

**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: Three months
- Renewal: Six months

### Quantity limits

Product Name	Dosage Form	Indication	Quantity Limit	
C1 esterase inhibitor (Cinryze)	500 unit single use vial for IV administration	HAE prophylaxis	20 vials/30 days	
C1 esterase inhibitor (Haegarda)	2000 unit single use vial for SQ administration		Weight based 60 iu/kg twice weekly, refer to chart below for quantity	
	3000 unit single use vial for SQ administration			
lanadelumab (Takhzyro)	300 mg/2 mL single dose vial for SQ administration			4 mL/28 days
berotralstat (Orladeyo)	110 mg capsules			28 capsules/28 days
	150 mg capsules			
C1 esterase inhibitor (Berinert)	500 unit single use vial for IV administration	Treatment of acute HAE attacks	Weight based 20 iu/kg, refer to chart below	
C1 esterase inhibitor (Ruconest)	2100 unit 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)	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

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

### 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 NOT prescribed more than one agent FDA-approved for prophylaxis (e.g., Cinryze, Haegarda, Takhzyro, Orladeyo); **AND**
    - b. The member has a history of at least one of the following criteria for HAE prophylaxis:
      - i. History of  $\geq 2$  severe HAE attacks per month (e.g., airway swelling, debilitating cutaneous or gastrointestinal complications)
      - ii. The member is disabled  $\geq 5$  days per month by HAE
      - iii. The member has a history of HAE laryngeal attacks; **AND**
    - c. The member has had a trial and failure or intolerance to one of the following or has a contraindication to **ALL**:
      - i. danazol
      - ii. aminocaproic acid
      - iii. tranexamic acid; **AND**
    - d. “On demand” therapy (e.g., icatibant [Firazyr], icatibant [Sajazir], Berinert, Ruconest, Kalbitor) has been ineffective, contraindicated, or not tolerated; **AND**
    - e. The member is  $\geq 6$  years of age; **AND**
      - i. The request is for 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**
    - f. The member is  $\geq 12$  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), OR Berinert is requested; **OR**
      - a. Ruconest is requested; **AND**
      - b. Treatment with Berinert AND generic icatibant/icatibant (Sajazir), have been ineffective, contraindicated, or not tolerated; **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  $\geq 6$  years of age; **AND**
    - a. Documentation of current weight within the last six months, to dose appropriately; **OR**
  - v. **For Ruconest:** the member is  $\geq 13$  years of age; **OR**
  - vi. **For icatibant (generic Firazyr):** the member is  $\geq 18$  years of age; **OR**
  - vii. **For icatibant (Sajazir):** the member is  $\geq 18$  years of age; **AND**
    - a. Generic icatibant has been ineffective, not tolerated, or contraindicated; **OR**
  - viii. **For brand Firazyr:** the member is  $\geq 18$  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; **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 medication is prescribed by, or in consultation with one of the following specialists: allergist, immunologist, dermatologist, hematologist, pulmonologist, medical geneticist; **AND**
- IV. The member continues to be evaluated for potentially treatable triggers of HAE attacks and is being managed to avoid triggers; **AND**

- V. The member has been seen and evaluated for medication efficacy and safety in the past 12 months; **AND**
- VI. 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**
- VII. Documentation the member has experienced functional improvement **AND** improvement in the number, severity, or duration of attacks; **AND**
- VIII. **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:** Documentation that the dose will be de-escalated to 300 mg (2 mL) every four weeks **OR** documentation of medical necessity is provided for maintaining the dose at 300 mg (2 mL) every two weeks; **OR**
  - D. The request is for **Orladeyo**; **OR**
- IX. **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 is 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. 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. Options for treatment include androgens (danazol), antifibrinolytics (aminocaproic acid, tranexamic acid), C1 esterase inhibitors (Cinryze, Haegarda), and kallikrein inhibitor (Takhzyro, Orladeyo). 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.
  - VIII. Androgens and antifibrinolytics are widely available and have been used historically with success in many patients. Danazol is FDA-approved 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. Antifibrinolytic therapies have a more favorable safety profile compared to androgens (danazol) for the prophylactic treatment of HAE. Aminocaproic acid and tranexamic acid are both generally well tolerated, common adverse events include nausea, vomiting, and diarrhea.
  - IX. 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.



- X. 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  $\geq 3$  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.
- XI. 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 of berotralstat (Orladeyo), 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 (Orladeyo) 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.

- XII. There are no direct head-to-head studies comparing lanadelumab (Takhzyro) 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.

### References

1. Takhzyro [Prescribing Information]. Shire. Lexington, MA. September 2018.
2. Berinert [Prescribing Information]. Kankakee, IL. CSL Behring LLC. July 2016.
3. Haegarda [Prescribing information]. Kankakee, IL: CSL Behring LLC; September 2020.
4. Firazyr [Prescribing Information]. Lexington, MA. Shire Orphan Therapies, LLC. November 2015.
5. Cinryze [Prescribing Information]. Lexington, MA. ViroPharma Biologics, Inc. June 2018.
6. Ruconest [Prescribing Information]. Raleigh, NC. Santarus, Inc. February 2015.
7. Kalbitor [Prescribing Information]. Dyax Corporation. Burlington, MA. 2014.
8. Orladeyo [Prescribing Information]. BioCryst Pharmaceuticals, Inc. Durham, NC. 2020.
9. Craig T, Aygören-Pürsün EA, Bork K, et al. World Allergy Organization (WAO) guideline for the management of hereditary angioedema. *World Allergy Organ J.* 2012; 5(12):182-199.
10. Zuraw BL, Banerji A, Bernstein JA, Busse PJ, Christiansen SC, Davis-Lorton M, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol: In Practice* 2013;1:458-67. <http://dx.doi.org/10.1016/j.jaip.2013.07.002>.
11. Bowen et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy, Asthma & Clinical Immunology.* 2010. 6(24):1-13.
12. Aygören-pürsün E, Soteres D, Moldovan D, et al. Preventing Hereditary Angioedema Attacks in Children Using Cinryze Interim Efficacy and Safety Phase 3 Findings. *Int Arch Allergy Immunol.* 2017;173(2):114-119.
13. Germenis AE., SpeletasM. Genetics of hereditary angioedema revisited. *Clin Rev Allergy Immunol.* 2016;51(2); 170-182.
14. MM, MM, IA, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. *Allergy.* 2018;73(8): 1575-1596.
15. U.S. Food and Drug Administration Announcement. Approval of Haegarda for Prevention of Hereditary Angioedema Attacks in Pediatric Patients. Accessed October 2020. Available at: <https://www.cslbehring.com/newsroom/2020/haegarda-pediatric-label-update>
16. BLA 761090 Multi-disciplinary Review and Evaluation of Takhzyro (lanadelumab). Center for Drug Evaluation and Research. 2017. Available at: [https://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2018/761090Orig1s000MultidisciplineR.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761090Orig1s000MultidisciplineR.pdf). Accessed December 17, 2020.



17. Zuraw B, Lumry WR, Johnston DT, et al. Oral once-daily berotralstat for the prevention of hereditary angioedema attacks: a randomized, double-blind, placebo-controlled phase 3 trial, *J. Allergy Clin. Immunol* (2020), <https://doi.org/10.1016/j.jaci.2020.10.015> (pre-proof)
18. Icatibant Injection. Drug Facts and Comparisons. Facts & Comparisons eAnswers. Wolters Kluwer Health, Inc. Riverwoods, IL. Accessed October 18, 2021. <http://online.factsandcomparisons.com>

### Policy Implementation/Update:

Action and Summary of Changes	Date
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 $\geq 12$ 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