of the liver caused by excess fat cell deposits in it (steatotic liver disease). MASH is characterized by histological features of hepatocellular ballooning and lobular inflammation. Chronic inflammation causes progressive liver damage. MASL refers to the presence of MASLD in the absence of steatohepatitis.(19,27,28) Metabolic dysfunction-associated steatotic liver disease (MASLD) has become the most common chronic liver disease, and its prevalence will likely continue to rise. Often, MASLD has no symptoms. When symptoms do occur, they may include fatigue, weakness, weight loss, loss of appetite, nausea, abdominal pain, spider-like blood vessels, yellowing of the skin and eyes (jaundice), itching, fluid buildup and swelling of the legs (edema) and abdomen (ascites), and mental confusion. MASLD is initially suspected if blood tests show high levels of liver enzymes with an absence of chronic alcohol intake. However, other liver

	diseases are first ruled out through additional tests (e.g., Wilson's disease, hepatitis).(19,20,21)
	
	The presence of MASLD is tightly linked to type 2 diabetes (T2D), obesity and other cardiometabolic risk factors. Studies suggest that one-third to two-thirds of people with type 2 diabetes have MASLD. Research suggests that MASLD is present in up to 75% of people who are overweight and in more than 90% of people who have severe obesity. MASLD is associated with an increased risk of cardiovascular events, chronic kidney disease, hepatic and extrahepatic malignancies, and liver-related outcomes, including liver failure and hepatocellular carcinoma (HCC). Therefore, the high socio-economic burden of MASLD poses a global health challenge that needs to be addressed by medical societies and policymakers.(19,27,28)
	
	The following are the adult cardiometabolic risk factors (at least 1 out of 5) in the definition of MASLD:(27,28)
	
	• Weight (BMI or WC) Overweight or Obesity Body mass index(BMI):
	  ○ Greater than or equal to 25 kg/m^2 (greater than or equal to 23 kg/m^2 in people of Asian ethnicity) OR
	  ○ Waist Circumference (WC): 94 cm (male), 80 cm (female) or ethnicity adjusted equivalent
	• Prediabetes or type 2 diabetes:
	  ○ Fasting serum glucose greater than or equal to 5.6 mmol/L (100mg/dL) OR
	  ○ 2-hour post load glucose levels greater than or equal to 7.8 mmol/L (greater than or equal to 140 mg/dL) OR
	  ○ HbA1c greater than or equal to 5.7% OR
	  ○ Type 2 diabetes OR
	  ○ Treatment for type 2 diabetes
	• Plasma triglycerides:
	  ○ Greater than or equal to 1.7 mmol/L (greater than or equal to 150 mg/dL) OR
	  ○ Lipid-lowering treatment
	• HDL cholesterol:
	  ○ Less than or equal to 1.0 mmol/L (less than or equal to 39 mg/dL) in men and less than or equal to 1.3 mmol/L (less than or equal to 50 mg/dL) in women OR
	  ○ Lipid-lowering treatment
	• Blood pressure:
	  ○ Greater than or equal to 130/85 mmHG OR

	○ Specific antihypertensive drug treatment The 2021 AACE and 2023 AASLD practice guidelines suggest the following: Clinicians should identify individuals with obesity, metabolic syndrome traits, pre-diabetes, or type 2 diabetes, as well as those showing hepatic steatosis on imaging or persistently high plasma aminotransferase levels (over six months) as "high risk" and recommend screening for NAFLD/MASLD and advanced fibrosis. Metabolic syndrome is characterized by any three of the following: obesity, hypertension, high blood triglycerides, low HDL cholesterol, and insulin resistance.(19,21) An initial evaluation for individuals suspected of having hepatic steatosis based on imaging findings should include tests to rule out other causes of liver disease (e.g., hepatitis B and C serology, autoantibody panels, and metabolic syndrome evaluations). It's important to note that many laboratory normal ranges are higher than the accepted thresholds for NAFLD/MASLD, where normal alanine aminotransferase (ALT) levels typically range from 29 to 33 U/L in men and from 19 to 25 U/L in women.(19,21,22) The American Gastroenterology Association (AGA) guidelines recommend best practices for diagnosing MASH/MASLD:(24) • A Fibrosis 4 Index score below 1.3 is linked with a strong negative predictive value for advanced hepatic fibrosis and may be helpful in ruling out advanced fibrosis in NAFLD/MASLD patients • A combination of two or more NITs, incorporating serum biomarkers and/or imaging biomarkers, should be used for staging and risk assessment • In patients with a Fibrosis 4 Index score above 1.3. FIB-4 risk categories from low risk (<1.3) to intermediate risk (1.3–2.67) to high risk (>2.67) can be used to evaluate clinical progression • NITs should be evaluated in the context of relevant clinical data (e.g., physical examination, biochemical tests, and imaging) to enhance positive predictive value in identifying patients with advanced fibrosis • Liver biopsy should be considered for patients with indeterminate or conflicting NIT results, discrepancies with other clinical or laboratory findings, or when other liver disease causes are suspected NITs (non-invasive tests) derived from clinical variables can estimate the presence of advanced fibrosis. Several have been developed (e.g., FIB-4, NAFLD/MASLD Fibrosis Score, AST Platelet Ratio Index); however, FIB-4 is the most validated. FIB-4 is calculated using a simple algorithm based upon age,

	ALT, AST, and platelet count and outperforms other calculations in its ability to identify patients with a low probability of advanced fibrosis. The FIB-4 index can be calculated from age and three parameters obtained in routine laboratory assessments: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet count. A change in FIB-4 status category from low risk (<1.3) to intermediate risk (1.3–2.67) to high risk (>2.67) may be used to assess clinical progression. Although FIB-4 is statistically inferior to other serum-based fibrosis markers such as the Enhanced Liver Fibrosis (ELF) panel, FIBROSpect II, and imaging-based elastography methods to detect advanced fibrosis, FIB-4 is still recommended as a first-line assessment for general practitioners and endocrinologists based on its simplicity and minimal added cost.(19,23,24) Those who may have a moderate or high risk of advanced disease based on FIB-4 should undergo secondary risk assessment. Vibration-controlled transient elastography (VCTE) (e.g., FibroScan) is the most commonly used method to assess liver stiffness and can be used to exclude significant hepatic fibrosis. Magnetic resonance elastography (MRE) is more sensitive than VCTE in the detection of fibrosis stage greater than 2 and is considered to be the most accurate noninvasive imaging-based biomarker of fibrosis in NAFLD/MASLD. Although MRE is not a first-line approach to risk stratification in a patient with NAFLD/MASLD, it can be an important tool if clinical uncertainty exists, if there is a need for concomitant cross-sectional imaging, or when other elastography techniques are unavailable. Among patients with cirrhosis, a baseline liver stiffness measure (LSM) by MRE predicts future risk of incident hepatic decompensation and death. Controlled Attenuation Parameter (CAP) as a point-of-care technique may also be used to identify steatosis. A liver biopsy is the optimal approach to confirm the diagnosis and stage of the severity of liver fibrosis. However, it is recognized that this may not be feasible or acceptable to several individuals.(19,23,24) Research findings have suggested that patients with NAFLD/MASLD exhibit lower levels of biologically active incretin hormones when compared to healthy individuals and this may be attributed to either an increased degradation of these hormones by dipeptidyl peptidase-4 (DPP-4) or a diminished production of these hormones. GLP-1RAs can exert control over energy intake and weight gain through mechanisms such as prolonging gastric emptying and suppressing appetite. These effects help regulate food consumption and contribute to weight management. Additionally, GLP-1RAs have shown the ability to enhance liver enzyme functions, alleviate liver steatosis, and notably reduce liver fat content. Semaglutide, a second-generation GLP-1-RA, is available in both oral (daily administration) and subcutaneous (weekly administration) formulations. Clinical studies have provided evidence of the favorable effects of semaglutide in

	patients with NAFLD/MASLD. Nevertheless, there is a lack of comprehensive systematic reviews or meta-analyses that have extensively summarized and quantified these effects. Hence, this systematic review and meta-analysis aimed to evaluate the influence of a 24-week administration of semaglutide in patients with NAFLD/MASLD or NASH/MASH.(18) A systematic review and meta-analysis was conducted (six hundred studies were screened and eight were included) to evaluate the efficacy and safety of 24 weeks of semaglutide treatment in patients with NAFLD/MASLD or NASH/MASH. The following were concluded:(18) • Semaglutide could be used in patients with non-alcoholic fatty liver disease or non-alcoholic steatohepatitis • It significantly improves liver enzymes, reduces liver stiffness, and improves metabolic parameters in these patients • Gastrointestinal adverse effects and gallbladder-related diseases could be a major concern The 2024 European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) guidelines suggest in adults with MASLD, lifestyle modification which includes weight loss, dietary changes, physical exercise and discouraging alcohol consumption. In addition, they recommend optimal management of comorbidities, including use of incretin-based therapies (e.g., semaglutide, tirzepatide) for type 2 diabetes or obesity, if indicated. Bariatric surgery is also an option in individuals with MASLD and obesity. If locally approved and dependent on the label, adults with non-cirrhotic MASH and significant liver fibrosis (stage greater than or equal 2) should be considered for a MASH-targeted treatment with resmetirom, which demonstrated histological effectiveness on steatohepatitis and fibrosis with an acceptable safety and tolerability profile. No MASH-targeted pharmacotherapy can currently be recommended for the cirrhotic stage. Management of MASH-related cirrhosis includes adaptations of metabolic drugs, nutritional counselling, surveillance for portal hypertension and HCC, as well as liver transplantation in decompensated cirrhosis.(27) While an initial study with liraglutide indicated a histological benefit in MASH, drugs that are being developed for MASH now include semaglutide, and dual GLP1-GIP (e.g., tirzepatide), dual GLP1-glucagon (e.g., cotadutide, survodutide, efinopegdutide) or triple GLP1-GIP-glucagon (e.g., retatrutide) agonists. The largest available trial on semaglutide in MASH (vs. placebo over an 18-month treatment period) demonstrated resolution of steatohepatitis but no fibrosis

	improvement. A large registrational, phase III study with semaglutide is ongoing. Combining semaglutide with lipogenesis inhibitors may provide additional benefit and such approaches are being tested in larger trials. Histology data are not yet available for the newer dual and triple agonists. Tirzepatide (GLP1-GIP RA) has been shown to significantly reduce both liver and visceral fat in those with type 2 diabetes, in association with major weight loss (comparable to bariatric surgery), and promising results on steatohepatitis resolution from a phase II study in MASH have been communicated. Dual GLP1-glucagon RAs (cotadutide and efinopegdutide) have also been shown to improve liver steatosis, liver enzymes and indexes of fibrosis in individuals with MASLD.(17,27)
Efficacy	SELECT Trial (Wegovy) Study 1 (NCT03574597) was a multi-national, multi-center, placebo-controlled, double-blind trial to determine the effect of Wegovy relative to placebo on major adverse cardiovascular events (MACE) when added to current standard of care, which included management of CV risk factors and individualized healthy lifestyle counseling (including diet and physical activity). The primary endpoint, MACE, was the time to first occurrence of a three-part composite outcome which included cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. All patients were 45 years or older, with an initial BMI of 27 kg/m2 or greater and established cardiovascular disease (prior myocardial infarction, prior stroke, or peripheral arterial disease). Patients with a history of type 1 or type 2 diabetes were excluded.(2) In this trial, 17,604 patients were randomized to Wegovy or placebo. At baseline, the mean age was 62 years and 12,732 patients (72.3%) were male. The mean BMI was 33 kg/m^2, and 12,580 patients (71.5%) met the BMI criterion for obesity (≥30). The mean glycated hemoglobin level was 5.8%, and 11,696 patients (66.4%) met the glycated hemoglobin criterion for prediabetes (defined as a mean level of 5.7 to 6.4%). At baseline, prior myocardial infarction was reported in 76% of randomized individuals, prior stroke in 23%, and peripheral arterial disease in 9%. Heart failure was reported in 24% of patients. At baseline, cardiovascular disease and risk factors were managed with lipid lowering therapy (90%), platelet aggregation inhibitors (86%), angiotensin converting enzyme inhibitors or angiotensin II receptor blockers (74%), and beta blockers (70%). A total of 10% had moderate renal impairment (eGFR 30 to <60 mL/min/1.73m2) and 0.4% had severe renal impairment eGFR <30 mL/min/1.73m2.(2,16)

	Patients were randomly assigned, with the use of a centralized system in a double-blind manner and in a 1:1 ratio without stratification, to receive once-weekly subcutaneous semaglutide at a dose of 2.4 mg or placebo. The starting dose of semaglutide was 0.24 mg once weekly, and the dose was increased every 4 weeks (to once weekly doses of 0.5, 1.0, 1.7, and 2.4 mg) until the target dose of 2.4 mg was reached after 16 weeks. If dose escalation led to unacceptable adverse effects, the dose-escalation intervals could be extended, treatment could be paused, or maintenance doses below the 2.4 mg per week target dose could be used.(16) Among the 17,604 patients with a BMI of 27 or greater and preexisting cardiovascular disease but without diabetes, treatment with once-weekly subcutaneous semaglutide at a dose of 2.4 mg for a mean duration of 33 months reduced the risk of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke by 20% (hazard ratio, 0.80; 95% CI, 0.72 to 0.90). NASH Trial A 72-week, double-blind phase 2 trial (NCT02970942) involving patients with biopsy-confirmed NASH and liver fibrosis of stage F1, F2, or F3 patients were randomly assigned to receive once-daily subcutaneous semaglutide at a dose of 0.1, 0.2, or 0.4 mg or corresponding placebo. The primary end point was resolution of NASH with no worsening of fibrosis. The confirmatory secondary end point was an improvement of at least one fibrosis stage with no worsening of NASH. The analyses of these end points were performed only in patients with stage F2 or F3 fibrosis; other analyses were performed in all the patients.(25) In total, 320 patients (of whom 230 had stage F2 or F3 fibrosis) were randomly assigned to receive semaglutide at a dose of 0.1 mg (80 patients), 0.2 mg (78 patients), or 0.4 mg (82 patients) or to receive placebo (80 patients). The percentage of patients in whom NASH resolution was achieved with no worsening of fibrosis was 40% in the 0.1-mg group, 36% in the 0.2-mg group, 59% in the 0.4-mg group, and 17% in the placebo group (P<0.001 for semaglutide 0.4 mg vs. placebo). An improvement in fibrosis stage occurred in 43% of the patients in the 0.4-mg group and in 33% of the patients in the placebo group (P = 0.48). The mean percent weight loss was 13% in the 0.4-mg group and 1% in the placebo group.(17,25,26) This phase 2 trial involving patients with NASH showed that treatment with semaglutide resulted in a significantly higher percentage of patients with NASH resolution than placebo. However, the trial did not show a significant between-

	group difference in the percentage of patients with an improvement in fibrosis stage.(25)

Safety	Liraglutide has the following:(1)
	
	• Contraindications:
	  ○ Patients with a personal or family history of medullary thyroid carcinoma (MTC) or patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
	  ○ Patients with a prior serious hypersensitivity reaction to liraglutide or to any of the product components.
	  ○ Pregnancy
	• Boxed warnings:
	  ○ Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Saxenda causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.
	  ○ Saxenda is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC with use of Saxenda and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Saxenda.
	
	Semaglutide has the following:(2)
	
	• Contraindications:
	  ○ Personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
	  ○ Known hypersensitivity to semaglutide or any of the excipients in Wegovy.
	• Boxed warnings:
	  ○ In rodents, semaglutide causes thyroid C-cell tumors at clinically relevant exposures. It is unknown whether Wegovy causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in

	humans as the human relevance of semaglutide-induced rodent thyroid C-cell tumors has not been determined ○ Wegovy is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors Tirzepatide has the following:(3) • Contraindications: ○ Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2. ○ Known serious hypersensitivity to tirzepatide or any of the excipients in Zepbound. • Boxed warnings: ○ In rats, tirzepatide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether Zepbound causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined. ○ Zepbound is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk for MTC with the use of Zepbound and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with Zepbound. **Co-Administration** None of the FDA approved weight loss agents have approval for co-administration with another weight loss agent. New guidelines do not support the use of co-administration of weight loss pharmacological agents.(4,5,10) Use of non-approved drug combinations for obesity treatment should be limited to clinical trials, and patients should be informed when drugs are being used off label alone or in combination.(6)

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ADDITIONAL QUANTITY LIMIT INFORMATION

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
6125207000D520	Wegovy	Semaglutide (Weight Mngmt) Soln Auto-Injector	0.25 MG/0.5ML	*This strength is not approvable for			

Wildcard	Target Brand Agent Name(s)	Target Generic Agent Name(s)	Strength	Additional QL Information	Targeted NDCs When Exclusions Exist	Effective Date	Term Date
				maintenance dosing			
6125207000D525	Wegovy	Semaglutide (Weight Mngmt) Soln Auto-Injector	0.5 MG/0.5ML	*This strength is not approvable for maintenance dosing for pediatric patients			
6125207000D530	Wegovy	Semaglutide (Weight Mngmt) Soln Auto-Injector	1 MG/0.5ML	*This strength is not approvable for maintenance dosing for pediatric patients			
61252580002018	Zepbound	tirzepatide (weight mngmt) soln	2.5 MG/0.5ML	*This strength is not approvable for maintenance dosing			
6125258000D520	Zepbound	tirzepatide (weight mngmt) soln auto-injector	2.5 MG/0.5ML	*This strength is not approvable for maintenance dosing			

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Rebate Eligible	**Initial Evaluation** **Target Agent(s)** will be approved when ALL the following are met: 1. ONE of the following: A. The patient has a diagnosis of noncirrhotic nonalcoholic steatohepatitis (NASH) or metabolic dysfunction associated steatohepatitis (MASH) (medical records required) AND ALL of the following: 1. The patient has stage F1, F2, or F3 fibrosis as confirmed by BOTH of the following (prior to therapy with the requested agent): A. A FIB-4 score consistent with stage F1, F2, or F3 fibrosis adjusted for age **AND** B. The patient has ONE of the following: 1. A liver biopsy **OR** 2. Vibration-controlled transient elastography (VCTE, e.g., Fibroscan) **OR** 3. Enhanced liver fibrosis (ELF) score **OR** 4. Magnetic resonance elastography (MRE) **AND** 2. The requested agent is Wegovy **AND** 3. The patient is an adult (18 years of age or over) **AND** 4. The patient has ONE of the following: A. A BMI greater than 25 kg/m^2 **OR** B. A BMI greater than 23 kg/m^2 if the patient is of South Asian, Southeast Asian, or East Asian descent **AND** 5. ONE of the following: A. If the patient's sex is female then the patient's alcohol consumption is less than 20 grams/day (Note: one standard alcoholic drink contains roughly 14 grams of pure alcohol, which is found in 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of distilled spirits) **OR** B. If the patient's sex is male then the patient's alcohol consumption is less than 30 grams/day (Note: one standard alcoholic drink contains roughly 14 grams of pure alcohol, which is found in 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of distilled spirits) **AND** 6. The patient does NOT have ANY of the following: A. Decompensated cirrhosis **AND** B. Moderate to severe hepatic impairment (Child-Pugh Class B or C) **AND** C. Any other liver disease (e.g., Wilson's disease, hepatocellular carcinoma, hepatitis) **AND**

Module	Clinical Criteria for Approval
	7. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hepatologist, gastroenterologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **OR** B. The requested use is to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease and the patient is either obese or overweight AND ALL of the following: 1. The request is for Wegovy **AND** 2. The patient has a history of ONE of the following: A. Myocardial infarction **OR** B. Stroke **OR** C. Peripheral artery disease as defined by intermittent claudication with ankle-brachial index less than 0.85 at rest, or peripheral arterial revascularization procedure, or amputation due to atherosclerotic disease **AND** 3. The patient has a BMI greater than or equal to 27 kg/m^2 **AND** 4. The patient does not have diabetes **AND** 5. The patient will maintain a reduced calorie diet and increased physical activity **AND** 6. The patient will use optimized pharmacotherapy for established cardiovascular disease in combination with the requested agent **OR** C. The patient is overweight or obese and is using the requested agent for weight management and ALL of the following: 1. Obesity is NOT restricted from coverage under the patient's benefit **AND** 2. The patient is new to therapy or attempting a repeat weight loss course of therapy **AND** 3. ONE of the following: A. The patient is an adult (18 years of age or over) AND has ONE of the following: 1. A BMI greater than or equal to 30 kg/m^2 **OR** 2. A BMI greater than or equal to 25 kg/m^2 if the patient is of South Asian, Southeast Asian, or East Asian descent **OR** 3. A BMI greater than or equal to 27 kg/m^2 with at least one weight-related comorbidity/risk factor/complication (e.g., hypertension, type 2 diabetes mellitus, obstructive sleep apnea, cardiovascular disease, dyslipidemia) **OR** B. The patient is pediatric (12 to 17 years of age) AND has ONE of the following:

Module	Clinical Criteria for Approval
	1. A BMI greater than or equal to 95th percentile for age and sex **OR** 2. A BMI greater than or equal to 30 kg/m^2 **OR** 3. A BMI greater than or equal to 85th percentile for age and sex AND at least one weight-related comorbidity/risk factor/complication **AND** 4. The patient has been on a weight loss regimen of a low-calorie diet, increased physical activity, and behavioral modifications for a minimum of 6 months **AND** 5. ONE of the following: A. The patient has NOT tried a targeted weight loss agent (e.g., Saxenda, Wegovy, Zepbound) in the past 12 months **OR** B. BOTH of the following: 1. The patient has tried a targeted weight loss agent for a previous course of therapy in the past 12 months **AND** 2. The prescriber anticipates success with repeating therapy with any targeted weight loss agent **AND** 6. If the requested agent is Saxenda, then ONE of the following: A. The patient is an adult (18 years of age or over) AND ONE of the following: 1. The patient is newly starting therapy **OR** 2. The patient is currently being treated and has received less than 16 weeks (4 months) of therapy **OR** 3. The patient has achieved and maintained a weight loss of greater than or equal to 4% from baseline (prior to initiation of pharmacotherapy) **OR** B. The patient is pediatric (12 to 17 years of age) AND BOTH of the following: 1. The requested agent is NOT being used to treat type 2 diabetes **AND** 2. ONE of the following: A. The patient is newly starting therapy **OR** B. The patient is currently being treated and has received less than 20 weeks (5 months) of therapy **OR** C. The patient has achieved and maintained a reduction in BMI of greater than or equal to 1% from baseline (prior to initiation of pharmacotherapy) **AND** 7. If the requested agent is Wegovy, then ONE of the following: A. The patient is newly starting therapy **OR**

Module	Clinical Criteria for Approval
	B. The patient is currently being treated and has received less than 52 weeks (1 year) of therapy **OR** C. The patient is an adult (18 years of age or over) AND has achieved and maintained a weight loss of greater than or equal to 5% from baseline (prior to initiation of pharmacotherapy) **OR** D. The patient is pediatric (12 to 17 years of age) AND has achieved and maintained a reduction in BMI of at least 5% from baseline (prior to initiation of pharmacotherapy) **AND** 8. If the requested agent is Zepbound, then ONE of the following: A. The patient is newly starting therapy **OR** B. The patient is currently being treated and has received less than 52 weeks (1 year) of therapy **OR** C. The patient has achieved and maintained a weight loss of greater than or equal to 5% from baseline (prior to initiation of pharmacotherapy) **OR** D. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. The patient will NOT be using the requested agent in combination with another weight loss agent (e.g., Contrave, phentermine, Qsymia, Xenical) for the requested indication **AND** 3. BOTH of the following: A. The patient is currently on a weight loss regimen of a low-calorie diet, increased physical activity, and behavioral modifications **AND** B. The patient will continue the weight loss regimen in combination with the requested agent **AND** 4. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 5. The patient will NOT be using the requested agent in combination with another GLP-1 receptor agonist (e.g., Saxenda, Wegovy, Zepbound, Mounjaro, Ozempic, Trulicity) **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 7. For Wegovy, Zepbound: 12 months 8. For Saxenda: Pediatric patients (12 to 17 years of age): 5 months; Adults: 4 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Clinical Criteria for Approval
	Renewal Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 9. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 10. ONE of the following: A. The patient has a diagnosis of noncirrhotic nonalcoholic steatohepatitis (NASH) or metabolic dysfunction associated steatohepatitis (MASH) (medical records required) AND ALL of the following: 1. The requested agent is Wegovy **AND** 2. ONE of the following: A. If the patient's sex is female then the patient's alcohol consumption is less than 20 grams/day (Note: one standard alcoholic drink contains roughly 14 grams of pure alcohol, which is found in 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of distilled spirits) **OR** B. If the patient's sex is male then the patient's alcohol consumption is less than 30 grams/day (Note: one standard alcoholic drink contains roughly 14 grams of pure alcohol, which is found in 12 ounces of regular beer, 5 ounces of wine, or 1.5 ounces of distilled spirits) **AND** 3. The patient does NOT have ANY of the following: A. Decompensated cirrhosis **AND** B. Moderate to severe hepatic impairment (Child-Pugh Class B or C) **AND** C. Any other liver disease (e.g., Wilson's disease, hepatocellular carcinoma, hepatitis) **AND** 4. The patient has had clinical benefit with the requested agent **AND** 5. The prescriber is a specialist in the area of the patient's diagnosis (e.g., hepatologist, gastroenterologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **OR** B. The requested use is to reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke) in adults with established cardiovascular disease AND ALL of the following: 1. The requested agent is FDA labeled for the requested indication and route of administration **AND** 2. The patient has a history of ONE of the following: A. Myocardial infarction **OR** B. Stroke **OR** C. Peripheral artery disease as defined by intermittent claudication with ankle-brachial index less than 0.85 at rest, or peripheral arterial

Module	Clinical Criteria for Approval
	revascularization procedure, or amputation due to atherosclerotic disease **AND** 3. The patient will use optimized pharmacotherapy for established cardiovascular disease in combination with the requested agent **AND** 4. The patient has had clinical benefit with the requested agent **OR** C. The patient is overweight or obese and is using the requested agent for weight management and ALL of the following: 1. Obesity is NOT restricted from coverage under the patient's benefit **AND** 2. The patient is continuing a current weight loss course of therapy **AND** 3. If the patient is pediatric (12 to 17 years of age), then the current BMI is greater than 85th percentile for age and sex **AND** 4. The patient meets ONE of the following: A. The patient has achieved and maintained a weight loss greater than or equal to 5% from baseline (prior to the initiation of requested agent) **OR** B. If the requested agent is Saxenda, then ONE of the following: 1. The patient is pediatric (12 to 17 years of age) AND BOTH of the following: A. The requested agent is NOT being used to treat type 2 diabetes **AND** B. The patient has achieved and maintained a reduction in BMI of greater than or equal to 1% from baseline (prior to initiation of pharmacotherapy) **OR** 2. The patient is an adult (18 years of age or over) AND has achieved and maintained a weight loss greater than or equal to 4% from baseline (prior to initiation of pharmacotherapy) **OR** C. If the requested agent is Wegovy, then ONE of the following: 1. The patient has received less than 52 weeks of therapy on the maximum-tolerated dose **OR** 2. The patient is pediatric (12 to 17 years of age) AND has achieved and maintained a reduction in BMI of at least 5% from baseline (prior to initiation of pharmacotherapy) **AND** D. If the requested agent is Zepbound, the patient has received less than 52 weeks of therapy on the maximum-tolerated dose **OR** D. The patient has another FDA labeled indication for the requested agent and route of administration AND has had clinical benefit with the requested agent **AND** 11. The patient will NOT be using the requested agent in combination with another weight loss agent (e.g., Contrave, phentermine, Qsymia, Xenical) for the requested indication **AND** 12. BOTH of the following:

Module	Clinical Criteria for Approval
	A. The patient is currently on a weight loss regimen of a low-calorie diet, increased physical activity, and behavioral modifications **AND** B. The patient will continue the weight loss regimen in combination with the requested agent **AND** 13. The patient will NOT be using the requested agent in combination with another GLP-1 receptor agonist (e.g., Saxenda, Wegovy, Zepbound, Mounjaro, Ozempic, Trulicity) **AND** 14. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. If requested agent is Wegovy 0.5 mg or 1 mg AND the intended use is for maintenance therapy, then ALL of the following: 1. The patient is an adult **AND** 2. The patient has an inability to use an FDA labeled strength indicated for maintenance therapy **AND** 3. The patient has achieved weight loss on the lower requested strength from baseline (prior to initiation of pharmacotherapy) **OR** B. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** C. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** D. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Weight Loss Agents

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Adipex-P®, Lomaira™, Phentermine*~ Tablet Capsule	Short-term (a few weeks) adjunct in a regimen of weight reduction based on exercise, behavioral modification and caloric restriction in the management of exogenous obesity in patients with an initial BMI greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 in the presence of other risk factors (e.g., controlled hypertension, diabetes, hyperlipidemia).	*generic available ~ The safety and efficacy of coadministration with other weight loss drug products, including prescribed drugs, over-the-counter preparations, and herbal products have not been established. Therefore, coadministration is not recommended.	5,6,11
Benzphetamine*~ Tablet	Short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction in the management of exogenous obesity for patients with an initial body mass index greater than or equal to 30 kg/m^2 who have not responded to appropriate weight reducing regimen (diet and/or exercise) alone.	*generic available ~ The safety and efficacy of coadministration with other weight loss drug products, including prescribed drugs, over-the-counter preparations, and herbal products have not been established. Therefore,	2

Agent(s)	FDA Indication(s)	Notes	Ref#
		coadministration is not recommended.	
Contrave® (naltrexone/bupropion)~ Tablet ER	Adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of: • Greater than or equal to 30 kg/m^2 (obese), or • Greater than or equal to 27 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity (e.g., hypertension, type 2 diabetes mellitus, or dyslipidemia) Limitations of Use: • Effect on cardiovascular morbidity and mortality has not been established	~ The safety and efficacy of coadministration with other weight loss drug products, including prescribed drugs, over-the-counter preparations, and herbal products have not been established. Therefore, coadministration is not recommended.	3
Diethylpropion* Tablet Tablet ER	Short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction in the management of exogenous obesity for patients with an initial body mass index (BMI) greater than or equal to 30 kg/m^2 and who have not responded to appropriate weight reducing regimen (diet and/or exercise) alone. Indicated for use as monotherapy only.	*generic available	9
Phendimetrazine* Capsule ER	Short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction in the management of exogenous obesity for patients with an initial BMI greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 in the presence of other risk factors (e.g., controlled hypertension, diabetes, hyperlipidemia) who have not responded to appropriate weight reducing regimen alone (diet and/or exercise)	*generic available	7

Agent(s)	FDA Indication(s)	Notes	Ref#
	Indicated for use as monotherapy only.		
Phendimetrazine* Tablet	Short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction in the management of exogenous obesity for patients with an initial BMI greater than or equal to 30 kg/m^2 who have not responded to appropriate weight reducing regimen alone (diet and/or exercise). Indicated for use as monotherapy only.	*generic available	10

Qsymia®
 	
(phentermine/topiramate)~
 	
Capsule
	Adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in:
	• Adults with an initial BMI of:
	  ○ Greater than or equal to 30 kg/m^2 (obese)
	  ○ Greater than or equal to 27 kg/m^2 (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia
	• Pediatric patients aged 12 years and older with BMI in the 95th percentile or greater standardized for age and sex
	
	Limitations of Use:
	• Effect on cardiovascular morbidity and mortality has not been established
		~ The safety and efficacy of coadministration with other weight loss drug products, including prescribed drugs, over-the-counter preparations, and herbal products have not been established. Therefore, coadministration is not recommended.	1

Xenical®, Orlistat Capsule	Obesity management including weight loss and weight maintenance when used in conjunction with a reduced-calorie diet and to reduce the risk for weight regain after prior weight loss. It is indicated for obese patients with an initial body mass index (BMI) greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 in the presence of other		4,20

Agent(s)	FDA Indication(s)	Notes	Ref#
	risk factors (e.g., hypertension, diabetes, dyslipidemia)		

CLINICAL RATIONALE

Obesity	Obesity rates have increased sharply over the last 30 years, creating a global public health crisis. The National Health and Nutrition Examination Surveys show that nearly 2 of 3 US adults are overweight or obese, and 1 of 3 adults are obese. Adults with body mass index (BMI) 25-29.9 kg/m^2 are considered overweight; those with BMI greater than or equal to 30 kg/m^2 are considered obese.(14) Weight loss is difficult for most people and weight loss medications help reinforce behavioral strategies to lose weight. Medications for weight loss do not work on their own. Numerous guidelines recommend the addition of weight loss medications only in conjunction with lifestyle and behavioral modifications.(13,14,15,21)
	
	The American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity recommends the following:(14)
	
	• The principal outcome and therapeutic target in the treatment of obesity should be to improve the health of the patient by preventing or treating weight related complications using weight loss, not the loss of body weight per se
	• For overweight (BMI 25-29.9 kg/m^2) or obese (BMI greater than or equal to 30 kg/m^2) patients, evaluate for adiposity related complications:
	  ○ Metabolic syndrome
	  ○ Prediabetes
	  ○ Type 2 diabetes (T2DM)
	  ○ Dyslipidemia
	  ○ Hypertension
	  ○ Cardiovascular disease
	  ○ Non-alcoholic fatty liver disease
	  ○ Polycystic ovary syndrome
	  ○ Female infertility
	  ○ Male hypogonadism
	  ○ Obstructive sleep apnea
	  ○ Asthma/reactive airway disease

	○ Osteoarthritis ○ Urinary stress incontinence ○ Gastroesophageal reflux disease ○ Depression • Pharmaceutical therapy should only be used as adjunct to lifestyle modifications and depends on the staging of obesity: ○ Overweight Stage 0 (BMI 25-29.9 kg/m^2 or 23-24.9 kg/m^2 in certain ethnicities* with no complications) ▪ Lifestyle therapy – reduced-calorie healthy meal plan/physical activity/behavioral interventions ○ Obesity Stage 0 (BMI greater than or equal to 30 kg/m^2 or greater than or equal to 25 kg/m^2 in certain ethnicities* with no complications) ▪ Lifestyle therapy – reduced-calorie healthy meal plan/physical activity/behavioral intervention ▪ Weight loss medications – consider if lifestyle therapy fails to prevent progressive weight gain (BMI greater than or equal to 27 kg/m^2) ○ Obesity Stage 1 (BMI greater than or equal to 25 kg/m^2 or greater than or equal to 23 kg/m^2 in certain ethnicities* with greater than or equal to 1 mild/moderate complications) ▪ Lifestyle therapy – reduced-calorie healthy meal plan/physical activity/behavioral interventions ▪ Weight loss medications – consider if lifestyle therapy fails to achieve therapeutic target or initiate concurrently with lifestyle therapy (BMI greater than or equal to 27 kg/m^2) ○ Obesity Stage 2 (BMI greater than or equal to 25 kg/m^2 or greater than or equal to 23 kg/m^2 in certain ethnicities* with greater than or equal to 1 severe complications): ▪ Lifestyle therapy – reduced-calorie healthy meal plan/physical activity/behavioral interventions ▪ Weight loss medication – initiate concurrently with lifestyle therapy (BMI greater than or equal to 27 kg/m^2) ▪ Consider bariatric surgery (BMI greater than or equal to 35 kg/m^2) *Certain ethnicities (A BMI cutoff point value of greater than or equal to 23 kg/m^2 should be used in the screening and confirmation of excess adiposity in South Asian, Southeast Asian, and East Asian adults)

	The Endocrine Society clinical practice guidelines suggests medications approved for chronic weight management can be useful adjuncts to lifestyle change for patients who have been unsuccessful with diet and exercise alone. They recommend adherence to American Heart Association Guidelines (2013) [see below] which include advice for assessment and treatment with diet and exercise, as well as bariatric surgery for appropriate candidates.(13) • Diet, exercise, and behavioral modification should be included in all overweight and obesity management approaches for BMI greater than or equal to 25 kg/m^2 and other tools [e.g., pharmacotherapy (if BMI greater than or equal to 27 kg/m^2 with comorbidity or BMI greater than 30 kg/m^2) and bariatric surgery (BMI greater than or equal to 35 kg/m^2 with comorbidity or BMI greater than 40 kg/m^2)] should be used as adjuncts to behavioral modification to reduce food intake and increase physical activity when possible. Patients who have a history of being unable to successfully lose and maintain weight and who meet label indications are candidates for weight loss medications. • Assessment of efficacy and safety of prescribed weight loss medications should be performed at least monthly for the first 3 months, then at least every 3 months thereafter. • Clinicians are recommended to perform annual and symptom-based screening for major obesity related chronic conditions in all adult patients with a BMI greater than or equal to 30 kg/m^2, including diabetes, cardiovascular disease, hypertension, hyperlipidemia, obstructive sleep apnea, non-alcoholic fatty liver disease, osteoarthritis, and major depression. • Prescribers should identify chronic medications, for concomitant medical conditions, that contribute to weight gain, and prescribe drugs that are weight neutral or that will promote weight loss when possible. • If a patient's response to a weight loss medication is deemed effective (weight loss greater than or equal to 5% of body weight at 3 months) and safe, it is recommended that the medication be continued. If deemed ineffective (weight loss less than 5% at 3 months) or if there are safety or tolerability issues at any time, the medication should be discontinued and alternative medications or referral for alternative treatment approaches instead considered. • Given the wide clinical prescribing of phentermine for greater than 20 years and lack of evidence of serious side effects, even in the absence of long-term controlled safety and efficacy data, it seems reasonable for clinicians to prescribe phentermine long term as long as the patient: 1) has no evidence of serious cardiovascular disease; 2) does not have serious psychiatric disease or a history of substance abuse; 3) has been

	informed about weight loss medications that are FDA approved for long-term use and told that these have been documented to be safe and effective whereas phentermine has not; 4) does not demonstrate a clinically significant increase in pulse or BP when taking phentermine; and 5) demonstrates a significant weight loss while using the medication. These aspects of care should be documented in the patient's medical record, and the off-label nature of the prescribing should be documented at each visit. Medication should be started at 7.5 or 15 mg/day initially and only increased if the patient is not achieving clinically significant weight loss. Patients should be followed at least monthly during dose escalation and then at least every 3 months when on a stable dose. The American Heart Association/American College of Cardiology/Obesity Society Guideline (2013) suggests if weight and lifestyle history indicates the patient has never participated in a comprehensive lifestyle intervention program as defined in the guidelines (i.e., trained interventionist or nutritional professional supervision of diet, exercise, and behavior therapy), it is recommended that the patient undertake such a program before addition of adjunctive therapies (e.g., pharmacotherapy), since a substantial proportion of patients will lose sufficient weight to improve health with comprehensive lifestyle management alone. If a patient has been unable to lose weight or sustain weight loss with comprehensive lifestyle intervention and has BMI greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 with greater than or equal to 1 obesity-associated comorbid condition(s), adjunctive therapy may be considered. The expert panel did not review comprehensive evidence on pharmacotherapy for weight loss. Medications should be FDA approved and clinicians should be knowledgeable about the product label. The provider should weigh potential risks of the medication vs. potential benefits of successful weight loss for the individual patient. If the patient is currently taking an obesity medication but has not lost at least 5% of initial body weight after 12 weeks on a maximal dose of the medication, the provider should reassess the risk-to-benefit ratio of that medication for the patient and consider discontinuation of that drug.(15) The Veterans Affairs and Department of Defense (VA/DoD) Clinical Practice Guideline (2020), suggests offering prescribed pharmacotherapy in patients with a BMI greater than or equal to 30 kg/m^2 or greater than or equal to 27 kg/m^2 with greater than or equal to 1 obesity-associated comorbid condition(s), in conjunction with a comprehensive lifestyle intervention.(18) Four centrally-acting noradrenergic agents (phentermine, diethylpropion, phendimetrazine, benzphetamine) are FDA-approved for the "short-term" (usually considered less than or equal to 12 weeks) management of obesity. However,

	the short-term designation was given since all were approved before the necessity of long-term treatment for obesity was established.(12) Since then some of these agents, such as phentermine and diethylpropion, have had literature published in support of long-term use.(13,19) Given the wide clinical prescribing of phentermine for greater than 20 years and lack of evidence of serious side effects, even in the absence of long-term controlled safety and efficacy data, it seems reasonable for clinicians to prescribe phentermine long term.(13) A clinical study found that diethylpropion plus a standard dietary intervention produced sustained and clinically significant weight loss over 1 year, and demonstrated safety under the cardiovascular and psychiatric point of view.(19)
Pediatric Obesity	Pediatric obesity has become an epidemic and international problem. In the United States, the prevalence of obesity in children has risen from 5% in 1970 to 17% in 2004. Genetics and environment are the underlying causes of the increase in pediatric obesity. Obese children and adolescents are at risk of developing the same comorbid conditions as obese and overweight adults. Obesity and overweight children are defined on percentages specific for age and gender defined BMI values. The American Academy of Pediatrics (AAP) define obesity as a BMI greater than or equal to 95th percentile or a BMI greater than or equal to 30 kg/m^2, whichever is lower, and overweight as a BMI within 85th to the 94th percentile for children and adolescents 2 years of age and older.(8,17) The AAP recommends that clinicians should assess medical and behavioral risks in any child with a BMI above the 85th percentile before initiating any intervention.(8,17) The Endocrine Society Pediatric Obesity Treatment Guidelines also recommend that clinicians should evaluate for potential comorbidities in children and adolescents with a BMI greater than or equal to 85th percentile.(16) The 2023 AAP guidelines recommend the use of weight loss agents in conjunction with lifestyle and behavioral changes. Pediatricians and other primary healthcare providers should treat children and adolescents for overweight with comorbidities (BMI greater than or equal to 85th percentile; comorbidities such as dyslipidemia, prediabetes, Type 2 diabetes, fatty liver disease, hypertension) and obesity (BMI greater than or equal to 95th percentile).(8) The 2017 Endocrine Society guidelines only recommend the use of FDA approved pharmacotherapy in pediatric patients as adjunctive therapy to lifestyle modifications of the highest intensity available and only by clinicians who are experienced in the use of anti-obesity agents.(16)

	• Suggest pharmacotherapy in children or adolescents with obesity (greater than or equal to 95th percentile for age and gender) only after a formal program of intense lifestyle modifications has failed to limit weight gain or to ameliorate comorbidities. • Recommend against using obesity agents in children and adolescents less than 16 years of age who are overweight, but not obese, except in the context of clinical trials. • Anti-obesity agents should be discontinued, and patients reevaluated if the patient does not have a greater than 4% BMI reduction after 12 weeks at the medication's full dosage. • Discourages prescribing weigh loss medications off-label to pediatric patients less than 16 years of age. The CDC's 2000 Growth Charts are based on National Health and Nutrition Examination Survey (NHANES) data from the 1960s through the early 1990s and include age- and sex-specific BMI-for-age charts. The CDC Growth Charts provide a historical comparison of children's weight status relative to a time before the current obesity epidemic during that healthier growth patterns predominated; thus, percentiles on the Growth Charts do not equate to the current population distribution of BMI. The CDC Growth Charts are recommended for clinically tracking BMI patterns among US children and adolescents aged 2 to 18 years; although the CDC Growth Charts can be used for adolescents aged 19 to 21 years, in practice, most pediatricians and other PHCPs transition to adult BMI calculation and categorization for patients older than 18 years.(8)
Safety	Phentermine has the following contraindications:(5,6,11) • History of cardiovascular disease (e.g., coronary artery disease, stroke, arrhythmias, congestive heart failure, uncontrolled hypertension) • During or within 14 days following the administration of monoamine oxidase inhibitors • Hyperthyroidism • Glaucoma • Agitated states • History of drug abuse • Pregnancy • Nursing • Known hypersensitivity, or idiosyncrasy to the sympathomimetic amines Benzphetamine has the following contraindications:(2)

	• Patients with advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to sympathomimetic amines, and glaucoma
	• Benzphetamine should not be given to patients who are in an agitated state or who have a history of drug abuse
	• Hypertensive crises have resulted when sympathomimetic amines have been used concomitantly or within 14 days following use of monoamine oxidase inhibitors
	• Benzphetamine tablets should not be used concomitantly with other CNS stimulants
	• Benzphetamine is contraindicated in women who are or may become pregnant
	
	Phendimetrazine has the following contraindications:(7,10)
	
	• Immediate release:
	  ○ Known hypersensitivity or idiosyncratic reactions to sympathomimetics
	  ○ Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate and severe hypertension, hyperthyroidism, and glaucoma
	  ○ Highly nervous or agitated
	  ○ History of drug abuse
	  ○ Use in combination with other CNS stimulants, including monoamine oxidase inhibitors
	• Extended release:
	  ○ History of cardiovascular disease (e.g., coronary artery disease, stroke, arrhythmias, congestive heart failure, uncontrolled hypertension, pulmonary hypertension)
	  ○ During or within 14 days following the administration of monoamine oxidase inhibitors
	  ○ Hyperthyroidism
	  ○ Glaucoma
	  ○ Agitated states
	  ○ History of drug abuse
	  ○ Pregnancy
	  ○ Nursing
	  ○ Use in combination with other anorectic agents or CNS stimulants

	○ Known hypersensitivity or idiosyncratic reactions to sympathomimetics Diethylpropion has the following contraindications:(9) • Pulmonary hypertension, advanced arteriosclerosis, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma, severe hypertension • Agitated states • Patients with a history of drug abuse • Use in combination with other anorectic agents is contraindicated • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result Phentermine/topiramate has the following contraindications:(1) • Pregnancy • Glaucoma • Hyperthyroidism • During or within 14 days following the administration of monoamine oxidase inhibitors • Known hypersensitivity or idiosyncrasy to the sympathomimetic amines Naltrexone/bupropion (NB) has the following:(3) • Contraindications: ○ Uncontrolled hypertension ○ Seizure disorder or a history of seizures ○ Use of other bupropion-containing products (including, but not limited to, Wellbutrin, Wellbutrin SR, Wellbutrin XL, Aplenzin, and Zyban) ○ Bulimia or anorexia nervosa, which increase the risk for seizure ○ Chronic opioid or opiate agonist (e.g., methadone) or partial agonists (e.g., buprenorphine) use, or acute opiate withdrawal ○ Patients undergoing an abrupt discontinuation of alcohol, benzodiazepines, barbiturates, and antiepileptic drugs ○ Concomitant administration of monoamine oxidase inhibitors (MAOI). At least 14 days should elapse between discontinuation of MAOI and initiation of treatment with Contrave. There is an increased risk of hypertensive reactions when Contrave is used concomitantly with MAOIs. Starting Contrave in a patient treated

	with reversible MAOIs such as linezolid or intravenous methylene blue is also contraindicated ○ Known allergy to bupropion, naltrexone or any other component of Contrave. Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported with bupropion • Boxed warnings: ○ Contrave is not approved for use in the treatment of major depressive disorder or other psychiatric disorders. Contrave contains bupropion, the same active ingredient as some other antidepressant medications (including, but not limited to, Wellbutrin, Wellbutrin SR, Wellbutrin XL, and Aplenzin). Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term trials. These trials did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in subjects over age 24; there was a reduction in risk with antidepressant use in subjects aged 65 and older. In patients of all ages who are started on Contrave, monitor closely for worsening, and for the emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. Contrave is not approved for use in pediatric patients. Orlistat has the following contraindications:(4) • Pregnancy • Chronic malabsorption syndrome • Cholestasis • Known hypersensitivity to Orlistat or to any component of this product **Co-Administration** None of the FDA approved weight loss agents have approval for co-administration with another weight loss agent. New guidelines do not support the use of co-administration of weight loss pharmacological agents.(13,14,18) Use of non-approved drug combinations for obesity treatment should be limited to clinical trials, and patients should be informed when drugs are being used off label alone or in combination.(12)

REFERENCES

Number	Reference
1	Qsymia prescribing information. Vivus, Inc. June 2023.
2	Benzphetamine prescribing information. Nivagen Pharmaceuticals. January 2016.
3	Contrave prescribing information. Nalpropion Pharmaceuticals LLC. November 2021.
4	Xenical prescribing information. H2-Pharma, LLC. November 2022.
5	Adipex-P prescribing information. Teva Pharmaceuticals. September 2020.
6	Phentermine prescribing information. Aurolife Pharma LLC. January 2019.
7	Phendimetrazine ER prescribing information. Virtus Pharmaceuticals, LLC. May 2020.
8	American Academy of Pediatrics (AAP) Clinical Practice Guideline for the Evaluation and Treatment of Children and Adolescents with Obesity. Pediatrics. 2023 Jan;151(2):1-100.
9	Diethylpropion prescribing information. Lannett Company, Inc. December 2019.
10	Phendimetrazine prescribing information. KVK-Tech, Inc. December 2019.
11	Lomaira prescribing information. KVK-Tech Inc. December 2023.
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14	American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines for Medical Care of Patients with Obesity. Endocr Pract. 2016 Jul:22(Suppl 3):1-203.
15	Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart

Number	Reference
	Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014;129(25 Suppl 2):S102–S138.
16	Styne DM, Arslanian SA, Connor EL, et al. Pediatric Obesity – Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017 Jan;102(3):709–757.
17	Barlow SE, et al. Expert Committee Recommendations Regarding the Prevention, Assessment, and Treatment of Child and Adolescent Overweight and Obesity: Summary Report. Pediatrics. 2007 Dec;120(Suppl 4):S164-S192.
18	Department of Veterans Affairs and the Department of Defense Clinical Practice Guideline for the Management of Adult Overweight and Obesity – Version 3.0. 2020. Available at: https://www.healthquality.va.gov/guidelines/CD/obesity/.
19	Cercato C, Roizenblatt VA, Leanca CC, et al. A Randomized Double-Blind Placebo-Controlled Study of the Long-Term Efficacy and Safety of Diethylpropion in the Treatment of Obese Subjects. Int J Obes (Lond). 2009 Aug;33(8):857-865.
20	Orlistat prescribing information. H2-Pharma, LLC. June 2022.
21	American Gastroenterological Association (AGA) Clinical Practice Guideline on Pharmacological Interventions for Adults with Obesity. Gastroenterology. 2022 Nov;163(5):1198-1225.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** (Patient new to therapy or attempting a repeat weight loss course of therapy) **Target Agent(s)** will be approved when ALL the following are met: 1. ONE of the following: A. The patient is an adult (18 years of age or over) AND ALL of the following: 1. ONE of the following: A. The patient has a diagnosis of obesity, confirmed by a BMI greater than or equal to 30 kg/m^2 OR a BMI greater than or equal to 25 kg/m^2 if

Module	Clinical Criteria for Approval
	the patient is of South Asian, Southeast Asian, or East Asian descent **OR** B. The patient has a BMI greater than or equal to 27 kg/m^2 with at least one weight-related comorbidity/risk factor/complication (e.g., diabetes, dyslipidemia, coronary artery disease) **AND** 2. The patient has been on a weight loss regimen of a low-calorie diet, increased physical activity, and behavioral modifications for a minimum of 6 months prior to initiating therapy with the requested agent **AND** 3. The patient is currently on and will continue a weight loss regimen of a low-calorie diet, increased physical activity, and behavioral modifications **OR** B. The patient is pediatric (12 to 17 years of age) AND ALL of the following: 1. ONE of the following: A. The patient has a diagnosis of obesity, confirmed by a BMI greater than or equal to 95th percentile for age and gender **OR** B. The patient has a diagnosis of obesity, confirmed by a BMI greater than or equal to 30 kg/m^2 **OR** C. The patient has a BMI greater than or equal to 85th percentile for age and gender AND at least one weight-related comorbidity/risk factor/complication (e.g., hypertension, dyslipidemia, type 2 diabetes, or obstructive sleep apnea) **AND** 2. The patient has been on a weight loss regimen of a low-calorie diet, increased physical activity, and behavioral modifications for a minimum of 6 months (prior to initiating therapy with the requested agent) **AND** 3. The patient is currently on and will continue a weight loss regimen of a low-calorie diet, increased physical activity, and behavioral modifications **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. ONE of the following: A. The patient has NOT tried a targeted weight loss agent (e.g., benzphetamine, Contrave, diethylpropion, phendimetrazine, phentermine, Qsymia, Xenical/Orlistat) in the past 12 months **OR** B. BOTH of the following: 1. The patient has tried a targeted weight loss agent for a previous course of therapy in the past 12 months **AND** 2. The prescriber anticipates success with repeating therapy with any targeted weight loss agent **AND**

Module	Clinical Criteria for Approval
	4. ONE of the following: A. The requested agent is benzphetamine, diethylpropion, phendimetrazine, or phentermine **OR** B. The requested agent is Qsymia AND ONE of the following: 1. The requested dose is 3.75mg/23mg **OR** 2. The patient is currently being treated with Qsymia, the requested dose is greater than 3.75 mg/23 mg AND ONE of the following: A. ONE of the following: 1. For a pediatric patient, the patient has experienced a reduction of at least 5% of baseline BMI (prior to initiation of the requested agent) **OR** 2. For an adult, the patient has demonstrated and maintained a weight loss of greater than or equal to 5% from baseline (prior to initiation of the requested agent) **OR** B. The patient received less than 14 weeks of therapy **OR** C. The patient's dose is being titrated upward **OR** D. The patient has received less than 12 weeks (3 months) of therapy on the 15mg/92mg strength **OR** 3. There is support for therapy for the requested dose for this patient **OR** C. The requested agent is Contrave AND ONE of the following: 1. The patient is newly starting therapy **OR** 2. The patient is currently being treated and has received less than 16 weeks (4 months) of therapy **OR** 3. The patient has achieved and maintained a weight loss of greater than or equal to 5% from baseline (prior to initiation of requested agent) **OR** D. The requested agent is Xenical (or Orlistat) AND ONE of the following: 1. The patient is 12 to 16 years of age AND ONE of the following: A. The patient is newly starting therapy **OR** B. The patient is currently being treated and has received less than 12 weeks (3 months) of therapy **OR** C. The patient has achieved and maintained a weight loss of greater than 4% from baseline (prior to initiation of requested agent) **OR** 2. The patient is 17 years of age or over AND ONE of the following: A. The patient is newly starting therapy **OR** B. The patient is currently being treated and has received less than 12 weeks (3 months) of therapy **OR** C. The patient has achieved and maintained a weight loss of greater than or equal to 5% from baseline (prior to initiation of requested agent) **AND**

Module	Clinical Criteria for Approval
	5. The patient will NOT be using the requested agent in combination with another weight loss agent (e.g., Contrave, phentermine, Qsymia, Xenical, Saxenda, Wegovy, Zepbound) for the requested indication **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 3 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** (Patient continuing a current weight loss course of therapy) **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient meets ONE of the following: A. The patient has achieved and maintained a weight loss greater than or equal to 5% from baseline (prior to initiation of requested agent) **OR** B. The requested agent is Qsymia AND ONE of the following: 1. For a pediatric patient (12 to 17 years of age), the patient has achieved and maintained a reduction of greater than or equal to 5% of baseline BMI (prior to initiation of the requested agent) **OR** 2. For an adult (18 years of age or over) the patient has achieved and maintained a weight loss greater than or equal to 5% from baseline (prior to initiation of the requested agent) **OR** 3. BOTH of the following: A. ONE of the following: 1. For a pediatric patient, the patient has achieved and maintained less than a 5% reduction of baseline BMI (prior to initiation of the requested agent) **OR** 2. For an adult, the patient has achieved and maintained a weight loss less than 5% from baseline (prior to initiation of requested agent) **AND** B. BOTH of the following: 1. The patient's dose is being titrated upward (for the 3.75 mg/23 mg, 7.5 mg/46 mg or 11.25 mg/69 mg strengths only) **AND**

Module	Clinical Criteria for Approval
	2. The patient has received less than 12 weeks of therapy on the 15mg/92mg strength **OR** C. The requested agent is Xenical (or Orlistat) AND ONE of the following: 1. The patient 12 to 16 years of age AND has achieved and maintained a weight loss greater than 4% from baseline (prior to initiation of requested agent) **OR** 2. The patient is 17 years of age or over AND has achieved and maintained a weight loss greater than or equal to 5% from baseline (prior to initiation of requested agent) **AND** 3. If the patient is pediatric, then the current BMI is greater than 85th percentile for age and gender **AND** 4. The patient is currently on and will continue to be on a weight loss regimen of a low-calorie diet, increased physical activity, and behavioral modifications **AND** 5. The patient will NOT be using the requested agent in combination with another weight loss agent (e.g., Contrave, phentermine, Qsymia, Xenical, Saxenda, Wegovy, Zepbound) for the requested indication **AND** 6. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** • Qsymia: greater than or equal to 5% weight loss from baseline (adults); greater than or equal to 5% reduction in BMI from baseline (pediatrics): 12 months • Qsymia: less than 5% weight loss from baseline (adults); less than 5% reduction in BMI from baseline (pediatrics): 3 months • All other agents: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR**

Module	Clinical Criteria for Approval
	B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months

Xdemvy

Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Xdemvy® (lotilaner) Ophthalmic solution	An ectoparasiticide (anti-parasitic) indicated for the treatment of Demodex blepharitis.		1

CLINICAL RATIONALE

Demodex blepharitis	Demodex blepharitis is a common disease of the eyelid, affecting approximately 25 million Americans.(3) Blepharitis is a chronic inflammation of the eyelid margin and a common cause of chronic ocular inflammation.(2) It is characterized by erythema, ocular irritation and discomfort, discharge and debris on the eyelids and lashes and eyelash anomalies. In more advanced stages, there may be corneal involvement. Although blepharitis can have various etiologies, including allergic, staphylococcal and seborrheic, one of the most common is Demodex mite infestation and accounts for more than 60% of those with blepharitis. It has long been accepted that the prevalence of Demodex increase with age, affecting more than 80% of those older than 60 years and 100% of those older than 70 years. Demodex prevalence is lower among younger university-based populations and reported between 2% and 27%. Demodex blepharitis is equally present in both sexes and infestation was similar regardless of ethnicity.(3) Collarettes are the pathognomonic sign of Demodex blepharitis. They are waxy in texture and composed of accumulated undigested material, keratinized cells, dead or living mites, eggs and egg casings of mites that form a cylindrical collar that remain at the base of the eyelash follicle. Collarettes can be readily identified at the base of the upper lash margin on downward gaze using a slitlamp. Ocular itching is the symptom most commonly associated with Demodex blepharitis, and evidence suggests that patients consider this to be one of the most bothersome symptoms associated with the disease. It is more likely

	to occur at night or early morning after periods of mite activity, distinguishing it from daytime, allergy-related itching. In addition to itching, other symptoms include dryness, discharge, eye redness, burning, tearing, foreign body sensation, pain, and blurred (or fluctuating) vision.(3) The American Academy of Ophthalmology notes that a cure is usually not possible for blepharitis but many treatments or treatment combinations may be helpful including: warm compresses, eyelid cleansing, topical and/or systemic antibiotics, and topical anti-inflammatory agents. Patients with recalcitrant blepharitis have responded to therapy directed at decreasing or eradicating the Demodex mites. Oral ivermectin has been reported to be of benefit in some cases of recalcitrant Demodex blepharitis.(2) Ivermectin has long been used safely by dermatologists to treat Demodex-related skin conditions and is known to have an acaricidal effect. Ivermectin improves the signs and symptoms of Demodex blepharitis along with reducing the mite density.(3)
Efficacy	The safety and efficacy of Xdemvy for the treatment of Demodex blepharitis was evaluated in a total of 833 patients (415 of which received Xdemvy) in two 6-week, randomized, multicenter, double-masked, vehicle-controlled studies (Saturn-1 and Saturn-2). Patients with Demodex blepharitis were randomized to either Xdemvy or Vehicle at a 1:1 ratio dosed twice daily in each eye. Efficacy was demonstrated by improvement in lids (reduction of collarettes to no more than 2 collarettes per upper lid) in each study (Saturn-1 and Saturn-2) by Day 43. The endpoints of mite eradication (mite density of 0 mites/lash) and erythema cure (Grade 0) of Xdemvy vs. Vehicle demonstrated statistically significant improvement at Day 43 across both Saturn-1 (Table 1) and Saturn-2 (Table 2) studies.(1)
Safety	Xdemvy has no FDA labeled contraindications for use.

REFERENCES

Number	Reference
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Number	Reference
3	Rhee MK, Yeu E, Barnett M, et al. Demodex Blepharitis: A Comprehensive review of the disease, current management, and emerging therapies. *Eye & Contact Lens*. 2023;49(8):311-318. doi:10.1097/icl.0000000000001003

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **Length of Approval:** up to 12 months

Xhance

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Xhance® (fluticasone propionate) Nasal spray	Treatment of chronic rhinosinusitis with nasal polyps (CRSwNP) in adults Treatment of chronic rhinosinusitis without nasal polyps (CRSsNP) in adults		1

CLINICAL RATIONALE

Chronic rhinosinusitis	Chronic rhinosinusitis is an inflammatory condition affecting the paranasal sinuses that is diagnosed by the presence of both subjective and objective evidence of chronic sinonasal inflammation. Hallmarks of the disease consist of at least two out of four cardinal symptoms (i.e., facial pain/pressure, hyposmia/anosmia, nasal drainage, and nasal obstruction) for at least 12 consecutive weeks. The objective evidence of sinonasal inflammation and nasal polyps is needed to confirm the diagnosis may be obtained by physical examination (anterior rhinoscopy, nasal endoscopy) or from sinus computed tomography (CT).(2-4) The exact cause of CRSwNP is unknown, but biopsies of nasal polyps have shown elevated levels of eosinophils.(2) First line therapy for chronic rhinosinusitis is nasal saline irrigation and intranasal corticosteroid sprays.(2-4) The American Academy of Family Physicians notes that no one intranasal corticosteroid is superior to another or that increased dosing provides greater effectiveness. The American Academy of Otolaryngology recommends a short course of oral corticosteroids if no response is seen with intranasal corticosteroids after 3-months of appropriate use.(4) Short courses of oral corticosteroids (up to three weeks) can improve sinonasal symptoms and endoscopic findings. Surgical intervention may be required in patients who fail medical management.(2,3)
Safety	Xhance is contraindicated in patients with hypersensitivity to any of its ingredients.(1)

REFERENCES

Number	Reference
1	Xhance prescribing information. OptiNose US, Inc. March 2024.
2	Stevens WW, Schleimer RP, Kern RC. Chronic Rhinosinusitis with Nasal Polyps. *The Journal of Allergy and Clinical Immunology: In Practice*. 2016;4(4):565-572. doi:10.1016/j.jaip.2016.04.012
3	Sedaghat AR. Chronic rhinosinusitis. AAFP. Published October 15, 2017. https://www.aafp.org/pubs/afp/issues/2017/1015/p500.html
4	Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical Practice Guideline (UPDATE): Adult sinusitis. *Otolaryngology and Head and Neck Surgery*. 2015;152(S2). doi:10.1177/0194599815572097

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
PA	**Initial Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The patient has a diagnosis of chronic rhinosinusitis with nasal polyps (CRSwNP) **OR** B. The patient has a diagnosis of chronic rhinosinusitis without nasal polyps (CRSsNP) **OR** C. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response after 90 days of therapy with ONE generic OR OTC intranasal corticosteroid **OR** B. The patient has an intolerance or hypersensitivity to therapy with ONE generic or OTC intranasal corticosteroids that is not expected to occur with the requested agent **OR** C. The patient has an FDA labeled contraindication to ALL generic AND OTC intranasal corticosteroids that is not expected to occur with the requested agent **AND**

Module	Clinical Criteria for Approval
	4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months Note: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months Note: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Xolair (omalizumab)

Prior Authorization

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Xolair® (omalizumab) Injection for subcutaneous use	Moderate to severe persistent asthma in adults and pediatric patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with inhaled corticosteroids Chronic rhinosinusitis with nasal polyps (CRSwNP) in adult patients 18 years of age and older with inadequate response to nasal corticosteroids, as add-on maintenance treatment Chronic spontaneous urticaria (CSU) in adults and adolescents 12 years of age and older who remain symptomatic despite H1 antihistamine treatment IgE-mediated food allergy in adult and pediatric patients aged 1 year and older for the reduction of allergic reactions (Type I), including anaphylaxis, that may occur with accidental exposure to one or more foods. To be used in conjunction with food allergen avoidance Limitations of use: • Not indicated for acute bronchospasms, or status asthmaticus • Not indicated for the emergency treatment of allergic reactions, including anaphylaxis • Not indicated for other allergic conditions, or other forms of urticaria		1

CLINICAL RATIONALE

Asthma	Asthma is a chronic inflammatory disorder of the airways.(2,3) It is characterized by variable and recurring clinical symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation.(2) Symptoms of asthma include wheezing, coughing, recurrent difficulty breathing, shortness of breath, and chest tightness. Generally, these symptoms will occur or worsen with exposure to allergens and irritants, infections, exercise, changes in weather, stress, or menstrual cycles. Guidelines recommend the use of detailed medical history, physical examination, and spirometry to make a diagnosis of asthma.(2,3) The Global Initiative for Asthma (GINA) guidelines recommend a stepwise approach for managing asthma. Long-term goals for asthma management are to achieve good control of symptoms, maintain normal activity level, and to minimize the future risk of exacerbations, fixed airflow limitation, and side-effects. IgE is the antibody responsible for activation of allergic reactions and is important to the pathogenesis of allergic asthma and the development and persistence of inflammation. GINA guidelines define moderate asthma as that which is well controlled with Step 3 or Step 4 treatment (e.g., low- or medium-dose inhaled corticosteroids [ICS] in combination with a long-acting beta agonist [LABA] in either treatment track). Severe asthma is defined as asthma that remains uncontrolled despite optimized treatment with high-dose ICS-LABA, or that requires high-dose ICS-LABA to prevent it from becoming uncontrolled. Severe asthma must be distinguished from asthma that is difficult to treat due to inadequate or inappropriate treatment, or persistent problems with adherence or comorbidities such as chronic rhinosinusitis or obesity, as they need very different treatment compared with if asthma is relatively refractory to high-dose ICS-LABA or even oral corticosteroids (OCS). Early initiation of low dose ICS in patients with asthma has led to greater improvement in lung function than initiation of ICS after symptoms have been present for more than 2 to 4 years. The 2023 GINA guidelines recommend every adult and adolescent with asthma should receive ICS-containing controller medication to reduce the risk of serious exacerbation, even in patients with infrequent symptoms.(3) 2023 GINA STEP recommendations for adults and adolescents (12 years of age and over) are intended to reduce the risk of serious exacerbations and are broken into two tracks based on reliever therapy.

	Track 1 is the preferred approach recommended by GINA, because using low dose ICS-formoterol as the reliever reduces the risk of exacerbations compared with regimens with short-acting β2-agonist (SABA) as the reliever, and is a simpler regimen:(3)
	
	• Step 1:
	  ○ As-needed-only low dose ICS-formoterol
	• Step 2:
	  ○ As-needed-only low dose ICS-formoterol
	• Step 3: address and treat modifiable risk factors (e.g., adherence, technique) before considering step up
	  ○ Controller: low dose ICS-formoterol
	  ○ Reliever: as-needed low dose ICS-formoterol
	• Step 4:
	  ○ Controller: medium dose ICS-formoterol
	  ○ Reliever: as-needed low dose ICS-formoterol
	• Step 5: patients with uncontrolled symptoms and/or exacerbations despite Step 4 treatment should be assessed for contributory factors, have their treatment optimized, and be referred for expert assessment including severe asthma phenotype, and potential add on treatment
	  ○ Controller: at least medium dose ICS-formoterol; consider high dose ICS-formoterol
	  ○ Reliever: as-needed low dose ICS-formoterol
	  ○ Refer for phenotypic assessment +/- biologic therapy
	  ○ Add-on treatments include:
	  ▪ Long-acting muscarinic antagonist (LAMA) for patients greater than or equal to 18 years (greater than or equal to 6 years for tiotropium) in separate or combination inhalers
	  ▪ Anti-IgE (subcutaneous (SC) omalizumab in patients greater than or equal to 6 years) for severe allergic asthma
	  ▪ Anti-interleukin (IL) 5 or anti-IL5R or anti-IL4R for severe eosinophilic/Type 2 asthma
	  • Anti-IL5: SC mepolizumab for patients greater than or equal to 6 years OR intravenous (IV) reslizumab for patients greater than or equal to 18 years of age
	  • Anti-IL5R: SC benralizumab for patients greater than or equal to 12 years
	  • Anti-IL4R: SC dupilumab for patients greater than or equal to 6 years
	  ▪ Anti-thymic stromal lymphopoietin (TSLP) for severe asthma (SC tezepelumab for patients greater than or equal to 12 years)

	▪ Add-on azithromycin three days/week reduces exacerbations, but increases antibiotic resistance ○ Maintenance oral corticosteroids (OCS) should be used only as last resort, because short-term and long-term systemic side-effects are common and serious • Note, ICS-formoterol should not be used as the reliever by patients taking any other (non-formoterol) ICS-LABA or ICS-LABA-LAMA **Track 2** is an alternative approach if Track 1 is not possible or is not preferred by a patient with no exacerbations on their current therapy. Before considering a regimen with SABA reliever, the clinician should consider whether the patient is likely to be adherent with their controller therapy; if not, they will be exposed to the higher risk of exacerbations with SABA-only treatment:(3) • Step 1: ○ Take ICS whenever SABA taken ○ Reliever: as-needed ICS-SABA or as needed SABA • Step 2: ○ Controller: low dose ICS ○ Reliever: as-needed ICS-SABA or as-needed SABA ○ Alternative options with limited indications, or less evidence for efficacy and/or safety: ▪ Low dose ICS whenever SABA taken ▪ Daily leukotriene receptor antagonist (LTRA). These are less effective than daily ICS, particularly for preventing exacerbations, and there is a US FDA boxed warning about the risk of serious mental health effects with montelukast ▪ Daily low-dose ICS-LABA as initial therapy leads to faster improvement in symptoms and FEV1 than ICS alone but is costlier, and the reduction in exacerbations compared with SABA is similar to that with ICS ▪ For adults with rhinitis who are allergic to house dust mite and have FEV1 > 70% predicted, consider adding sublingual immunotherapy (SLIT) • Step 3: address and treat modifiable risk factors (e.g., adherence, technique) before considering step up ○ Controller: low dose ICS-LABA ○ Reliever: as-needed ICS-SABA or as-needed SABA ○ Alternative options: ▪ Medium dose ICS ▪ Low-dose ICS plus LTRA

	▪ For adults with rhinitis who are allergic to house dust mite and have FEV1 > 70% predicted, consider adding SLIT • Step 4: ○ Controller: medium/high dose ICS-LABA ○ Reliever: as-needed ICS-SABA or as-needed SABA ○ Alternative options: ▪ Add-on LAMA for patients greater than or equal to 18 years (greater than or equal to 6 years for tiotropium) in separate or combination inhalers. Before considering add-on LAMA for patients with exacerbations, increase ICS dose to at least medium ▪ Add-on LTRA or low-dose sustained-release theophylline to a medium or high-dose ICS ▪ For adults with rhinitis who are allergic to house dust mite and have FEV1 > 70% predicted, consider adding sublingual immunotherapy (SLIT) • Step 5: patients with uncontrolled symptoms and/or exacerbations despite Step 4 treatment should be assessed for contributory factors, have their treatment optimized, and be referred for expert assessment including severe asthma phenotype, and potential add on treatment ○ Controller: medium/high dose ICS-LABA ○ Reliever: as-needed ICS-SABA or as-needed SABA ○ Refer for phenotypic assessment +/- biologic therapy ○ Add-on treatments include: ▪ Long-acting muscarinic antagonist (LAMA) for patients greater than or equal to 18 years (greater than or equal to 6 years for tiotropium) in separate or combination inhalers ▪ Anti-IgE (SC omalizumab in patients greater than or equal to 6 years) for severe allergic asthma ▪ Anti-interleukin (IL) 5 or anti-IL5R or anti-IL4R for severe eosinophilic/Type 2 asthma • Anti-IL5: SC mepolizumab for patients greater than or equal to 6 years OR IV reslizumab for patients greater than or equal to 18 years of age • Anti-IL5R: SC benralizumab for patients greater than or equal to 12 years • Anti-IL4R: SC dupilumab for patients greater than or equal to 6 years ▪ Anti-thymic stromal lymphopoietin (TSLP) for severe asthma (SC tezepelumab for patients greater than or equal to 12 years)

	▪ Add-on azithromycin three days/week reduces exacerbations, but increases antibiotic resistance ○ Maintenance oral corticosteroids (OCS) should be used only as last resort, because short-term and long-term systemic side-effects are common and serious 2023 GINA STEP recommendations for children (6 to 11 years of age) are intended to reduce the risk of serious exacerbations:(3) • Step 1: ○ Low dose ICS taken whenever SABA taken ○ Reliever: as-needed SABA • Step 2 ○ Preferred Controller: daily low dose ICS ○ Reliever: as-needed SABA ○ Alternative options: ▪ Low-dose ICS whenever SABA is taken using separate inhalers ▪ Daily LTRA is less effective for exacerbation reduction. Advise parents about US FDA warning on montelukast • Step 3: check inhaler technique and adherence, and treat modifiable risk factors before considering step up: ○ Preferred options: ▪ Medium-dose ICS maintenance plus as-needed SABA ▪ Low-dose ICS-LABA maintenance plus as-needed SABA ▪ Maintenance and reliever therapy (MART) with a very low dose of budesonide-formoterol dry powder inhaler (DPI) ○ Alternative option: Low dose ICS plus LTRA. The FDA boxed warning for montelukast also applies to children • Step 4: Individual children's responses vary, so each of the Step 3 options may be tried before considering a step-up to Step 4. ○ Preferred options: ▪ Medium dose ICS-LABA plus as-needed SABA • If asthma is not well controlled on medium-dose ICS, refer for expert assessment and advice. ▪ Low dose ICS-formoterol MART ○ Alternative options: ▪ High dose ICS-LABA plus as-needed SABA ▪ Add-on tiotropium ▪ Add-on LTRA • Step 5: ○ Refer for phenotypic assessment

	○ Controller: Continue controller from step 4 or consider higher dose ICS-LABA ○ Reliever: as needed SABA (or ICS-formoterol reliever for MART) ○ Add on treatments include: ▪ Therapy with anti-IgE, anti-IL4R, or anti-IL5 ▪ As a last resort consider add on low dose OCS but consider side effects **Severe Asthma Phenotype and Eosinophilic Asthma Subphenotype** Roughly 3% to 10% of adults with asthma have severe asthma as defined by the GINA 2023 guidelines.(3) The European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines (2014; updated 2020) and the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group mirror the GINA definition of severe asthma.(2,12) The ERS/ATS definition uncontrolled asthma for adult and pediatric patients 6 years of age and over:(17) • Frequent severe exacerbations (i.e., two or more bursts of systemic corticosteroids within the past 12 months) • Serious exacerbations (i.e., at least one hospitalization, intensive care unit stay, or mechanical ventilation in the past 12 months) • Airflow limitation (i.e., FEV1 less than 80% predicted) • Asthma that worsens upon tapering of high-dose ICS or systemic corticosteroids A specialist, preferably in a multidisciplinary severe asthma clinic (if available) performs further assessment, which includes the patient's inflammatory phenotype (i.e., Type 2 or non-Type 2).(3) Type 2 inflammation is characterized by the presence of cytokines such as interleukin (IL)-4, IL-5, and IL-13, which are often produced by the adaptive immune system on recognition of allergens. It is also characterized by eosinophilia or increased fraction of exhaled nitric oxide (FeNO) and may be accompanied by atopy. In many patients with asthma, Type 2 inflammation rapidly improves when ICS are taken regularly and correctly; this is classified as mild or moderate asthma. In severe asthma, Type 2 inflammation may be relatively refractory to high dose ICS. Type 2 inflammation is considered refractory if any of the following are found while the patient is taking high dose ICS or daily OCS:(3) • Blood eosinophils greater than or equal to 150 cells/microliter

	• FeNO greater than or equal to 20 ppb
	• Sputum eosinophils greater than or equal to 2%
	• Asthma is clinically allergen-driven
	
	Biologic agents should be considered as add-on therapy for patients with refractory Type 2 inflammation with exacerbations or poor symptom control despite taking at least high dose ICS/LABA, and who have allergic or eosinophilic biomarkers or need maintenance OCS. 2023 GINA recommends the biologics below based on patient eligibility factors:(3)
	
	• Anti-IgE (omalizumab):
	  ○ Sensitization on skin prick testing or specific IgE
	  ○ Total serum IgE and weight within dosage range
	  ○ Exacerbations in the last year
	• Anti-IL5/Anti-IL5R (benralizumab, mepolizumab, reslizumab):
	  ○ Exacerbations in the last year
	  ○ Blood eosinophils greater than or equal to 150 cells/microliter (for benralizumab and mepolizumab) or greater than or equal to 300 cells/microliter (for reslizumab)
	• Anti-IL4R (dupilumab):
	  ○ Exacerbations in the last year
	  ○ Blood eosinophil greater than or equal to 150 cells/microliter but less than or equal to 1500 cells/microliter, or FeNO greater than or equal to 25 ppb, or taking maintenance OCS
	• Anti-TSLP (tezepelumab):
	  ○ Exacerbations in the last year
	
	Patient response should be evaluated 4 months after initiating therapy and follow up should occur every 3 to 6 months thereafter. 2023 GINA recommends the following step-down therapy process in patients responding well to targeted biologic therapy:(3)
	
	• Reevaluate the need for each asthma medication every 3 to 6 months, but inhaled therapy should not be completely stopped
	• Oral treatments: gradually decreased starting with OCS due to significant adverse effects.
	• Inhaled treatments: consider reducing ICS dose after 3 to 6 months, but do not completely stop inhaled therapy. Continue at least medium dose ICS and remind patients of the importance of continued inhaled controller therapy
	• Biologic treatments: trial withdrawal after 12 months of treatment and only if patient's asthma remains well controlled on medium dose ICS, and

	for allergic asthma, there is no further exposure to a previous allergic trigger
Chronic Spontaneous Urticaria (CSU)	Chronic spontaneous urticaria (CSU) can be a debilitating condition that can significantly affect a patient's quality of life. Routine diagnostic work-up for CSU is limited to blood tests for complete blood count and inflammatory markers, such as C-reactive protein and/or erythrocyte sedimentation rate, mostly to rule out other potential diseases. Skin prick testing, typically used to identify specific allergens, is not useful for CSU as the condition is rarely caused by type 1 allergy. CSU is also referred to as chronic urticaria (CU) or chronic idopathic urticaria (CIU).(13) Urticaria is characterized by the development of wheals (hives), angioedema, or both. Chronic urticaria is defined by the presence of urticaria that has been continuously or intermittently present for more than 6 weeks.(5,6) Treatment goals for CIU involves symptom control and improvement in quality of life that is acceptable to the patient.(6) The 2021 EAACI/GA LEN/EDF/WAO guidelines, endorsed by the American Academy of Allergy, Asthma, and Immunology, American Academy of Dermatology, American College of Asthma, and Allergy, and Immunology, recommend the following for the treatment of CIU:(6) • Recommend discontinuing medications suspected to worsen CIU (e.g., NSAIDs) • First line treatment: second-generation H-1 antihistamine (cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine) dosed daily • Second-line treatment: Increase the dose up to 4 times the FDA max if inadequate control after 2-4 weeks of therapy at the FDA max • Third-line treatment: addition of omalizumab First-line treatment with second generation H-1 antihistamines is consistent in other guidelines but recommend omalizumab as second-line treatment and ciclosporin (off-label use) as third-line treatment.(13)
Chronic Rhinosinusitis with Nasal Polyps	Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory condition affecting the paranasal sinuses.(9) The exact cause of CRSwNP is unknown, but biopsies of nasal polyps have shown elevated levels of eosinophils. Sinus computed tomography (CT) and/or nasal endoscopy are needed to determine the presence of sinonasal inflammation and nasal polyps.(8)

	The International Consensus Statement on Allergy and Rhinology: Rhinosinusitis (ICAR-RS) indicates that the diagnostic criteria for CRSwNP consist of ALL the following:(11)
	
	• Symptoms greater than or equal to 12 weeks
	• Two of the following symptoms:
	  ○ Nasal discharge (rhinorrhea or post-nasal drainage)
	  ○ Nasal obstruction or congestion
	  ○ Hyposmia (loss or decreased sense of smell)
	  ○ Facial pressure or pain
	• One or more of the following findings:
	  ○ Evidence of inflammation on nasal endoscopy or computed tomography
	  ○ Evidence of purulence coming from paranasal sinuses or ostiomeatal complex
	• Presence of nasal polyps
	
	Topical saline irrigation and intranasal corticosteroids (INCS) are recommended in the guidelines as initial treatment for CRSwNP.(7,9,11) Nasal saline irrigation used as adjunct treatment with other therapies improves symptoms and quality of life (QoL) outcomes and is considered an important aspect of management of CRSwNP. Saline irrigation can improve nasal mucosa function through the mechanical clearance of thick mucus and inflammatory mediators, including eosinophilic mucin.(7,11)
	
	INCS can have a positive impact on the disease and improve symptoms, reduce nasal polyp size, and improve sense of smell.(7,11) The ICAR-RS strongly recommends INCS before or after sinus surgery.(11) INCS are well tolerated and long term treatment is effective and safe. Many different INCS have been used in the treatment of CRSwNP, including triamcinolone, mometasone, fluticasone, and budesonide, but no differences were shown to recommend a specific formulation.(7) For patients using INCS for at least 4 weeks and who continue to have high disease burden, biologics may be considered and preferred over other medical treatment choices.(9)
	
	Oral systemic corticosteroids (OCS), used as a short course, can result in a significant reduction in symptoms and nasal polyps for up to three months after the start of treatment. Up to 2 courses per year, taken in addition to INCS, can be useful for patients with partially or uncontrolled disease.(7) The ICAR-RS strongly recommends the use of OCS in the short term management of CRSwNP, but

	does not recommend longer term use due to the increased risk of adverse effects.(11) Endoscopic sinus surgery (ESS) is aimed at improving symptoms and creating better conditions for local treatment. Sinus surgery should be considered when disease is refractory and remains symptomatic despite trial of primary medical therapy (e.g., nasal sinus irrigation, INCS, oral corticosteroids). Based on current evidence, delaying surgical intervention can be detrimental to symptom improvement and outcomes.(7,11) After surgery, patients need to continue other treatments due to the chronic nature of the disease and nasal polyps potentially reoccurring despite surgery.(7,8) INCS can help to prevent nasal polyp recurrence.(7,11) Biologics can be considered in patients where their disease remains uncontrolled despite appropriate medical treatment and sinus surgery. (9,10) Biologics vary in their magnitude of benefits and harms and certainty of evidence across outcomes. Dupilumab and omalizumab are the most beneficial for most patient important outcomes when comparing with other biologics, followed by mepolizumab.(9)
IgE-Mediated Food Allergy	Food allergies have been increasing in prevalence in the past few decades affecting about 3-10% of children and up to 10% of adults. Food allergies can be classified based on the underlying mechanism as follows: IgE-mediated (type I hypersensitivity), non-IgE mediated (type III or type IV hypersensitivity), or mixed IgE and non-IgE mediated (combination of IgE and cellular mechanisms). The European Academy of Allergy and Clinical Immunology (EAACI) defines IgE-mediated food allergy as both of the following:(14) • Typical symptoms that usually develop with 2 hours of exposure to the allergen and are reproducible upon re-exposure • Evidence of IgE sensitization and/or effector cell response to the allergen Symptoms of IgE-mediated food allergy can be cutaneous, gastrointestinal, ocular, respiratory, cardiovascular, and/or neurological related. Signs and symptoms may clinically manifest in an isolated or concomitant manner, with the same timing or differing. Reactions can range from being mild and localized to being systemic and fatal, including anaphylaxis.(15) Diagnosing IgE-mediated food allergy typically involves a detailed allergy-focused clinical history as a first step. In patients with a history of suspected IgE-mediated food allergy, the EAACI strongly recommends IgE sensitizations tests, such as a skin prick test (SPT) and/or a serum specific IgE test, as first line to support the diagnosis. If the results are contradictory or equivocal with the

	clinical history, additional tests may need to be performed, including an oral food challenge (OFC). The EAACI strongly recommends a supervised OFC as the reference diagnostic procedure to confirm or exclude food allergy in patients with an unclear diagnosis despite IgE sensitization tests.(14) Due to patient and physician fears of severe reactions and logistic considerations, OFC should be reserved for cases that cannot be clarified with IgE sensitization tests.(14,15) Strict avoidance of trigger foods and training in the use of rescue medication for allergic reactions have been the main approach to manage food allergies. Strict avoidance of trigger foods can lead to reduced diet diversity, social restrictions impacting quality of life, potential risk of nutritional deficiencies, and anxiety over the possible accidental random exposure of the trigger food.(15) The Global Allergy and Asthma Excellence Network (GA2LEN) 2022 food allergy guidelines suggest that people with a documented food allergy avoid the offending food unless their individual circumstances and risks allow for some consumption, as advised by their healthcare professional.(16) When severe reactions occur, prompt administration of epinephrine should be used, which is the drug of choice for anaphylaxis. Allergen immunotherapy is an option for some food allergies as a disease-modifying therapy. Allergen immunotherapy uses sequential doses of increased amounts of the allergen in an attempt to desensitize the patient to the allergen.(15) The GA2LEN guidelines show that allergen immunotherapy can be a treatment option for some specific food allergies (i.e., peanut, hen's egg, cow's milk) for select children with substantial risk of severe reactions and/or substantially impaired quality of life. However, no recommendation was made for using allergen immunotherapy in adults, even though it may be useful for select adults if potential benefits outweigh the risks.(16)
Efficacy	**Asthma(1)** The safety and efficacy of Xolair in adult and adolescent patients 12 years of age and older were evaluated in three randomized, double-blind, placebo-controlled, multicenter trials. In all three trials an exacerbation was defined as a worsening of asthma that required treatment with systemic corticosteroids or a doubling of the baseline inhaled corticosteroid dose. In two of these trials patients had a forced expiratory volume in 1 second (FEV1) between 40 and 80% predicted. All patients had a FEV1 improvement of at least 12% following beta-2-agonist administration. All patient were required to have a baseline IgE between 30 and 700 IU/mL and a body weight not more than 150 kg. Dosing information includes weights of at least 30 kg. In both of these trials the number of exacerbations per patient was reduced in patients treated with Xolair compared with placebo. In the third trial there was no restriction on screening FEV1. The number of exacerbations in patients treated with Xolair was similar to that in the placebo-

	treated patients. The absence of an observed treatment effect may be related to differences in the patient population compared with the other two trials. In all three trials, a reduction of asthma exacerbations was not observed in the Xolair treated patients who had an FEV1 > 80% at the time of randomization. Reductions in exacerbations were not seen in patients who required oral steroids as maintenance therapy. The safety and efficacy of Xolair in pediatric patients 6 to less than 12 years of age with moderate to severe asthma is based on one randomized, double-blind, placebo controlled, multicenter trial and an additional supportive study. The primary efficacy variable was the rate of asthma exacerbations during the 24-week, fixed steroid treatment phase. An asthma exacerbation was defined as a worsening of asthma symptoms as judged clinically by the investigator, requiring doubling of the baseline inhaled corticosteroid dose for at least 3 days and/or treatment with rescue systemic (oral or IV) corticosteroids for at least 3 days. At 24 weeks, the Xolair group had a statistically significantly lower rate of asthma exacerbations (0.45 vs 0.64) with an estimated rate ratio of 0.69 (95% CI). Dosing for pediatric patients between the ages of 6 to less than 12 years is based on weight and IgE level with dosing available for weights less than or equal to 150 kg and IgE levels between 30 and 1300 IU/mL. **Chronic Rhinosinusitis with Nasal Polyps (CRSwNP)(1)** The safety and efficacy of Xolair was evaluated in two, randomized, multicenter, double-blind, placebo-controlled clinical trials that enrolled patients with CRSwNP with inadequate response to nasal corticosteroids. The co-primary endpoints in both trials were nasal polyp score (NPS) and average daily nasal congestion score (NCS) at Week 24. In both trials, patients who received Xolair has statistically significant greater improvement from baseline at Week 24 in NPS and weekly average NCS, than patients who received placebo. **Chronic Spontaneous Urticaria (CSU)(1)** The safety and efficacy of Xolair for the treatment of CSU, previously referred to as chronic idiopathic urticaria (CIU) was assessed in two placebo-controlled, multiple-dose clinical trials of 24 and 12 weeks duration. Disease severity was measured by a weekly urticaria activity score (UAS7), which is a composite of the weekly itch severity score and the weekly hive count score. All patients were required to have a UAS7 of greater than or equal to 16 and a weekly itch severity score greater than or equal to 8 for the 7 days prior to randomization, despite having used an H1 antihistamine for at least 2 weeks. In both trials patients who

	received Xolair 150 mg and 300 mg had greater decreases from baseline in weekly itch severity score and weekly hive count scores than placebo at week 12. **IgE-Mediated Food Allergy(1)** The safety and efficacy of Xolair was evaluated in a multi-center, randomized, double-blind, placebo-controlled Food Allergy (FA) trial (NCT03881696) in adult and pediatric patients 1 year of age to less than 56 years who were allergic to peanut and at least two other foods, including mild, egg, wheat, cashew, hazelnut, or walnut (i.e., studied foods). The FA trial enrolled patients who experienced dose-limiting symptoms (e.g., moderate to severe skin, respiratory, or gastrointestinal symptoms) to a single dose of less than or equal to 100 mg of peanut protein and less than or equal to 300 mg protein for each of the other two foods during the screening double-blind placebo-controlled food challenge (DBPCFC). Patients with a history of severe anaphylaxis (defined as neurological compromise or requiring intubation) were excluded from the study. Patients were randomized 2:1 to receive a subcutaneous dosage of Xolair (based on serum IgE level measured before the start of treatment and body weight) or placebo every 2 to 4 weeks for 16 to 20 weeks. After 16 to 20 weeks of treatment, each patient completed a DBPCFC consisting of placebo and each of their 3 studied foods. Efficacy of Xolair was based on 165 pediatric patients who were included in the efficacy analyses. The efficacy of Xolair in adults is supported by the adequate and well-controlled trial of Xolair in pediatric patients, disease similarity in pediatric and adult patients, and pharmacokinetic (PK) similarity. The primary efficacy endpoint was the percentage of patients who were able to consume a single dose of greater than or equal to 600 mg of peanut protein without dose-limiting symptoms (e.g., moderate to severe skin, respiratory, or gastrointestinal symptoms) during DBPCFC. Xolair treatment led to a statistically higher response rate (68%) than placebo (5%). The secondary efficacy endpoints were the percentage of patients who were able to consume a single dose of greater than or equal to 10000 mg of cashew, milk, or egg protein without dose-limiting symptoms during DBPCFC. The study met secondary endpoints and demonstrated that Xolair treatment led to statistically higher response rates than placebo for all three foods.
Safety	Omalizumab has a boxed warning due to risk of anaphylaxis. Because of the risk of anaphylaxis, therapy should be initiated in a healthcare setting. Selection of patients for self-administration should be based on criteria to mitigate risk from

	anaphylaxis. Patient-specific factors including the following criteria should be considered:(1) • Patient should have no prior history of anaphylaxis, including to Xolair or other agents such as foods, drugs, biologics, etc • Patient should receive at least 3 doses of Xolair under the guidance of a healthcare provider with no hypersensitivity reactions • Patient or caregiver is able to recognize symptoms of anaphylaxis • Patient or caregiver is able to treat anaphylaxis appropriately • Patient or caregiver is able to perform SC injections with Xolair prefilled syringe with proper technique according to the prescribed dosing regimen and Instructions for Use Omalizumab is contraindicated in patients with history of hypersensitivity to omalizumab or any ingredients of omalizumab.(1)

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** All Target Agents are eligible for continuation of therapy 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR** 2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. ONE of the following: A. The patient has a diagnosis of moderate to severe persistent asthma AND ALL of the following: 1. ONE of the following: A. The patient is 6 to less than 12 years of age AND BOTH of the following: 1. The pretreatment IgE level is 30 IU/mL to 1300 IU/mL **AND** 2. The patient's weight is 20 kg to 150 kg **OR** B. The patient is 12 years of age or over AND BOTH of the following: 1. The pretreatment IgE level is 30 IU/mL to 700 IU/mL **AND** 2. The patient's weight is 30 kg to 150 kg **AND** 2. Allergic asthma has been confirmed by a positive skin test or in vitro reactivity test to a perennial aeroallergen **AND** 3. The patient has a history of uncontrolled asthma while on asthma control therapy as demonstrated by ONE of the following:

Module	Clinical Criteria for Approval
	A. Frequent severe asthma exacerbations requiring two or more courses of systemic corticosteroids (steroid burst) within the past 12 months **OR** B. Serious asthma exacerbations requiring hospitalization, mechanical ventilation, or visit to the emergency room or urgent care within the past 12 months **OR** C. Controlled asthma that worsens when the doses of inhaled and/or systemic corticosteroids are tapered **OR** D. The patient has baseline (prior to therapy with the requested agent) Forced Expiratory Volume (FEV1) that is less than 80% of predicted **OR** B. The patient has a diagnosis of chronic spontaneous urticaria (CSU) (otherwise known as chronic idiopathic urticaria [CIU]) AND ALL of the following: 1. The patient has had over 6 weeks of hives and itching **AND** 2. If the patient is currently being treated with medications known to cause or worsen urticaria, then ONE of the following: A. The prescriber has reduced the dose or discontinued any medications known to cause or worsen urticaria (e.g., NSAIDs) **OR** B. A reduced dose or discontinuation of any medications known to cause or worsen urticaria is not appropriate **AND** 3. ONE of the following: A. The patient has tried and had an inadequate response to the FDA labeled maximum dose of a second-generation H-1 antihistamine (e.g., cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine) after at least a 2-week duration of therapy AND ONE of the following: 1. The patient has tried and had an inadequate response to a dose titrated up to 4 times the FDA labeled maximum dose of a second-generation H-1 antihistamine **OR** 2. The patient cannot be treated with a dose titrated up to 4 times the FDA labeled maximum dose of a second-generation H-1 antihistamine **OR** B. The patient has an intolerance or hypersensitivity to second-generation H-1 antihistamine therapy **OR**

Module	Clinical Criteria for Approval
	C. The patient has an FDA labeled contraindication to ALL second-generation H-1 antihistamines **OR** C. The patient has a diagnosis of chronic rhinosinusitis with nasal polyps (CRSwNP) AND ALL of the following: 1. The patient has at least TWO of the following symptoms consistent with chronic rhinosinusitis (CRS): A. Nasal discharge (rhinorrhea or post-nasal drainage) B. Nasal obstruction or congestion C. Loss or decreased sense of smell (hyposmia) D. Facial pressure or pain **AND** 2. The patient has had symptoms consistent with chronic rhinosinusitis (CRS) for at least 12 consecutive weeks **AND** 3. The patient's diagnosis was confirmed by ONE of the following: A. Anterior rhinoscopy or endoscopy **OR** B. Computed tomography (CT) of the sinuses **AND** 4. ONE of the following: A. The patient has tried and had an inadequate response to intranasal corticosteroids (e.g., fluticasone, Sinuva) after at least a 4-week duration of therapy **OR** B. The patient has an intolerance or hypersensitivity to therapy with intranasal corticosteroids (e.g., fluticasone, Sinuva) **OR** C. The patient has an FDA labeled contraindication to ALL intranasal corticosteroids **OR** D. The patient has a diagnosis of IgE-mediated food allergy AND ALL of the following: 1. The patient has a confirmed IgE-mediated food allergy confirmed by an allergy diagnostic test (e.g., skin prick test, serum specific IgE test, oral food challenge) **AND** 2. The patient will avoid known food allergens while treated with the requested agent **AND** 3. The requested agent will NOT be used for the emergency treatment of allergic reactions, including anaphylaxis **OR** E. The patient has another FDA labeled indication for the requested agent **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR**

Module	Clinical Criteria for Approval
	B. There is support for using the requested agent for the patient's age for the requested indication **OR** C. The patient has another indication that is supported in compendia for the requested agent **AND** 2. If the patient has a diagnosis of moderate to severe persistent asthma, ALL of the following: A. ONE of the following: 1. The patient is NOT currently being treated with the requested agent AND is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **OR** 2. The patient is currently being treated with the requested agent AND ONE of the following: A. Is currently treated with an inhaled corticosteroid for at least 3 months that is adequately dosed to control symptoms **OR** B. Is currently treated with a maximally tolerated inhaled corticosteroid for at least 3 months **OR** 3. The patient has an intolerance or hypersensitivity to inhaled corticosteroid therapy **OR** 4. The patient has an FDA labeled contraindication to ALL inhaled corticosteroids **AND** B. ONE of the following: 1. The patient is currently being treated for at least 3 months with ONE of the following: A. A long-acting beta-2 agonist (LABA) **OR** B. Long-acting muscarinic antagonist (LAMA) **OR** C. A Leukotriene receptor antagonist (LTRA) **OR** D. Theophylline **OR** 2. The patient has an intolerance or hypersensitivity to therapy with long-acting beta-2 agonists (LABA), long-acting muscarinic antagonists (LAMA), leukotriene receptor antagonist (LTRA), or theophylline **OR** 3. The patient has an FDA labeled contraindication to ALL long-acting beta-2 agonists (LABA) AND long-acting muscarinic antagonists (LAMA) **AND** C. The patient will continue asthma control therapy (e.g., ICS, ICS/LABA, LTRA, LAMA, theophylline) in combination with the requested agent **AND** D. The requested dose is based on the patient's pretreatment serum IgE level and body weight as defined in FDA labeling AND does NOT exceed 375 mg every 2 weeks **AND** 3. If the patient has a diagnosis of chronic rhinosinusitis with nasal polyps (CRSwNP), ALL of the following: A. The patient is currently treated with standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids) **AND**

Module	Clinical Criteria for Approval
	B. The patient will continue standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids) in combination with the requested agent **AND** C. The requested dose is based on the patient's pretreatment serum IgE level and body weight as defined in FDA labeling AND does NOT exceed 600 mg every 2 weeks **AND** 4. If the patient has a diagnosis of chronic spontaneous urticaria (CSU) (otherwise known as chronic idiopathic urticaria [CIU]), the requested dose is within FDA labeled dosing AND does NOT exceed 300 mg every 4 weeks **AND** 5. If the patient has a diagnosis of IgE-mediated food allergy, the requested dose is based on the patient's pretreatment serum IgE level and body weight as defined in FDA labeling AND does NOT exceed 600 mg every 2 weeks **AND** 6. If the patient has another FDA labeled indication for the requested agent, the requested dose is within FDA labeled dosing for the requested indication **AND** 7. If the patient has another indication that is supported in compendia for the requested agent, the requested dose is supported in compendia for the requested indication **AND** 8. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist, otolaryngologist, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 9. ONE of the following (Please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (copy of support required, e.g., clinical trials, phase III studies, guidelines) **AND** 10. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 6 months for asthma, chronic idiopathic urticaria, IgE-mediated food allergy, and chronic rhinosinusitis with nasal polyps (CRSwNP) 12 months for all other indications **Renewal Evaluation**

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. ONE of the following: A. The patient has a diagnosis of moderate to severe persistent asthma AND ALL of the following: 1. The patient has had improvements or stabilization with the requested agent from baseline (prior to therapy with the requested agent) as indicated by ONE of the following: A. Increase in percent predicted Forced Expiratory Volume (FEV1) **OR** B. Decrease in the dose of inhaled corticosteroid required to control the patient's asthma **OR** C. Decrease in need for treatment with systemic corticosteroids due to exacerbations of asthma **OR** D. Decrease in the number of hospitalizations, need for mechanical ventilation, or visits to the emergency room or urgent care due to exacerbations of asthma **AND** 2. The patient is currently treated and is compliant with standard therapy [i.e., inhaled corticosteroids (ICS), ICS/long-acting beta-2 agonist (ICS/LABA), leukotriene receptor antagonist (LTRA), long-acting muscarinic antagonist (LAMA), theophylline] **AND** 3. The requested dose is based on the patient's pretreatment serum IgE level and body weight as defined in FDA labeling AND does NOT exceed 375 mg every 2 weeks **OR** B. The patient has a diagnosis of chronic spontaneous urticaria (CSU) (otherwise known as chronic idiopathic urticaria [CIU]) AND BOTH of the following: 1. The patient has had clinical benefit with the requested agent **AND** 2. The requested dose is within FDA labeled dosing for the requested indication AND does NOT exceed 300 mg every 4 weeks **OR** C. The patient has a diagnosis of chronic rhinosinusitis with nasal polyps (CRSwNP) AND ALL of the following: 1. The patient has had clinical benefit with the requested agent **AND** 2. The patient will continue standard nasal polyp maintenance therapy (e.g., nasal saline irrigation, intranasal corticosteroids) in combination with the requested agent **AND**

Module	Clinical Criteria for Approval
	3. The requested dose is based on the patient's pretreatment serum IgE level and body weight as defined in FDA labeling AND does NOT exceed 600 mg every 2 weeks **OR** D. The patient has a diagnosis of IgE-mediated food allergy, AND the requested dose is based on the patient's pretreatment serum IgE level and body weight as defined in FDA labeling AND does NOT exceed 600 mg every 2 weeks **OR** E. The patient has another FDA labeled indication for the requested agent AND BOTH of the following: 1. The patient has had clinical benefit with the requested agent **AND** 2. The requested dose is within FDA labeled dosing for the requested indication **OR** F. The patient has another indication that is supported in compendia for the requested agent AND BOTH of the following: 1. The patient has had clinical benefit with the requested agent **AND** 2. The requested dose is supported in compendia for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., allergist, immunologist, otolaryngologist, pulmonologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. ONE of the following (Please refer to "Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with another immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (copy of support required, e.g., clinical trials, phase III studies, guidelines) **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, DrugDex 1 or 2a level of evidence, or NCCN 1 or 2a recommended use **Length of Approval:** 12 months

CONTRAINDICATION AGENTS

Contraindicated as Concomitant Therapy
Agents NOT to be used Concomitantly Abrilada (adalimumab-afzb) Actemra (tocilizumab) Adalimumab Adbry (tralokinumab-ldrm) Amjevita (adalimumab-atto) Arcalyst (rilonacept) Avsola (infliximab-axxq) Benlysta (belimumab) Bimzelx (bimekizumab-bkzx) Cibinqo (abrocitinib) Cimzia (certolizumab) Cinqair (reslizumab) Cosentyx (secukinumab) Cyltezo (adalimumab-adbm) Dupixent (dupilumab) Enbrel (etanercept) Entyvio (vedolizumab) Fasenra (benralizumab) Hadlima (adalimumab-bwwd) Hulio (adalimumab-fkjp) Humira (adalimumab) Hyrimoz (adalimumab-adaz) Idacio (adalimumab-aacf) Ilaris (canakinumab) Ilumya (tildrakizumab-asmn) Inflectra (infliximab-dyyb) Infliximab Kevzara (sarilumab) Kineret (anakinra) Leqselvi (deuruxolitinib) Litfulo (ritlecitinib) Nemluvio (nemolizumab-ilto) Nucala (mepolizumab) Olumiant (baricitinib) Omvoh (mirikizumab-mrkz) Opzelura (ruxolitinib)

Contraindicated as Concomitant Therapy
Orencia (abatacept)
Otezla (apremilast)
Pyzchiva (ustekinumab-ttwe)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rinvoq (upadacitinib)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Saphnelo (anifrolumab-fnia)
Selarsdi (ustekinumab-aekn)
Siliq (brodalumab)
Simlandi (adalimumab-ryvk)
Simponi (golimumab)
Simponi ARIA (golimumab)
Skyrizi (risankizumab-rzaa)
Sotyktu (deucravacitinib)
Spevigo (spesolimab-sbzo) subcutaneous injection
Stelara (ustekinumab)
Taltz (ixekizumab)
Tezspire (tezepelumab-ekko)
Tofidence (tocilizumab-bavi)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tyenne (tocilizumab-aazg)
Tysabri (natalizumab)
Velsipity (etrasimod)
Wezlana (ustekinumab-auub)
Xeljanz (tofacitinib)
Xeljanz XR (tofacitinib extended release)
Xolair (omalizumab)
Yuflyma (adalimumab-aaty)
Yusimry (adalimumab-aqvh)
Zeposia (ozanimod)
Zymfentra (infliximab-dyyb)

Xolremdi (mavorixafor)

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Xolremdi™ (mavorixafor) Capsule	Patients 12 years of age and older with WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes		1

CLINICAL RATIONALE

WHIM (warts, hypogammaglobulinemia, infections and myelokathexis) Syndrome	Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome is a rare primary immunodeficiency caused by gain-of-function mutations in the *CXCR4* gene. CXCR4 normally promotes homing of circulating senescent neutrophils to bone marrow and inhibits egress of nascent bone marrow neutrophils to blood. Myelokathexis is a kind of neutropenia caused by neutrophil retention in bone marrow and in WHIM syndrome is associated with lymphopenia and monocytopenia.(2,4) It is estimated to occur in about 1 in 5 million live births. Approximately 60 cases have been reported in the medical literature.(3) While symptoms vary, patients with WHIM syndrome can have serious and/or frequent infections, including pneumonia, sinusitis, and skin infections and are at risk for life-threatening bacterial and viral infections.(2,4,5) Xolremdi is a selective CXCR4 antagonist and is the first therapy specifically indicated in patients with WHIM syndrome. Mavorixafor is a selective allosteric antagonist of the CXCR4 receptor that increases mobilization and trafficking of leukocytes from the bone marrow.(5)
Efficacy	The efficacy of Xolremdi in patients aged 12 years and older with WHIM syndrome was demonstrated in the 52-week, randomized, double-blind, placebo-controlled portion of Study 1 (NCT03995108). Enrolled patients had a genotype-confirmed variant of CXCR4 consistent with WHIM syndrome, and a confirmed absolute neutrophil count (ANC) less than or equal to 400 cells/microliter (or total white blood cell [WBC] count less than or equal to 400 cells/microliter if

	ANC was below the lower limit of detection) obtained during no clinical evidence of infection.(1,6) Patients were permitted to continue (but not initiate) immunoglobulin therapy at the same dose. Use of other CXCR4 antagonists was not permitted. Thirty-one patients were randomized 1:1 to receive either placebo (N=17) or Xolremdi (N=14) once daily for 52 weeks.(1) The efficacy of Xolremdi in the treatment of patients with WHIM syndrome was based on improvement in absolute neutrophil counts (ANC), improvement in absolute lymphocyte counts (ALC), and a reduction in infections. For ANC, the mean time (hours) above ANC threshold (TATANC) of 500 cells/microliter over a 24-hour period was assessed 4 times throughout the study (every 3 months for 12 months). The results over the 52-week period showed that TATANC was statistically significantly greater in patients treated with Xolremdi (LS mean [SE] 15.0 [1.89] hours) compared with placebo (2.8 [1.52] hours) (p value <0.0001).(1) For ALC, the mean time (hours) above ALC threshold (TATALC) of 1,000 cells/microliter over a 24-hour period was assessed 4 times throughout the study (every 3 months for 12 months). The results over the 52-week period showed that TATALC was statistically significantly greater in patients treated with Xolremdi (LS mean [SE] 15.8 [1.39] hours) compared with placebo (4.6 [1.15] hours) (p value <0.0001).(1) The efficacy of Xolremdi was further assessed in a composite endpoint consisting of total infection score and total wart change score using a Win-Ratio method. The Win-Ratio of 2.76 is the number of pairs of Xolremdi-treated patient “wins” divided by the number of pairs of placebo patient “wins.” Analyses of the individual components of this composite endpoint showed an approximately 40% reduction of total infection score, weighted by infection severity, in Xolremdi-treated patients compared with placebo-treated patients. The annualized infection rate was reduced approximately 60% in Xolremdi-treated patients [LS mean (SE) 1.7(0.5)] compared with placebo-treated patients [LS mean (SE) 4.2 (0.7)]. There was no difference in total wart change scores between the Xolremdi and placebo treatment arms over the 52-week period.(1)
Safety	Xolremdi has no boxed warnings, and is contraindicated with use of drugs that are highly dependent on CYP2D6 for clearance.(1)

REFERENCES

Number	Reference
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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Initial Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. ONE of the following: A. The requested agent is eligible for continuation of therapy AND ONE of the following: **Agents Eligible for Continuation of Therapy** Xolremdi (mavorixafor) 1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days **OR**

Module	Clinical Criteria for Approval
	2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed **OR** B. BOTH of the following: 1. ONE of the following: A. The patient has a diagnosis of WHIM (warts, hypogammaglobulinemia, infections and myelokathexis) syndrome AND ALL of the following: 1. Genetic analysis confirms mutation in the CXC chemokine receptor 4 (CXCR4) gene **AND** 2. Confirmed absolute neutrophil count (ANC) OR total white blood cell (WBC) count is less than or equal to 400 cells/microliter (prior to therapy with the requested agent AND during no clinical evidence of infection) **AND** 3. The prescriber has assessed baseline status (prior to therapy with the requested agent) of the patient's symptoms (e.g., absolute neutrophil counts [ANC], absolute lymphocyte counts [ALC], number of infections) **OR** B. The patient has another FDA labeled indication for the requested agent and route of administration **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The patient will NOT be using the requested agent in combination with any other CXCR4 antagonists (e.g., plerixafor) for the requested indication **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., geneticist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval**: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

Module	Clinical Criteria for Approval
	Renewal Evaluation **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The patient will NOT be using the requested agent in combination with any other CXCR4 antagonists (e.g., plerixafor) for the requested indication **AND** 4. The prescriber is a specialist in the area of the patient's diagnosis (e.g., geneticist, immunologist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval**: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
Universal QL	**Quantity limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support for why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **OR** C. BOTH of the following:

Module	Clinical Criteria for Approval
	1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of Approval:** up to 12 months

Zeposia

Prior Authorization with Quantity Limit

FDA LABELED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Zeposia® (ozanimod) Capsule	• Treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults • Moderately to severely active ulcerative colitis (UC) in adults		1

CLINICAL RATIONALE

Multiple sclerosis	Multiple sclerosis (MS) is a disorder of the central nervous system (CNS) characterized by demyelination, inflammation, and degenerative changes. Most people with MS experience relapses and remissions of neurological symptoms, particularly early in the disease, and clinical events are usually associated with areas of CNS inflammation. Gradual worsening or progression, with or without subsequent acute attacks of inflammation or radiological activity, may take place early, but usually becomes more prominent over time. While traditionally viewed as a disease solely of CNS white matter, more advanced imaging techniques have demonstrated significant early and ongoing CNS gray matter damage as well.(2) Those diagnosed with MS may have many fluctuating and disabling symptoms (including, but not limited to, fatigue, pain, bladder and bowel issues, sexual dysfunction, movement and coordination problems, visual disturbances, and cognition and emotional changes.(18) There are currently four major types of MS: clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS).(9)
Clinically isolated syndrome	CIS is a first episode of neurologic symptoms caused by inflammation and demyelination in the central nervous system. The episode, which by definition must last for at least 24 hours, is characteristic of multiple sclerosis but does not yet meet the criteria for a diagnosis of MS because people who experience a CIS may or may not go on to develop MS.(9) When caused by an acute inflammatory

	demyelinating event, approximately 85% of all patients subsequently develop MS. The relationship between conventional brain MRI features and the short-term risk of CIS patients developing definite MS has been assessed by several studies and allows for the diagnosis of MS based on the 2017 McDonald criteria. However, in CIS patients with initial multifocal clinical symptom presentation the abnormal MRI did not stratify the risk for clinically definite disease conversion.(17) CIS cohort studies spanning 7 through 20 years of follow-up investigated the long-term risk of MS development and found conversions rates of 65-80% for patients with an abnormal conventional MRI and 8-20% for those with an inconspicuous baseline MRI.(17)
Relapsing remitting multiple sclerosis	RRMS is characterized by clearly defined attacks (relapses) of new or increasing neurologic symptoms. These relapses are followed by periods of partial or complete recovery. There is no or minimal disease progression during the periods between disease relapses, though individual relapses may result in severe residual disability. The course of MS varies, however, about 85-90% of individuals with MS demonstrate a relapsing pattern at onset, which transitions over time in the majority of untreated patients to a pattern of progressive worsening with few or no relapses or MRI activity.(9)
Secondary progressive multiple sclerosis	SPMS begins as RRMS, but over time the disease enters a stage of steady deterioration in function, unrelated to acute attacks. Most people with RRMS will transition to SPMS. In SPMS there is no progressive worsening of symptoms over time with no definite periods of remission.(9)
2017 McDonald Criteria for the diagnosis of Multiple Sclerosis:	Diagnostic criteria for multiple sclerosis combining clinical, imaging, and laboratory evidence have evolved over time. The increasing incorporation of paraclinical assessments, especially imaging, to supplement clinical findings has allowed earlier, more sensitive, and more specific diagnosis.(7,8) The diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in the CNS in space and time.(7) Misdiagnosis of multiple sclerosis remains an issue in clinical practice, and several factors that potentially increase this risk have been identified. Multiple sclerosis has heterogeneous clinical and imaging manifestations, which differ between patients over time. There is no single pathognomonic clinical feature or diagnostic test; diagnosis of multiple sclerosis relies on the integration of clinical, imaging, and laboratory findings. MRI abnormalities associated with other diseases and non-specific MRI findings, which are common in the general population, can be mistaken for multiple sclerosis. The increasingly strong focus

on timely diagnosis to alleviate uncertainty for patients and allow initiation of disease-modifying therapies might also increase the risk of misdiagnosis.(7)

With increasing availability and use of MRI, incidental T2 hyperintensities on brain imaging are common, the subset of individuals with MRI findings that are strongly suggestive of multiple sclerosis lesions but with no neurological manifestations or other clear-cut explanation are said to have radiologically isolated syndrome. There is no consensus on whether patients with radiologically isolated syndrome will develop MS. Some practitioners argue that these patients have a high likelihood of developing MS while others argue that up to two-thirds of these patients will not receive a diagnosis of MS in 5 years. A consensus panel decided to require clinical manifestations to make the diagnosis of MS (2017 McDonald Criteria for the diagnosis of Multiple Sclerosis).(7)

The 2017 McDonald criteria to diagnose MS is shown in the chart below.(7,8)

Clinical Presentation	**Additional Data needed to make MS diagnosis**
In a person with a typical attack/CIS at onset	
Greater than or equal to 2 attacks and objective clinical evidence of greater than or equal to 2 lesions OR Greater than or equal to 2 attacks and objective clinical evidence of 1 lesion with historical evidence of prior attack involving lesion in different location	None. Dissemination in space* and dissemination in time** have been met
Greater than or equal to 2 attacks and objective clinical evidence of 1 lesion	**ONE** of these criteria: Additional clinical attack implicating different CNS site OR Greater than or equal to 1 symptomatic or asymptomatic MS-typical T2 lesions in greater than or equal to 2 areas of CNS:

		periventricular, juxtacortical/cortical, infratentorial, or spinal cord
	1 attack and objective clinical evidence of greater than or equal to 2 lesions	**ONE** of these criteria: Additional clinical attack OR Simultaneous presence of both enhancing and non-enhancing symptomatic or asymptomatic MS-typical MRI lesions OR New T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) OR CSF specific (i.e., not in serum) oligoclonal bands
	1 attack and objective clinical evidence of 1 lesion	**ONE** of these criteria: Additional attack implicating different CNS site OR Greater than or equal to 1 MS-Typical symptomatic or asymptomatic T2 lesions in greater than or equal to 2 areas of CNS: periventricular, juxtacortical/cortical, infratentorial, or spinal cord **AND** **ONE** of these criteria: Additional clinical attack OR Simultaneous presence of both enhancing and non-enhancing symptomatic or asymptomatic MS-typical MRI lesions OR New T2 enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) OR CSF-specific (i.e., not in serum) oligoclonal bands

	* - Dissemination in space is defined as one or more T2-hyperintense lesions that are characteristic of multiple sclerosis in 2 or more of four areas of the CNS (periventricular, cortical or juxtacortical, and infratentorial brain regions, and the spinal cord) demonstrated by an additional clinical attack implicating a different CNS site or by MRI.(8) ** - Dissemination in time is defined as simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI. The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.(8)
Treatment of MS	Both the Multiple Sclerosis Coalition and the American Academy of Neurology recommend initiating treatment with a DMA FDA approved for the patient's phenotype as soon as possible following the diagnosis of multiple sclerosis. There are several DMAs with at least 10 mechanisms of action available to people with MS. The factors affecting choice of therapy at any point in the disease course are complex and most appropriately analyzed and addressed through a shared decision-making process between the individual and the treating clinician.(2,5) There is a subgroup of RRMS patients who have a more aggressive disease course marked by a rapid accumulation of physical and cognitive deficit, despite treatment with 1 or more DMTs. In the past, this disease phenotype was called aggressive MS; it is now called highly active MS. It is generally agreed that the severe nature of this phenotype requires different treatment decisions. There is no consensus on the definition of highly active MS or the treatment algorithm.(12) The National Institute for Health and Care Excellence (NICE) defines rapidly evolving severe RRMS as two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.(6) The Multiple Sclerosis Coalition recommends that clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, natalizumab or ocrelizumab for newly diagnosed individuals with highly active MS. Clinicians should also consider prescribing a high efficacy medication for individuals who have breakthrough activity on another DMA regardless of the number of previously used agents.(2) The American Academy of Neurology has recommended alemtuzumab, fingolimod, and natalizumab as options for patients with MS with highly active MS. There lacks a consensus for

	what constitutes as highly active MS, however.(5) The National Institute for Health and Care Excellence (NICE) defines rapidly evolving severe RRMS as two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI.(19) Lack of response to DMAs is hard to define, as most patients with MS are not free of all disease activity. Relapses or new MRI detected lesions may develop after initiation of a DMA and before the treatment becomes effective for patients. When determining efficacy, sufficient time for the DMA therapy to take full effect and patient adherence are important considerations. Evidence of one or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination while being treated with a DMA for a 1 year period suggests a sub-optimal response, an alternative regimen (e.g., different mechanism of action) should be considered to optimize therapeutic benefit.(5) A National MS Society consensus statement recommends changing from one disease modifying therapy to another only for medically appropriate reasons (e.g. lack of efficacy, adverse effects, or if better treatments options become available).(2) Existing MS therapies are partly effective in halting ongoing inflammatory tissue damage and clinical progression. MS pathogenesis is complex and probably heterogeneous among patients, suggesting that combination therapy strategies that target a range of disease mechanisms might be more effective than medications used as monotherapy. Although preliminary studies have provided favorable results, however, several subsequent large, randomized, controlled trials have had negative of conflicting results. There also may be more adverse reactions associated with combination therapies due to the additive effect.(10) In 2020 a Canadian MS working group published recommendations on optimal therapy in relapsing forms of MS. This group notes that there are few studies that have directly compared injectable and oral DMTs. A recent network meta-analysis suggested that pegylated interferon-β-1a and dimethyl fumarate have superior efficacy to other base therapies, there is insufficient data to demonstrate that one base injectable or oral DMT is superior to another. As a result, the choice of initial treatment will need to be individualized according to disease activity, severity, and comorbidities.(11) In addition to base therapies, the working group considers 5 DMTs to be of higher efficacy which although can be used as initial therapy, they are generally reserved for patients with a poor response or tolerability with a base therapy. Patients presenting with high disease activity or aggressive/rapidly evolving MS

at onset could be considered to initiate therapy with one of these more effective therapies, but the most common treatment initiation is to start on a base therapy with the view of switching within 6-12 months. The 5 agents considered to be of higher efficacy are:(11)

- Oral agents
  - Fingolimod
  - Cladribine
- Monoclonal antibodies
  - Natalizumab
  - Ocrelizumab
  - Alemtuzumab

The MS working group discussed the criteria for switching therapies in RRMS and recommends a change in DMT is indicated for patients who meet any of the Major criteria below:(11)

	Minor	**Major**
Relapse rate	• One relapse in first 2 years of treatment	• Greater than or equal to 2 relapses in first year of treatment
Severity	• Mild • No functional impairment (school, work, daily activities, etc.) • No motor/cerebellar/brain stem /sphincter involvement	• Moderate to severe • Functional impairment • Motor/cerebellar/brain stem/sphincter involvement
Recovery	• Full recovery at 6 months • No functional impairment • EDSS change from baseline less than or equal to 1 point at 6 months unless	• Incomplete recovery • Functional impairment • If EDSS at baseline was 0 then a greater than 1.5 point change from baseline • If EDSS is greater than 0 but less than 5.5 at baseline then

	baseline EDSS greater than 5.5	greater than 1 point change at 6 months • If EDSS is greater than 5.5 any change would be a major concern
MRI	• One new lesion	• Greater than or equal to 3 new lesions during treatment excluding spinal cord lesions • Greater than 1 spinal cord lesion

The workgroup does note that on-treatment relapses should only be performed once the drug has achieved a full clinical effect (typically 2-6 months after drug initiation). Relapses that occur before the maximal efficacy of the drug has been reached should be given less weight, but major criteria should take precedence regardless of timing.(11)

For patients with SPMS, the workgroup states that is generally advised to continue with the current DMT after onset of SPMS since many patients will have ongoing inflammatory disease and subclinical disease activity may worsen if treatment is withdrawn. A change in treatment may be warranted in patients with active SPMS who continue to have relapses or new MRI lesions, with the caveat that there is insufficient evidence to identify criteria for a suboptimal response in patients with SPMS.(11)

For patients with primary progressive MS, clinicians should offer ocrelizumab to patients with active disease provided the benefits outweigh the risks. Caution is recommended when considering treatment for PPMS subgroups that are less likely to benefit from treatment, such as older patients, those with long-standing stable disease, and/or significant neurological deficits, since the limited benefits may not justify the risk associated with treatment. Rituximab may be considered as an alternative therapy for PPMS in regions that permit off-label use in MS due to cost or other considerations.(11)

The Institute for Clinical and Economic Review (ICER) evaluated a new IV treatment, ublituximab against current FDA and accepted use DMT for adults with RRMS. Only in the case of ublituximab vs placebo/no DMT is ublituximab superior rated. The ratings are noted below.(3)

Adults with RRMS

Treatment	Comparator	Evidence Rating
Ublituximab	Natalizumab	I: Insufficient
	Ofatumumab	I: Insufficient
	Ocrelizumab	I: Insufficient
	Rituximab	I: Insufficient
	Fumarate class (dimethyl, diroximel, monomethyl	C++: Comparable or better
	Fingolimod	C++: Comparable or better
	Ozanimod	C++: Comparable or better
	Ponesimod	C++: Comparable or better
	Siponimod	I: Insufficient
	Teriflunomide	B: Incremental
	Placebo/no DMT	A: Superior

A: Superior - High certainty of a substantial (moderate-large) net health benefit
B: Incremental - High certainty of a small net health benefit
C++: Comparable or better - Moderate certainty of a comparable, small, or substantial net health benefit, with which certainty of at least a comparable net

	health benefit I: Insufficient - Any situation where the level of certainty in the evidence is low ICER does note that payers should consider the following:(3) Payors should remove barriers to access to rituximab for RMS patients who are appropriate candidates for this therapy. This includes coverage of biosimilar rituximab with little or no prior authorization given the lack of concern regarding use in appropriate patients and how inexpensive it is compared with other monoclonal antibodies of equal effectiveness Payers should not unilaterally implement policies to switch RMS patients who are stable on their chosen DMT over to lower-cost biosimilar rituximab

Ulcerative Colitis (UC)	Ulcerative colitis (UC) is a chronic immune-mediated inflammatory condition affecting the large intestine associated with inflammation of the rectum, but that can extend to involve additional areas of the colon. The American College of Gastroenterology (ACG) recommends a treat-to-target approach and recommend therapeutic management should be guided by diagnosis (i.e., Montreal classification), assessment of disease activity (i.e., mild, moderate, and severe), and disease prognosis. The ACG treatment recommendations are further broken down into induction therapies and maintenance of remission. The 2019 ACG treatment guidelines recommend the following for therapeutic management of UC:(14)
	
	Induction of remission:
	
	• Mildly active disease:
	  ○ Rectal 5-ASA at a dose of 1 g/day with or without oral 5-ASA at a dose of at least 2 g/day for left-sided UC
	  ○ Rectal 5-ASA at a dose of 1 g/day for ulcerative proctitis
	  ○ Oral 5-ASA at a dose of at least 2 g/day for extensive UC
	  ○ Add oral budesonide multi-matrix (MMX) 9 mg/day for patients that are intolerant or non-responsive to oral and/or rectal and oral 5-ASA at appropriate doses
	• Moderately active disease:
	  ○ Oral budesonide multi-matrix (MMX) 9 mg/day for induction of remission
	• Moderately to severely active disease:
	  ○ Oral systemic corticosteroids, TNF inhibitors (i.e., adalimumab, golimumab, or infliximab), tofacitinib, or vedolizumab to induce remission

	○ Combination of infliximab with thiopurine therapy when using infliximab for induction ○ Switch to tofacitinib or vedolizumab for induction in patients that have failed TNF inhibitors ○ Patients with initial response to TNF inhibitors that lose response should have antibody levels and serum drug levels tested to assess reason for loss of response. If serum levels are adequate, use of another TNF inhibitor is not likely to be of benefit. Maintenance of remission: • Previously mildly active disease: ○ Rectal 5-ASA at a dose of 1 g/day in patients with ulcerative proctitis ○ Oral 5-ASA at a dose of at least 2 g/day in patients with left-sided or extensive UC • Previously moderately to severely active disease: ○ Thiopurines in patients that achieved remission due to corticosteroid induction ○ Continue TNF inhibitors (i.e., adalimumab, golimumab, or infliximab) for remission due to TNF induction ○ Continue vedolizumab for remission due to vedolizumab induction ○ Continue tofacitinib for remission due to tofacitinib induction The American Gastroenterology Association (AGA) published recommendations for the management of mild to moderate UC:(15) • Use either standard-dose mesalamine (2-3 g/day) or diazo-bonded 5-ASA for patients with extensive UC for induction of remission and maintenance of remission • May add rectal mesalamine to oral 5-ASA in patients with extensive or left-sided UC for induction of remission and maintenance of remission • Use high dose mesalamine (greater than 3 g/day) with rectal mesalamine in patients with suboptimal response to standard-dose mesalamine, diazo-bonded 5-ASA, or with moderate disease activity for induction of remission and maintenance of remission • Add either oral prednisone or budesonide MMX in patients that are refractory to optimized oral and rectal 5-ASA regardless of disease extent

	The American Gastroenterology Association (AGA) published recommendations for the management of moderate to severe UC:(16)
	
	• Standard of care is to continue agents initiated for induction therapy as maintenance therapy, if they are effective (excluding corticosteroids and cyclosporine)
	• Adult outpatients with moderate to severe UC:
	  ○ Infliximab, adalimumab, golimumab, vedolizumab, tofacitinib or ustekinumab are strongly recommended over no treatment
	  ○ Biologic naïve patients:
	  ▪ infliximab or vedolizumab are conditionally recommended over adalimumab for induction of remission
	  ▪ Recommend tofacitinib only be used in the setting of a clinical or registry study
	  ○ Previous exposure to infliximab, particularly those with primary non-response, ustekinumab or tofacitinib are conditionally recommended over vedolizumab or adalimumab for induction of remission
	  ○ Conditionally recommend against use of thiopurine monotherapy for induction, but may be used for maintenance of remission over no treatment

Safety	Zeposia (ozanimod) is contraindicated in:(1) • In patients who in, the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure • Presence of Mobitz type II second-degree or third degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker • Severe untreated sleep apnea • Concomitant use with a monoamine oxidase inhibitor

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PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

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Module	Clinical Criteria for Approval

	TNF inhibitors				
SC: adalimumab product(s)***, Entyvio, Skyrizi, Stelara, Tremfya	Oral: Rinvoq, Xeljanz*, Xeljanz XR*	SC: Omvoh Simponi (an adalimumab product*** is a required Step 1 agent)	SC: Zymfentra Oral: Zeposia	N/A	Oral: Velsipity

* A trial of either or both Xeljanz products (Xeljanz and Xeljanz XR) collectively counts as ONE product.
** Allowable preferred adalimumab product(s): Adalimumab-aaty, Adalimumab-adaz, Hadlima, Simlandi
*** Allowable preferred adalimumab product(s): Adalimumab-aaty, Adalimumab-adaz, Hadlima, Humira, Simlandi

Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
   A. The requested agent is eligible for continuation of therapy AND ONE of the following:

Agents Eligible for Continuation of Therapy
Zeposia (ozanimod)

   1. The patient has been treated with the requested agent within the past 90 days **OR**
   2. The prescriber states the patient has been treated with the requested agent within the past 90 days AND is at risk if therapy is changed **OR**

   B. BOTH of the following:
      1. ONE of the following:

Module	Clinical Criteria for Approval
	A. The patient has a relapsing form of multiple sclerosis (MS) AND ONE of the following: 1. The patient will NOT be using the requested agent in combination with another disease modifying agent (DMA) used for the requested indication (Please refer to "MS DMA Agents" contraindicated table) **OR** 2. The patient will be using the requested agent in combination with another DMA used for the treatment of MS AND BOTH of the following: A. The requested agent will be used in combination with Mavenclad (cladribine) **AND** B. There is support for the use of the requested agent in combination with Mavenclad (e.g., relapse between cycles of Mavenclad (cladribine) **OR** B. The patient has a diagnosis of moderately to severely active ulcerative colitis (UC) AND ALL of the following: 1. ONE of the following: A. The patient has tried and had an inadequate response to ONE conventional agent (i.e., 6-mercaptopurine, azathioprine, balsalazide, corticosteroids, cyclosporine, mesalamine, sulfasalazine) used in the treatment of UC for at least 3-months **OR** B. The patient has severely active ulcerative colitis **OR** C. The patient has an intolerance or hypersensitivity to ONE of the conventional agents used in the treatment of UC **OR** D. The patient has an FDA labeled contraindication to ALL of the conventional agents used in the treatment of UC **OR** E. The patient's medication history indicates use of another biologic immunomodulator agent that is FDA labeled or supported in compendia for the treatment of UC **AND** 2. ONE of the following: A. The patient has tried and had an inadequate response to at least TWO Step 1 immunomodulatory agents (see Immunomodulatory Agent Step table) **OR** B. The patient has an intolerance or hypersensitivity to at least TWO Step 1 immunomodulatory agents **OR**

Module	Clinical Criteria for Approval
	C. The patient has an FDA labeled contraindication to ALL Step 1 immunomodulatory agents **AND** 3. ONE of the following (Please refer to "Immunomodulatory Agents NOT to be used Concomitantly" table): A. The patient will NOT be using the requested agent in combination with an immunomodulatory (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** B. The patient will be using the requested agent in combination with an immunomodulatory agent AND BOTH of the following: 1. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent **AND** 2. There is support for the use of combination therapy (copy of support required, i.e., clinical trials, phase III studies, guidelines) **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The prescriber has performed an electrocardiogram within 6 months prior to initiating treatment **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist for the diagnosis of multiple sclerosis, gastroenterologist for the diagnosis of ulcerative colitis) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Compendia Allowed:** AHFS, or DrugDex 1 or 2a level of evidence **Length of Approval:** 12 months. NOTE: The starter dose can be approved for the FDA labeled starting dose and the maintenance dose can be approved for the remainder of 12 months. NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation**

Module	Clinical Criteria for Approval
	Target Agent(s) will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., neurologist for the diagnosis of multiple sclerosis, gastroenterologist for the diagnosis of ulcerative colitis) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. ONE of the following: A. The patient has a diagnosis of multiple sclerosis AND ONE of the following: 1. The patient will NOT be using the requested agent in combination with another disease modifying agent (DMA) for the requested indication (Please refer to "MS DMA Agents" contraindicated use table **OR** 2. The patient will be using the requested agent in combination with another DMA used for the treatment of the requested indication AND BOTH of the following: A. The requested agent will be used in combination with Mavenclad (cladribine) **AND** B. There is support for the use of the requested agent in combination with Mavenclad (e.g., relapse between cycles of Mavenclad) **OR** B. The patient has a diagnosis of ulcerative colitis AND ONE of the following (Please refer to "Immunomodulatory Agents NOT to be used Concomitantly" table: 1. The patient will NOT be using the requested agent in combination with an immunomodulatory agent (e.g., TNF inhibitors, JAK inhibitors, IL-4 inhibitors) **OR** 2. The patient will be using the requested agent in combination with another immunomodulatory agent AND BOTH of the following: A. The prescribing information for the requested agent does NOT limit the use with another immunomodulatory agent AND B. There is support for the use of combination therapy (copy of support required, i.e., clinical trials, phase III studies, guidelines) 5. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
QL Standalone	**Quantity Limit for the Requested Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. The requested quantity (dose) exceeds the program quantity limit AND ONE of the following: A. BOTH of the following: 1. The requested agent does NOT have a maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **OR** B. BOTH of the following: 1. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** 2. There is support why the requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** C. BOTH of the following: 1. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND** 2. There is support for therapy with a higher dose for the requested indication **Length of approval:** up to 12 months
Zeposia PA through preferred	**Quantity Limit for the Target Agent(s)** will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does not exceed the program quantity limit **OR** 3. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) exceeds the maximum FDA labeled dose for the requested indication **AND**

Module	Clinical Criteria for Approval
	C. There is support for therapy with a higher dose for the requested indication **Length of Approval**: up to 12 months. NOTE: The starter dose can be approved for the FDA labeled starting dose and the maintenance dose can be approved for the remainder of 12 months.

CONTRAINDICATION AGENTS

Contraindicated as Concomitant Therapy
MS Disease Modifying Agents
Aubagio (teriflunomide)
Avonex (interferon b-1a)
Bafiertam (monomethyl fumarate)
Betaseron (interferon b-1b)
Briumvi (ublituximab-xiiy)
Copaxone (glatiramer)
dimethyl fumarate
Extavia (interferon b-1b)
fingolimod
Gilenya (fingolimod)
Glatopa (glatiramer)
glatiramer
Kesimpta (ofatumumab)
Mavenclad (cladribine)

Contraindicated as Concomitant Therapy
Mayzent (siponimod)
Plegridy (peginterferon b-1a)
Ponvory (ponesimod)
Rebif (interferon b-1a)
Tascenso ODT (fingolimod)
Tecfidera (dimethyl fumarate)
Vumerity (diroximel fumarate)
Zeposia (ozanimod)
Immunomodulatory Agents NOT to be used concomitantly
Abrilada (adalimumab-afzb)
Actemra (tocilizumab)
Adalimumab
Adbry (tralokinumab-ldrm)
Amjevita (adalimumab-atto)
Arcalyst (rilonacept)
Avsola (infliximab-axxq)
Benlysta (belimumab)
Bimzelx (bimekizumab-bkzx)
Cibinqo (abrocitinib)

Contraindicated as Concomitant Therapy
Cimzia (certolizumab)
Cinqair (reslizumab)
Cosentyx (secukinumab)
Cyltezo (adalimumab-adbm)
Dupixent (dupilumab)
Ebglyss (lebrikizumab-lbkz)
Enbrel (etanercept)
Entyvio (vedolizumab)
Fasenra (benralizumab)
Hadlima (adalimumab-bwwd)
Hulio (adalimumab-fkjp)
Humira (adalimumab)
Hyrimoz (adalimumab-adaz)
Idacio (adalimumab-aacf)
Ilaris (canakinumab)
Ilumya (tildrakizumab-asmn)
Inflectra (infliximab-dyyb)
Infliximab
Kevzara (sarilumab)
Kineret (anakinra)

Contraindicated as Concomitant Therapy
Leqselvi (deuruxolitinib)
Litfulo (ritlecitinib)
Nemluvio (nemolizumab-ilto)
Nucala (mepolizumab)
Olumiant (baricitinib)
Omvoh (mirikizumab-mrkz)
Opzelura (ruxolitinib)
Orencia (abatacept)
Otezla (apremilast)
Pyzchiva (ustekinumab-ttwe)
Remicade (infliximab)
Renflexis (infliximab-abda)
Riabni (rituximab-arrx)
Rinvoq (upadacitinib)
Rituxan (rituximab)
Rituxan Hycela (rituximab/hyaluronidase human)
Ruxience (rituximab-pvvr)
Saphnelo (anifrolumab-fnia)
Selarsdi (ustekinumab-aekn)
Siliq (brodalumab)

Contraindicated as Concomitant Therapy
Simlandi (adalimumab-ryvk)
Simponi (golimumab)
Simponi ARIA (golimumab)
Skyrizi (risankizumab-rzaa)
Sotyktu (deucravacitinib)
Spevigo (spesolimab-sbzo) subcutaneous injection
Stelara (ustekinumab)
Taltz (ixekizumab)
Tezspire (tezepelumab-ekko)
Tofidence (tocilizumab-bavi)
Tremfya (guselkumab)
Truxima (rituximab-abbs)
Tyenne (tocilizumab-aazg)
Tysabri (natalizumab)
Velsipity (etrasimod)
Wezlana (ustekinumab-auub)
Xeljanz (tofacitinib)
Xeljanz XR (tofacitinib extended release)
Xolair (omalizumab)
Yuflyma (adalimumab-aaty)

Contraindicated as Concomitant Therapy
Yusimry (adalimumab-aqvh) Zeposia (ozanimod) Zymfentra (infliximab-dyyb)

CLASS AGENTS

Class	Class Drug Agents
Class Ia antiarrhythmics	
Class Ia antiarrhythmics	NORPACE*Disopyramide Phosphate Cap
Class Ia antiarrhythmics	PROCAINAMIDE*Procainamide HCl Inj
Class Ia antiarrhythmics	QUINIDINE*Quinidine
Class III antiarrhythmics	
Class III antiarrhythmics	BETAPACE*Sotalol HCl Tab
Class III antiarrhythmics	Cordarone, Pacerone (amiodarone)
Class III antiarrhythmics	CORVERT*Ibutilide Fumarate Inj
Class III antiarrhythmics	MULTAQ*Dronedarone HCl Tab
Class III antiarrhythmics	TIKOSYN*Dofetilide Cap
MS Disease Modifying Agents drug class: CD20 monoclonal antibody	
MS Disease Modifying Agents drug class: CD20 monoclonal antibody	BRIUMVI*ublituximab-xiiy soln for iv infusion

Class	Class Drug Agents
MS Disease Modifying Agents drug classes: CD20 monoclonal antibody	
MS Disease Modifying Agents drug classes: CD20 monoclonal antibody	KESIMPTA*Ofatumumab Soln Auto-Injector
MS Disease Modifying Agents drug classes: CD20 monoclonal antibody	OCREVUS*Ocrelizumab Soln For IV Infusion
MS Disease Modifying Agents drug classes: CD52 monoclonal antibody	
MS Disease Modifying Agents drug classes: CD52 monoclonal antibody	LEMTRADA*Alemtuzumab IV Inj
MS Disease Modifying Agents drug classes: Fumarates	
MS Disease Modifying Agents drug classes: Fumarates	BAFIERTAM*Monomethyl Fumarate Capsule Delayed Release
MS Disease Modifying Agents drug classes: Fumarates	TECFIDERA*Dimethyl Fumarate Capsule Delayed Release
MS Disease Modifying Agents drug classes: Fumarates	VUMERITY*Diroximel Fumarate Capsule Delayed Release
MS Disease Modifying Agents drug classes: Glatiramer	
MS Disease Modifying Agents drug classes: Glatiramer	COPAXONE*Glatiramer Acetate Soln Prefilled Syringe

Class	Class Drug Agents
MS Disease Modifying Agents drug classes: Glatiramer	GLATOPA*Glatiramer Acetate Soln Prefilled Syringe
MS Disease Modifying Agents drug classes: IgG4k monoclonal antibody	
MS Disease Modifying Agents drug classes: IgG4k monoclonal antibody	TYSABRI*Natalizumab for IV Inj Conc
MS Disease Modifying Agents drug classes: Interferons	
MS Disease Modifying Agents drug classes: Interferons	AVONEX*Interferon beta-1a injection
MS Disease Modifying Agents drug classes: Interferons	BETASERON*Interferon beta-1b injection
MS Disease Modifying Agents drug classes: Interferons	EXTAVIA*Interferon beta-1b injection
MS Disease Modifying Agents drug classes: Interferons	PLEGRIDY*Peginterferon beta-1a injection
MS Disease Modifying Agents drug classes: Interferons	REBIF*Interferon beta-1a injection
MS Disease Modifying Agents drug classes: Purine antimetabolite	
MS Disease Modifying Agents drug classes: Purine antimetabolite	MAVENCLAD*Cladribine Tab Therapy Pack

Class	Class Drug Agents
MS Disease Modifying Agents drug classes: Pyrimidine synthesis inhibitor	
MS Disease Modifying Agents drug classes: Pyrimidine synthesis inhibitor	AUBAGIO*Teriflunomide Tab
MS Disease Modifying Agents drug classes: Sphingosine 1-phosphate (SIP) receptor modulator	
MS Disease Modifying Agents drug classes: Sphingosine 1-phosphate (SIP) receptor modulator	GILENYA*Fingolimod HCl Cap
MS Disease Modifying Agents drug classes: Sphingosine 1-phosphate (SIP) receptor modulator	MAYZENT*Siponimod Fumarate Tab
MS Disease Modifying Agents drug classes: Sphingosine 1-phosphate (SIP) receptor modulator	PONVORY*Ponesimod Tab
MS Disease Modifying Agents drug classes: Sphingosine 1-phosphate (SIP) receptor modulator	TASCENSO*fingolimod lauryl sulfate tablet disintegrating
MS Disease Modifying Agents drug classes: Sphingosine 1-phosphate (SIP) receptor modulator	ZEPOSIA*Ozanimod capsule

Zokinvy

Prior Authorization with Quantity Limit

FDA APPROVED INDICATIONS AND DOSAGE

Agent(s)	FDA Indication(s)	Notes	Ref#
Zokinvy® (lonafarnib) Capsule	Patients 12 months of age and older with a body surface area (BSA) of 0.39 m^2 and above: • To reduce the risk of mortality in Hutchinson-Gilford progeria syndrome (HGPS) • For the treatment of processing-deficient progeroid laminopathies with either: heterozygous *LMNA* mutation with progerin-like protein accumulation OR homozygous or compound heterozygous *ZMPSTE24* mutations Limitations of Use: Not indicated for other progeroid syndromes or processing-proficient progeroid laminopathies. Based upon its mechanism of action, Zokinvy would not be expected to be effective in these populations.		1

CLINICAL RATIONALE

Progeroid Syndromes	Progeroid syndromes are rare genetic diseases characterized by reduced lifespan and premature appearance of certain signs and symptoms of physiological aging. Major clinical features are hair loss, short stature, skin wrinkling, osteoporosis, and, usually, cardiovascular disease. The first genetically characterized group of progeroid syndromes were recessive diseases associated with mutations in genes encoding DNA repair and maintenance proteins (e.g., Werner syndrome, Bloom syndrome, Cockayne syndrome). A second group of progeroid syndromes, called progeroid laminopathies, were later identified, which are caused by mutations in *LMNA* gene that encodes A-type lamins, or mutations in *ZMPSTE24* gene that encodes the enzyme ZMPSTE24 essential for A-type lamin processing. A-type lamins compose (together with B-type lamins) the nuclear lamina, a critical meshwork of filaments at the interface between the inner nuclear membrane and chromatin. ZMPSTE24 enzyme is necessary for

	recognizing the farnesylated C-terminal region of prelamin A, catalyzing the proteolytic cleavage reaction to mature lamin A.(2) Progeroid laminopathies are very rare, generally have an earlier age of onset than most other progeroid syndromes, and display more severe symptoms of accelerated aging. The most prevalent of these rare diseases, Hutchinson-Gilford progeria syndrome (HGPS), is caused by a mutation in *LMNA*, the gene coding for A-type lamins. A single base mutation (typically Gly608Gly, in "classic" HGPS) introduces an alternative splice site that produces an abnormal lamin A protein called "progerin". Progerin lacks the proteolytic cleavage site normally used to remove the farnesylated carboxy terminus from lamin A during posttranslational processing.(2,3,4,5,6,8,10,11) The progerin (permanently farnesylated mutant lamin A) accumulates inside the nucleus, unable to be released for degradation due to persistent farnesylation.(3,4,6,7,9) Disease in HGPS is produced by a dominant negative mechanism; it is the effect of progerin, *not* the diminution of lamin A, which causes the disease phenotype.(3) Emerging evidence indicates that *LMNA*-linked progerias can be further grouped into two classes: 1) the processing-deficient, early onset "typical" progerias (e.g., HGPS), and 2) the processing-proficient "atypical" progeria syndromes (APS) that are later in onset.(5) Individuals with APS show many of the clinical features of HGPS, but their cells do not accumulate prelamin A or progerin.(9) Disease manifestations include severe failure to thrive, scleroderma-like skin, lipoatrophy, alopecia, joint contractures, skeletal dysplasia, and atherosclerosis, but intellectual development is normal.(2,4,6,8,9,10,11) Death at an average age of 13 years occurs from myocardial infarction or stroke.(4,5,6,8,10,11) Diagnosis of genotype HGPS is established with characteristic clinical features, along with identification of a heterozygous pathogenic variant in *LMNA* that results in production of progerin.(8) Mandibuloacral dysplasia (MAD) and restrictive dermopathy (RD) are caused by extreme accumulation of lamin A precursors (aka prelamin) due to a mutation in *ZMPSTE24* which leads to complete absence of the ZMPSTE24 enzyme.(2,5,6) Because of the absence of ZMPSTE24-enzyme's processing activity, the full-length prelamin A molecules in farnesylated form accumulate in the cell.(5,7) MAD can be associated with either homozygous or compound heterozygous mutations in *LMNA* (MAD-A), or a combination of a nonsense and missense mutation in *ZMPSTE24* (MAD-B).(6,7,8,9,10,11) MAD patients are characterized by postnatal growth retardation, craniofacial anomalies like mandibular hypoplasia (or osteolysis) and protruding mid-face as well as skeletal anomalies including progressive osteolysis of the terminal phalanges and clavicles. RD is caused by *LMNA*-linked heterozygous mutations that result in

	truncated proteins similar to progerin that accumulate inside the nucleus.(6,11) RD can also be linked to homozygous or compound heterozygous *ZMPSTE24* mutations.(6,7,10,11) Restrictive dermopathy (RD) is a rare and extremely severe congenital genodermatosis, characterized by a tight rigid skin with erosions at flexure sites, multiple joint contractures, low bone density and pulmonary insufficiency generally leading to death in the perinatal period.(7) Genetic testing in the United States can be achieved through the PRF (Progeria Research Foundation) Diagnostic Testing Program, provided at no cost to families. The genetic test is done by coordinating a blood sample submission by mail through home physicians, from anywhere in the world, to PRF. The PRF Diagnostic Testing Program offers genetic testing for any child suspected of having progeria, provided at no cost to families.(12) Management is supportive and involves ensuring optimal nutrition, monitoring of disease progression, and treatment of complications as they present. Without lonafarnib treatment, death typically occurs as a result of complications of cardiac or cerebrovascular disease. More than 80% of deaths are due to heart failure and/or myocardial infarction, most often between ages six and 20 years, with an average life span of approximately 14.5 years. Average life span is extended to approximately 17-19.5 years with lonafarnib therapy, with similar cause of death.(8)
Efficacy	Zokinvy (lonafarnib) is a farnesyltransferase inhibitor, preventing progerin farnesylation and subsequent accumulation of progerin and progerin-like proteins in the inner nuclear membrane.(1,4) Farnesylation inhibitors are not curative, as many features of disease persist despite treatment. However, evidence suggests that survival may be improved.(3,10,11) Clinical trials have shown improved cardiovascular status of children with HGPS, a potentially important finding because failure of this organ system is the ultimate cause of mortality. A nonrandomized, clinical trial of lonafarnib in 25 children with HGPS provided some evidence of efficacy in reducing the carotid artery echodensity and improving the bone structure in these patients.(4) A subsequent, nonrandomized study evaluated the effect of oral lonafarnib on all-cause mortality in a cohort of 27 patients (median age 8.4 years) with HGPS compared with 27 matched, untreated patients. The median treatment duration was 2.2 years. During this period, the observed mortality rate was 3.7 percent among patients receiving lonafarnib versus 33.3 percent in the untreated group.(1)
Safety	Zokinvy is contraindicated in patients taking:(1) • Strong or moderate CYP3A inhibitors or inducers • Midazolam

	• Lovastatin, simvastatin, or atorvastatin

REFERENCES

Number	Reference
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2	Marcelot A, Worman HJ, Zinn-Justin S. Protein Structural and Mechanistic Basis of Progeroid Laminopathies. FEBS J. 2020 Aug;1-16.
3	Gordon LB, Massaro J, D'Agostino RB, et al. Impact of Farnesylation Inhibitors on Survival in Hutchinson-Gilford Progeria Syndrome. Circulation. 2014 Jul;130(1):27-34.
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5	Kane MS, Lindsay ME, Judge DP, et al. LMNA-Associated Cardiocutaneous Progeria: A Novel Autosomal Dominant Premature Aging Syndrome with Late Onset. Am J Med Genet A. 2013 Jul;161(7):1599-1611.
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9	Carrero D, Soria-Valles C, Lopez-Otin C. Hallmarks of Progeroid Syndromes: Lessons from Mice and Reprogrammed Cells. Dis Model Mech. 2016;9:719-735.

Number	Reference
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12	The Progeria Handbook: A Guide for Families and Healthcare Providers of Children Living with Progeria - 2nd Edition. The Progeria Research Foundation. 2019. Available at: https://www.progeriaresearch.org/wp-content/uploads/2022/03/English-Progeria-Handbook-Edition-2.pdf.

PRIOR AUTHORIZATION CLINICAL CRITERIA FOR APPROVAL

<table>
<tr><th>Module</th><th>Clinical Criteria for Approval</th></tr>
<tr><td></td><td>
Initial Evaluation

Target Agent(s) will be approved when ALL of the following are met:

1. ONE of the following:
A. The requested agent is eligible for continuation of therapy AND ONE of the following:

<table><tr><th>Agents Eligible for Continuation of Therapy</th></tr><tr><td>Zokinvy</td></tr></table>
1. The patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days OR
2. The prescriber states the patient has been treated with the requested agent (starting on samples is not approvable) within the past 90 days AND is at risk if therapy is changed OR
B. BOTH of the following:
1. ONE of the following:
A. BOTH of the following:
1. The patient has a diagnosis of Hutchinson-Gilford progeria syndrome (HGPS) AND
</td></tr>
</table>

Module	Clinical Criteria for Approval
	2. Genetic testing has confirmed a pathogenic variant in the *LMNA* gene that results in production of progerin (medical record required) **OR** B. The patient has a processing-deficient progeroid laminopathy AND ONE of the following: 1. Genetic testing has confirmed heterozygous *LMNA* mutation with progerin-like protein accumulation (medical record required) **OR** 2. Genetic testing has confirmed homozygous or compound heterozygous *ZMPSTE24* mutations (medical record required) **AND** 2. If the patient has an FDA labeled indication, then ONE of the following: A. The patient's age is within FDA labeling for the requested indication for the requested agent **OR** B. There is support for using the requested agent for the patient's age for the requested indication **AND** 2. The patient has a body surface area (BSA) of greater than or equal to 0.39 m^2 **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent **Length of Approval:** 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria. **Renewal Evaluation** **Target Agent(s)** will be approved when ALL of the following are met: 1. The patient has been previously approved for the requested agent through the plan's Prior Authorization process [Note: patients not previously approved for the requested agent will require initial evaluation review] **AND** 2. The patient has had clinical benefit with the requested agent **AND** 3. The prescriber is a specialist in the area of the patient's diagnosis (e.g., cardiologist, geneticist) or the prescriber has consulted with a specialist in the area of the patient's diagnosis **AND** 4. The patient does NOT have any FDA labeled contraindications to the requested agent

Module	Clinical Criteria for Approval
	Length of Approval: 12 months NOTE: If Quantity Limit applies, please refer to Quantity Limit Criteria.

QUANTITY LIMIT CLINICAL CRITERIA FOR APPROVAL

Module	Clinical Criteria for Approval
	Quantity limit for the Target Agent(s) will be approved when ONE of the following is met: 1. The requested quantity (dose) does NOT exceed the program quantity limit **OR** 2. ALL of the following: A. The requested quantity (dose) exceeds the program quantity limit **AND** B. The requested quantity (dose) does NOT exceed the maximum FDA labeled dose for the requested indication **AND** C. The requested quantity (dose) cannot be achieved with a lower quantity of a higher strength that does NOT exceed the program quantity limit **Length of Approval:** up to 12 months