Hereditary Angioedema

EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO075

Description

C1 esterase inhibitor (Cinryze, Berinert, Haegarda, Ruconest), landadelumab (Takhzyro), and icatibant (Firazyr) are injectable medications for the treatment of hereditary angioedema (HAE).

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
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 (36 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, OR Takhzyro are requested; **AND**
            a. The member is not prescribed more than one agent FDA-approved for prophylaxis (e.g., Cinryze, Haegarda, Takhzyro); **AND**
            b. The member has a history of at least <u>one</u> of the following criteria for long-term HAE prophylaxis:
               i. History of ≥ 2 severe HAE attacks per month (e.g., airway swelling, debilitating cutaneous or gastrointestinal complications)
               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 has had a trial and failure or intolerance to danazol, aminocaproic acid, or tranexamic acid, or has a contraindication to all; **AND**
d. "On demand" therapy (e.g., Firazyr, Ruconest, Berinert) has been ineffective, contraindicated, or not tolerated; **AND**
e. For Cinryze: the member is ≥ 6 years of age; **OR**
f. For Takhzyro: The member is ≥ 12 years of age; **OR**
g. For Haegarda: the member is ≥ 6 years of age; **AND**
    i. Current weight (within the last six months has been documented to dose appropriately); **OR**

2. For acute treatment of HAE attacks;

i. Icatibant (Firazyr) OR Berinert are requested; **OR**
    a. Ruconest is requested; **AND**
    b. Treatment with Berinert AND Firazyr 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), Berinert, Ruconest, ecallantide (Kalbitor), etc.); **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 three months, to calculate appropriate dose); **OR**
v. For Ruconest: the member is ≥ 13 years of age; **OR**
vi. For icatibant (Firazyr): the member is ≥ 18 years of age; **AND**
    a. Generic icatibant is prescribed; **OR**
vii. For brand Firazyr: the member is ≥ 18 years of age; **AND**
    a. Treatment with generic icatibant has been ineffective, not tolerated or is contraindicated.

II. Medications used for HAE are considered <u>investigational</u> when used for all other conditions or scenarios, including but <u>not limited to</u>:
    A. Combination use of acute therapies (Berinert, Ruconest, icatibant (Firazyr), Kalbitor)
    B. Combination use of prophylactic therapies (Cinryze, Haegarda, Takhzyro)
    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. The medication is prescribed by, or in consultation with one of the following specialists: allergist, immunologist, dermatologist, hematologist, pulmonologist, medical geneticist; **AND**
II. The member continues to be evaluated for potentially treatable triggers of HAE attacks and is being managed to avoid triggers; **AND**
III. The member has been seen and evaluated for medication efficacy and safety in the past 12 months; **AND**
IV. 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**
V. The member has not been prescribed more than one medication FDA approved for HAE prophylaxis (Berinert, Ruconest, icatibant (Firazyr), etc.); **AND**
VI. Documentation of improvement in the number, severity, or duration of attacks, and the member has experienced functional improvement; **AND**
    - **For brand Firazyr:** the member has tried and failed, not tolerated, or has contraindication to generic icatibant; **OR**
    - **For Berinert and Haegarda**: documentation of current weight (within the last three months, to calculate appropriate dose); **OR**
    - **For Takhzyro**: Documentation that 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.

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. Patients with HAE may have one of three types (indicated as types 1-3). Types 1-2 may be detected through laboratory levels noted in criteria above. Other forms of HAE show normal complement lab measurements and prevalence of these types are rare. Clinical trials have evaluated HAE therapies in types 1-2.
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 reduces the number of disabling attacks and medication requirement. Common triggers include stress, NSAIDS, ACE inhibitors, antibiotics, trauma, illness, dental work, hormonal fluctuations, food sensitivities, and potentially many other patient specific triggers. Additionally, allergic/anaphylactic reactions and adverse effects of these foods and medications shall 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] – available generic), and kallikrein inhibitor (Kalbitor). Only one of these therapies should be prescribed and used at one time.

VI. Prophylactic therapy should be considered based on number of attacks, severity, comorbid conditions, emergency department visits, inadequate response or control using acute treatments, and/or where severe, debilitating, or laryngeal attacks are recurrent. Options include androgens (danazol), antifibrinolytics (aminocaproic acid, tranexamic acid), C1 esterase inhibitors (Cinryze, Haegarda) and kallikrein inhibitor (Takhzyro).

VII. 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.

VIII. HAE therapies, on-demand and prophylactic, have FDA-approvals for various age groups. 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 and limited available treatment options in a potentially life-threatening condition.

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. 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.
9. 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.
10. 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.
11. 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.
12. Germenis AE., SpeletasM. Genetics of hereditary angioedema revisited. Clin Rev Allergy Immunol. 2016;51(2); 170-182.
13. 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.
14. 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

Policy Implementation/Update:

Action and Summary of Changes	Date
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