Hereditary Angioedema

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO075

Description

C1 esterase inhibitors (Cinryze, Haegarda, Berinert, Ruconest) are injectable medications that regulate the activation of various systems that are thought to modulate the increased vascular permeability during HAE attacks by preventing the generation of bradykinin.

Lanadelumab (Takhzyro), icatibant (Firazyr), icatibant (Sajazir), and berotralstat (Orladeyo) are kallikrein inhibitors, the binding of these medications to plasma kallikrein results in the control of excess bradykinin generation in patients with HAE. Both lanadelumab (Takhzyro), icatibant (Firazyr), and icatibant (Sajazir) are injectable medications, and berotralstat (Orladeyo) is orally administered.

Length of Authorization

- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
C1 esterase inhibitor (Cinryze)	HAE prophylaxis	500 U single use vial for IV administration	20 vials/30 days
C1 esterase inhibitor (Haegarda)		2000 U single use vial for SQ administration	Weight based 60 IU/kg twice weekly, refer to chart below for quantity
		3000 U single use vial for SQ administration	
lanadelumab (Takhzyro)		300 mg/2 mL single dose vial for SQ administration	4 mL/28 days
		300 mg/2 mL prefilled syringe for SQ administration	2 syringes/28 day
		150 mg/mL prefilled syringe for SQ administration*	<u>Ages 2 – 5:</u> 1 syringe/28 day <u>Ages 6 – 12:</u> 2 syringes/28 day
berotralstat (Orladeyo)		110 mg capsules	28 capsules/28 days
		150 mg capsules	
C1 esterase inhibitor (Berinert)		500 U single use vial for IV administration	Weight based 20 IU/kg, refer to chart below
C1 esterase inhibitor (Ruconest)		2100 U single use vial for IV administration	16 vials/30 days
icatibant (Firazyr)		30 mg/3 mL SQ prefilled syringe	9 syringes (27 mL)/30 days

icatibant (generic Firazyr)	Treatment of acute HAE attacks	30 mg/3 mL SQ prefilled syringe	9 syringes (27 mL)/30 days
icatibant (Sajazir)		30 mg/3 mL SQ prefilled syringe	9 syringes (27 mL)/30 days

Initial Evaluation (All information must be supported by documentation and chart notes)

I. **Medications used for HAE** may be considered medically necessary when the following criteria below are met and supported by recent chart notes (within the past 12 months):
   A. Prescribed by, or in consultation with, one of the following specialists: allergist, immunologist, dermatologist, hematologist, pulmonologist, medical geneticist; **AND**
   B. A diagnosis of **hereditary angioedema** indicated by one of the following:
      1. **Type 1 HAE**: confirmed by documentation of the following laboratory values:
         i. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal; **AND**
         ii. C4 level below the lower limit of normal; **AND**
         iii. C1-INH functional level below the lower limit of normal; **AND**
         iv. Patient has a family history of HAE or a normal C1q level; **OR**
      2. **Type 2 HAE**: confirmed by documentation of the following laboratory values:
         i. Normal to elevated C1-INH antigenic level; **AND**
         ii. C4 level below the lower limit of normal; **AND**
         iii. C1-INH functional level below the lower limit of normal**; AND**
   C. The member has been evaluated for potentially treatable triggers of HAE attacks and is being managed to avoid triggers; **AND**
      1. **For prophylactic treatment of HAE**:
         i. Cinryze, Haegarda, Takhzyro, OR Orladeyo is requested; **AND**
            a. The member is <u>NOT</u> prescribed more than one agent FDA-approved for HAE <u>prophylaxis</u> (e.g., Cinryze, Haegarda, Takhzyro, Orladeyo); **AND**
            b. The member has a history of at least **<u>one</u>** of the following criteria for HAE prophylaxis:
               i. History of ≥ 2 severe HAE attacks per month (e.g., airway swelling, debilitating cutaneous or gastrointestinal complications) that required "on-demand" therapy (e.g., icatibant [Firazyr], icatibant [Sajazir], Berinert, Ruconest, Kalbitor)
               ii. The member is disabled ≥ 5 days per month by HAE
               iii. The member has a history of HAE laryngeal attacks; **AND**
            c. The member is ≥ 2 years to < 6 years of age; **AND**

i. The request is for Takhzyro 150 mg/mL prefilled syringe; **OR**

d. The member is ≥ 6 years of age; **AND**
   i. The request is for Cinryze; **OR**
   ii. The request is for Takhzyro; **OR**
   iii. The request is for Haegarda; **AND**
      1. Member's current weight within the last six months has been documented to dose appropriately; **OR**

e. The member is ≥ 12 years of age; **AND**
   i. The request is for Takhzyro, Orladeyo, or Cinryze; **OR**
   ii. The request is for Haegarda; **AND**
      1. Member's current weight within the last six months has been documented to dose appropriately; **OR**

2. **For acute treatment of HAE attacks;**
   i. Icatibant (Firazyr), icatibant (Sajazir), Ruconest, OR Berinert is requested;**AND**
   ii. The member is NOT prescribed more than one agent FDA-approved for HAE acute treatment (e.g., icatibant [Firazyr], icatibant [Sajazir], Berinert, Ruconest, Kalbitor); **AND**
   iii. The member has a history of attacks that induce significant burden of disease or impact to activities of daily living due to HAE (e.g., impairment in work performance/productivity, facial swelling, painful distortion of the affected area, laryngeal attacks or airway swelling, severe gastrointestinal complications); **AND**
   iv. **For Berinert**: the member is ≥ 6 years of age; **AND**
      a. Documentation of current weight within the last six months, to dose appropriately; **OR**
   v. **For Ruconest**: the member is ≥ 13 years of age; **AND**
      a. Treatment with Berinert AND generic icatibant/icatibant (Sajazir), have been ineffective, contraindicated, or not tolerated; **OR**
   vi. **For icatibant (generic Firazyr):** the member is ≥ 18 years of age; **OR**
   vii. **For icatibant (Sajazir):** the member is ≥ 18 years of age; **AND**
      a. Generic icatibant has been ineffective, not tolerated, or contraindicated; **OR**
   viii. **For brand Firazyr**: the member is ≥ 18 years of age; **AND**
      a. Generic icatibant has been ineffective, not tolerated, or contraindicated; **AND**

b. Icatibant (Sajazir) has been ineffective, not tolerated, or is contraindicated.

II. Medications used for HAE are considered investigational when used for all other conditions or scenarios, including but not limited to:
   A. Combination use of acute therapies (e.g., icatibant [Firazyr], Berinert, Ruconest, Kalbitor, icatibant [Sajazir])
   B. Combination use of prophylactic therapies (Cinryze, Haegarda, Takhzyro, Orladeyo)
   C. Angioedema due to other causes (e.g., type 3 HAE, medication induced, sepsis, cardiovascular comorbidities or conditions, allergic reaction, etc.)

Renewal Evaluation (All information must be supported by documentation and chart notes)

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. The member continues to be evaluated for potentially treatable triggers of HAE attacks and is being managed to avoid triggers; **AND**
IV. The member has been seen and evaluated for medication efficacy and safety in the past 12 months; **AND**
V. The quantity of medication prescribed does not exceed that needed to treat or prevent current average number of attacks or expected number of attacks; **AND**
VI. Documentation the member has experienced functional improvement AND improvement in the number, severity, or duration of attacks; **AND**
VII. **For prophylactic treatment of HAE**:
   A. The member has not been prescribed more than one medication FDA-approved for HAE prophylaxis (Cinryze, Haegarda, Takhzyro, Orladeyo), etc.; **AND**
   B. **For Haegarda**: documentation of current weight (within the last three months, to calculate appropriate dose); **OR**
   C. **For Takhzyro**: one of the following is met:
      i. The member has been free of acute attacks for ≥ 6 months; **AND**
         a. The dosing frequency for Takhzyro will be reduced to every 4 weeks (e.g., 150 mg/mL every 4 weeks, 300 mg/2 mL every 4 weeks) [Note: Dose reductions may not apply to members >2 years to <6 years of age]; **OR**

b. Documentation of medical necessity is provided for maintaining the dose at 'every two weeks' dosing interval; **OR**

D. The request is for **Orladeyo** or **Cinryze**; **OR**

VIII. **For acute treatment of HAE attacks:**

A. The member has not been prescribed more than one medication FDA approved for HAE treatment (e.g., icatibant [Firazyr], icatibant [Sajazir], Berinert, Ruconest, Kalbitor); **AND**

B. **For brand Firazyr:** the member has tried and failed, not tolerated, or has contraindication to generic icatibant AND icatibant (Sajazir); **OR**

C. **For icatibant (Sajazir):** the member has tried and failed, not tolerated, or has contraindication to generic icatibant

D. **For Berinert**: documentation of current weight within the last three months, to calculate appropriate dose

Supporting Evidence

I. Hereditary angioedema (HAE) is a rare disease characterized by recurrent and sometimes severe episodes of angioedema without urticarial or pruritus. Skin and mucosal tissues in the upper respiratory and gastrointestinal tracks are often affected and may have airway involvement leading to asphyxiation if not treated appropriately. It should be noted that it is not uncommon for patients to have mild and/or self-limiting attacks that do not require treatment. Non-pharmacologic and pharmacologic management of HAE is very complex and requires confirmatory tests and monitoring by, or in close consultation with, a specialist.

II. HAE is divided into two broad categories: HAE due to C1INH deficiency (HAE-C1INH) and HAE with normal C1INH (HAE-nl-C1INH). HAE-C1INH is further subdivided into type 1 and type 2, which appear to be clinically similar. HAE-nl-C1INH HAE was previously called type 3 HAE, however the "type 3" term has become obsolete. HAE-nl-C1INH HAE is further subdivided based on the underlying mutation or unknown in cases where the mutation has not been found. Clinical trials have only evaluated HAE therapies in patients with HAE-C1INH (types 1-2). Data on HAE therapies in the HAE-nl-C1INH setting are limited.

III. Normal C1-INH levels are generally 18-37 mg/dL, normal C4 levels are generally 10-40 mg/dL, normal functional level C1-INH is >67%, normal C1q levels are generally 5-8.6 mg/dL.

IV. Evaluation, documentation, and patient understanding of triggers is essential in the management of HAE and can reduce the number of disabling attacks and medication requirements. The most common triggers include stress, NSAIDS, ACE inhibitors, antibiotics, trauma, illness, dental work, hormonal fluctuations, and food sensitivities, although there are many other patient specific triggers. Furthermore, allergic/anaphylactic reactions and adverse effects related to foods and medications should be ruled out in light of an HAE diagnosis.

V. Hereditary angioedema treatment modalities include acute management and prophylactic methods. Acute therapies, also known as "on-demand" therapy, is essential in serious,

debilitating, and laryngeal attacks, options include C1 esterase inhibitors (Berinert, Ruconest), bradykinin antagonist (icatibant [Firazyr], icatibant [Sajazir] – available generic), and kallikrein inhibitor (Kalbitor). Only one of these therapies should be prescribed and used at one time.

VI. Generic icatibant and icatibant (Sajazir) are both available AP rated (**therapeutically equivalent)** generics to icatibant (Firazyr).

VII. In addition to treating attacks of angioedema, patients with HAE may require prophylactic treatment. The goal of prophylactic treatment is either to reduce the likelihood of swelling in a patient undergoing a stressor or procedure likely to precipitate an attack (short-term prophylaxis) or to decrease the overall number, severity, and burden of angioedema attacks.

VIII. Prophylactic therapy should be considered based on the number of attacks, severity of the attacks, comorbid conditions, emergency department visits, inadequate response or control using acute treatments, and/or where severe, debilitating, or laryngeal attacks are recurrent. Trauma or stress-related events, such as surgeries or dental procedures may entail the need for a short-term prophylaxis therapy. Current 2020 US HAEA Medical Advisory Board (HAEA MAB) guidelines recommend the use of a single dose of plasma derived C1 inhibitor (pdC1INH; e.g., Berinert) as the preferred agent for short-term prophylaxis or a course of anabolic androgen (e.g., danazol) when access to Berinert is limited.

IX. For long-term HAE prophylaxis, current guidelines recommend the use of IV or SQ replacement of pdC1INH as the first-line agents (e.g, Cinryze, Haegarda) along with kallikrein inhibitors (e.g., Takhzyro, Orladeyo). Before the advent of current HAE prophylactic agents, androgens (danazol), antifibrinolytics (aminocaproic acid, tranexamic acid) were used in practice for HAE prophylaxis based on their mechanisms of action and limited clinical trials (1970s and 1980s) indicating symptomatic benefits. However, the current HAEA MAB guidelines recommend these agents as second-line therapies. Use of the second-line prophylactic agents should be reserved for when first-line therapies are not available. Lack of strong clinical data coupled with significant risks of long-term adverse reactions, and lack of FDA approval in the setting of HAE prophylaxis has driven this change in practice in recent years. It should be noted that only danazol is approved in the US for HAE prophylaxis. However, dose-related side effects, considerations on populations to avoid use in (age <16, pregnant and breastfeeding women), and tolerability concerns limit its widespread use

X. Patients with HAE may also require short-term prophylactic treatment to reduce the likelihood of swelling in a patient before an invasive medical, surgical or dental procedure that is likely to precipitate in an attack. Either plasma-derived C1-inhibitor (pdC1INH) or a course of anabolic androgen is administered for short-term prophylaxis of HAE. The medications in this policy are not specifically FDA-approved for use in short-term prophylaxis at this time.

XI. Both on-demand and prophylactic HAE therapies have FDA-approvals for various age groups; therefore, the ages outlined in this policy are based on FDA-approval. Of note, pediatric populations are underrepresented in clinical trials; however, FDA-approval is often based on clinical experience from a few pediatric patients coupled with several years of safety data in other age populations with limited available treatment options for a potentially life-threatening condition.

XII. Lanadelumab (Takhzyro) was evaluated in two phase 3 studies in patients aged 12 years and older with HAE.

- Study DX2930-03 was a phase 3, multicenter, randomized, double-blind, placebo-controlled parallel-group study. The 26-week study included 125 patients 12 years of age and older with HAE-I or HAE-II who experienced at least one investigator-confirmed attack per 4 weeks during the run-in period. During the study run-in period, attack rates of ≥3 attacks/month were observed in 52% of patients. The primary endpoint was mean monthly attack rate from day 0 to 182, those in the Takhzyro 150 mg every 4 weeks arm had 0.48 mean monthly attack rate, those in the Takhzyro 300 mg every 4 weeks arm had 0.53 mean monthly attack rate and 0.26 mean monthly attack rate was observed in those who received Takhzyro 300 mg ever 2 weeks, while those in the placebo arm had a 1.97 mean monthly attack rate ($p<0.001$). This secondary endpoint of the study was mean number of monthly attacks requiring acute treatment from day 0 to 182. Clinically meaningful and statistically significant outcomes were observed across all Takhzyro arms. Participants in the placebo arm had a mean of 1.64 monthly attacks requiring acute treatment, compared to 0.31 (150 mg every 4 weeks), 0.42 (300 mg every 4 weeks) and 0.21 (300 mg every 2 weeks) [$p<0.001$] as observed across all Takhzyro arms.
- The open-label phase 3 extension study DX2930-04 evaluated the long-term safety of lanadelumab 300 mg Q2W in Types I and II HAE patients. The study consisted of rollover subjects who completed the double-blind treatment period of Trial DX2930-03 and non-rollover subjects who enrolled directly into the OLE study. A secondary objective of the study was to characterize the outer bounds of dosing frequency in the rollover subjects. The primary objective of the study was to provide long-term safety data which include adverse events/serious adverse events, clinical labs (hematology, chemistry, LFTs, UA, coagulation, pregnancy), ECG, vital signs, physical exam, and ADA testing.
- An open-label, single-arm, phase 3 trial (SPRING) measured safety, pharmacokinetics and pharmacodynamics (PK/PD) of lanadelumab (Takhzyro) in patients ≥ 2 years to 12 years of age (N=21) consisting of 17 participants in the 6 years to 12 years age group (group A) and 4 participants aged 2 years to 6 years of age (group B). At 52 weeks of treatment exposure, lanadelumab (Takhzyro) exhibited comparable PK/PD characteristics in pediatric patients (group A) to those for systemic drug exposure in adult patients. For group B patients (<6 years of age), the minimum steady-state plasma drug levels were 50% to 60% lower than those for adult patients (reported from previous clinical data), however were reported to produce a treatment response. During the SPRING trial, 76% (n=16) participants remained HAE attack-free during full treatment period and the rate of HAE attacks per month reduced by 94% versus baseline (1.84 attacks per month to 0.08 attacks). Although robust conclusions may not be drawn from this data due to open-label study design, limited sample size and lack of comparator, this data provides support to previously reported efficacy of lanadelumab (Takhzyro) in patients >12 years of

age. Additionally, no additional safety signals were reported during SPRING trial. 33% participants reported injection site reactions as the common AE, which did not lead to treatment interruptions, discontinuations or hospitalizations.

XIII. Berotralstat (Orladeyo) was evaluated in a three-part phase 3 study, and the approval was based on data submitted from part 1 (24 weeks). Parts 2 and 3 of this study are still ongoing to evaluate the long-term efficacy and safety or berotralstat (Orladyo), additional data on laboratory tests of interest from part 1 (such as LFT elevations) and HAE attack data.

- APeX-2 was a double-blind, randomized, placebo-controlled trial in 121 patients with type I or type II HAE. The primary efficacy outcome of part 1 was the rate of investigator confirmed HAE attacks per month at week 24, which was 1.31 ($p< 0.001$) for the berotralstat 150 mg arm, 1.65 ($p=0.024$) for the berotralstat 110 mg arm and 2.35 for placebo. Although berotralstat (Orladyeo) met its primary efficacy endpoint, the study failed to meet statistical significance in its secondary endpoint, which was the change from baseline of AE-QOL total scores at 24 weeks. The long-term efficacy and safety of this product is currently unknown due to the lack of published long-term data. The distribution of on-demand medication use during the study across all study arms was not provided; therefore, there is a risk the concomitant therapies confounded the outcome results.

XIV. There are no direct head-to-head studies comparing lanadelumab (Takhyzro) and berotralstat (Orladeyo) to establish superior safety or efficacy of one product over the other; however, lanadelumab (Takhzyro) has a more established safety profile, and favorable quality of evidence for efficacy.

Investigational or Not Medically Necessary Uses

I. Use of two or more therapies for the same indication (e.g., acute or prophylactic) has not been evaluated for safety and efficacy.

II. The medications listed in this policy have not been sufficiently evaluated for safety and efficacy outside of hereditary angioedema.

Appendix

Weight-based dosing for Haegarda and Berinert

Medication	Body Weight (kg)	Vial Configuration	Vials per Dose	Number of Vials per 30 days
Haegarda	Up to 33 kg	2000 unit	1	8
	34-50	3000 unit	1	8
	51-67	2000 unit	2	16
	68-100	3000 unit	2	16

	101-133	2000 unit	4	32
	134-150	3000 unit	3	32
Berinert	Up to 25	500 unit	1	4
	25 - 50		2	8
	50 - 75		3	12
	75 - 100		4	16
	100-125		5	20
	125-150		6	24

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Related Policies

Currently there are no related policies

Policy Implementation/Update:

Action and Summary of Changes	Date
Added expanded indication for Takhzyro (>2 years of age); In the prophylaxis setting, removed requirement of trial with danazol, aminocaproic acid, and tranexamic acid following updated guideline recommendations; updated supporting evidence. Removed requirement of specialist prescribing upon renewal. Increased initial approval duration from 3 months to 6 months.	04/2023
Addition of icatibant (Sajazir) to policy, requiring use of generic icatibant prior to use of Sajazir and allowing brand Firazyr coverage only if medical necessity established for brand over generic (generic icatibant and Sajazir)	10/2021
Added Orladeyo criteria for prophylactic treatment of HAE for P&T, added renewal criteria requiring initial policy criteria needs to be met, no continuation based on samples and must have had prior approval by plan.	02/2021
Age for Haegarda expanded down to six years of age (from previous 12)	10/2020
Added age restriction to Takhzyro of ≥ 12 years of age	03/2020
Policy created and criteria added to initial and renewal portions. Takhzyro combined with other agents. Specification on inappropriateness of dual therapy use, medical necessity of therapy, and addition of generic icatibant to the policy and use required prior to brand payment consideration.	10/2019
Takhzyro criteria created for P&T.	10/2018
Criteria updated to include Cinryze prophylactic therapy for patients six years of age and older, a new FDA approved age range.	01/2018
HAE indication review completed, agents included in policy were updated and questions added to align with clinical appropriateness and medical criteria.	11/2017
Criteria created	10/2016