Medical Drug Clinical Criteria

Subject:	Hereditary Angioedema Agents		
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Table of Contents

Overview

This document addresses the use of drugs for the treatment or prevention of hereditary angioedema (HAE) attacks. The agents are listed in the following table.

Agent	Prophylaxis or Treatment	Indication	Route of Administration	Safety
Cinryze **(C1 Esterase Inhibitor, Human)**	Prophylaxis	Routine prophylaxis against HAE attacks in adolescent (≥ 6 years) and adult patients	Intravenous infusion	✓ Risk of serious anaphylactic reactions ✓ Serious arterial and venous thromboembolic events ✓ Made from human plasma and may contain infectious agents
Haegarda **(C1 Esterase Inhibitor, Human)**	Prophylaxis	Routine prophylaxis against HAE attacks (≥ 6 years)	Subcutaneous	
Berinert **(C1 Esterase Inhibitor, Human)**	Treatment	Treatment of acute abdominal, facial, or laryngeal attacks of HAE in adult and pediatric patients (≥5 years)	Intravenous infusion	
Firazyr **(icatibant)**	Treatment	Treatment of acute attacks of HAE in adult patients (≥ 18 years)	Subcutaneous	✓ Laryngeal attacks
Kalbitor **(ecallantide)**	Treatment	Treatment of acute attacks of HAE in adult and pediatric patients (≥12 years)	Subcutaneous	✓ Black box warning: Risk of serious anaphylactic reactions
Ruconest **(C1 Esterase Inhibitor, Recombinant)**	Treatment	Treatment of acute attacks of HAE in adult and adolescent patients (≥13 years) Note: Effectiveness not established in patients with laryngeal attacks	Intravenous infusion	✓ Risk of serious anaphylactic reactions ✓ Serious arterial and venous thromboembolic events
Takhzyro (lanadelumab-flyo)	Prophylaxis	Routine prophylaxis against HAE attacks in adult and pediatric patients (≥2 years)	Subcutaneous	✓ Adverse events were mild to moderate, mainly injection-site reactions

Orladeyo **(berotralstat)**	Prophylaxis	Routine prophylaxis against HAE attacks in adult and pediatric patients (≥12 years)	Oral	✓ QT prolongation can occur in those taking more than one capsule per day

Hereditary Angioedema (HAE) is a chronic autosomal dominant disorder associated with recurrent, unpredictable, and potentially life-threatening acute attacks. There are three known types of HAE with types I and II being most common. Types I and II are associated with mutations to C1-INH. C1-INH deficiency results in an overproduction of bradykinin which is a vasodilator thought to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. Mutations that cause type I HAE lead to reduced levels of C1-INH. A serum C4 level is a useful screening test for HAE-C1INH. A normal C4 during an angioedema episode excludes the diagnosis of HAE-C1INH. HAE with normal C1-INH (HAE-nl-C1INH), previously referred to as Type III HAE, is extremely rare and occurs primarily in women. Treatments for HAE-nl-C1INH are not well established (Busse P, et al 2020).

The signs and symptoms associated with acute HAE attacks include intense and painful swelling of the face, larynx, gastrointestinal (GI) tract, limbs, or genitalia. Episodic attacks of HAE produce edema in three primary areas: periphery, abdomen, and larynx. Peripheral attacks are associated with painful disfigurement and physical disability; abdominal attacks result in severe abdominal pain, nausea, and vomiting; and laryngeal attacks may result in death by asphyxiation. An individual with HAE may be sensitive to multiple triggers related to HAE attacks, and it is often difficult or impossible to identify all of the triggers for a particular individual with HAE.

In the United States, plasma-derived C1-INH is a first-line long-term prophylactic agent for HAE-C1-INH without the need to have failed or experienced side effects from other medications such as androgens or antifibrinolytics (Maurer M, et al 2018). In some other countries, plasma-derived C1-INH may be restricted to patients who have had adverse effects to androgens or antifibrinolytics, were not adequately controlled on these agents, or who do not wish to take these agents.

Takhzyro (lanadelumab) is approved as the first monoclonal antibody for the prevention of angioedema attacks in patients 2 years and older. Takhzyro is a fully human monoclonal antibody that binds and inhibits plasma kallikrein. The strength and dosing intervals are dependent on patient age. In those 6 years of age or older, a dosing interval of every 4 weeks can be effective and may be considered if the individual is well-controlled (e.g. attack free) for more than 6 months.

Orladeyo (berotralstat) for prophylaxis to prevent attacks of hereditary angioedema (HAE) in adults and pediatric patients 12 years and older. This is the first FDA-approved, orally administered, non-steroidal treatment for HAE prophylaxis. Berotralstat is a plasma kallikrein inhibitor that binds to plasma kallikrein and inhibits its proteolytic activity. An increase in QT prolongation can occur at dosages higher than the recommended 150 mg once-daily dosage. Additional doses or doses of Orladeyo higher than 150 mg once daily are not recommended.

Haegarda carries the same warnings and precautions as Cinryze and Berinert related to severe hypersensitivity, thromboembolic events, and potential transmission of infectious agents.

Kalbitor has a black box warning for the risk of anaphylaxis and must be administered by a healthcare professional for management.

Ruconest also carries warning and precautions for severe hypersensitivity and thromboembolic events. Ruconest is an intravenous therapy for acute attacks in adults and adolescents with HAE but lacks established effectiveness to treat individuals with laryngeal attacks.

Clinical Criteria

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Hereditary Angioedema (HAE) Agents for Prophylaxis of Acute Attacks

Initial requests for Cinryze or Haegarda (C1 esterase inhibitor [human]) or Takhzyro (lanadelumab-flyo) may be approved if the following criteria are met:

I. Individual has a diagnosis of hereditary angioedema; **AND**
II. Individual is using for prophylaxis against acute attacks of hereditary angioedema for either of the following:
    A. Short-term prophylaxis prior to surgery, dental procedures or intubation; **OR**
    B. Long-term prophylaxis to minimize the frequency and/or severity of recurrent attacks;

AND

III. Individual is of appropriate age for the specific drug requested:
    A. 6 years of age or older for Cinryze; **OR**
    B. 6 years of age or older for Haegarda; **OR**

C. 2 years of age or older for Takhzyro;

AND

IV. Documentation is provided that diagnosis is verified by a C4 level below the lower limit of normal as defined by laboratory test AND any of the following:
   A. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by lab test; **OR**
   B. C1-INH functional level below the lower limit of normal as defined by lab test; **OR**
   C. Presence of a known HAE-causing C1-INH mutation;

AND

V. Individual has a history of moderate or severe attacks such as airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, or painful facial distortion.

Requests for Cinryze, Haegarda, or Takhzyro may not be approved for the following:

I. In combination with other HAE agents for prophylaxis of acute attacks (including but not limited to Cinryze, Haegarda, Orladeyo, or Takhzyro); **OR**
II. When the above criteria are not met and for all other indications.

Approval Duration Limits:

Initial Authorization for Cinryze, Haegarda: 6 months
Initial Authorization for Takhzyro: 8 months
Continuation of use (maintenance) criteria for Cinryze, Haegarda, Takhzyro: 1 year

Requests for Cinryze or Haegarda or Takhzyro may be approved for continuation of use in prophylactic care if the following criteria are met:

I. Individual has had a positive clinical response defined as a clinically significant reduction in the number and/or frequency of HAE attacks occurred.

Hereditary Angioedema (HAE) Agents for Treatment of Acute Attacks

Requests for Berinert (C1 esterase inhibitor [human]), Icatibant (Firazyr, Sajazir), Ruconest (C1 esterase inhibitor [recombinant]) or Kalbitor (ecallantide) may be approved if the following criteria are met:

I. Individual has a diagnosis hereditary angioedema; **AND**
II. Individual is using for the treatment of acute attacks (not prophylaxis); **AND**
III. Individual is of appropriate age for the specific drug requested:
   A. 5 years and older for Berinert; **OR**
   B. 13 years and older for Ruconest; **OR**
   C. 18 years and older for Icatibant (Firazyr, Sajazir); **OR**
   D. 12 years and older for Kalbitor;

AND

IV. Documentation is provided that diagnosis is verified by a C4 level below the lower limit of normal as defined by laboratory testing AND one of the following:
   A. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal as defined by laboratory testing; **OR**
   B. C1-INH functional level below the lower limit of normal as defined by the laboratory testing;

AND

V. Individual has a history of moderate or severe attacks such as airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, or painful facial distortion;

Requests for Ruconest may not be approved for the following:

I. Individuals using to treat laryngeal attacks; **OR**
II. In combination with other HAE agents for acute attacks (including but not limited to Berinert, Icatibant (Firazyr, Sajazir), or Kalbitor); **OR**
III. Individual has a known or suspected allergy to rabbits or rabbit-derived products; **OR**
IV. When the above criteria are not met and for all other indications.

Requests for Berinert, Icatibant (Firazyr, Sajazir), or Kalbitor may not be approved for the following:

I.
II. In combination with other HAE agents for acute attacks (including but not limited to Berinert, Icatibant (Firazyr, Sajazir), Kalbitor, or Ruconest); **OR**
III. When the above criteria are not met and for all other indications.

Step Therapy

Note: When a hereditary angioedema agent is deemed approvable based on the clinical criteria above, the benefit plan may have additional criteria requiring the use of a preferred[1] agent or agents.

Non-Preferred Hereditary Angioedema (HAE) for Prophylaxis of Acute Attacks Agents Step Therapy

A list of the preferred hereditary angioedema agent(s) for prophylaxis of acute hereditary angioedema attacks is available here. Requests for a non-preferred Hereditary Angioedema (HAE) acute attack agent for prophylaxis may be approved when the following criteria are met:

I. Individual has had a trial or intolerance to one preferred agent;

OR

II. Individual has a history of anaphylaxis with active or inactive ingredients in the preferred agent which is not also associated with the requested non-preferred agent;

OR

III. Cinryze or Haegarda is designated as a non-preferred agent and being requested for an individual greater than or equal to 6 years of age and less than 12 years of age;

OR

IV. Haegarda or Takhzyro is designated as a non-preferred agent and being requested for an individual who is unable to use home-infusion services OR individual is unable to access alternative settings due to unreasonable distance or other extenuating circumstances.

[1]Preferred, as used herein, refers to agents that were deemed to be clinically comparable to other agents in the same class or disease category but are preferred based upon clinical evidence and cost effectiveness.

Quantity Limits

Hereditary Angioedema (HAE) Acute Attack Agents

Drug	Limit
Berinert (C1 esterase inhibitor [human]) 500 IU kit	Up to 20 IU/kg once per attack (Max: 24 kits/30 days)
Icatibant (Firazyr, Sajazir) 30 mg prefilled syringe	Up to 3 syringes (90 mg) per attack (Max: 18 syringes/30 days)
Kalbitor (ecallantide) 10 mg vial	Up to 6 vials (60 mg) per attack (Max: 36 vials/30 days)
Ruconest (C1 esterase inhibitor [recombinant]) 2100 unit vial	Up to two 50 units/kg doses [max of 4200 units (2 vials) per dose] per attack (Max: 16 vials/30 days)

Hereditary Angioedema (HAE) for Prophylaxis of Acute Attacks Agents

Drug	Limit
Cinryze 500 units/vial	20 vials per 30 days
Haegarda 2,000IU/vial	24 vials per 28 days
Haegarda 3,000 IU/vial	16 vials per 28 days
Takhzyro (lanadelumab-flyo) 300 mg	1 syringe/vial per 28 days*
Takhzyro (lanadelumab-flyo) 150	1 syringe per 28 days*
Override Criteria	
*Initial authorization period for those 6 years of age or older: Requests for an additional Takhzyro syringe for a total of 2 syringes per 28 days may be approved for the initial 8 months as part of the titration period. For Takhzyro maintenance therapy for those 6 years of age or older: if an individual is well-controlled (attack free) for the last 6 months, continue authorization for one year with 1 syringe per 28 days. Two syringes per 28 days may be approved for one year if a provider submits documentation providing rationale for the 2 syringes per 28 days dosing (i.e. patient has an attack in the last 6 months or history of very severe attacks i.e. laryngeal attack) or if the provider submits supporting documentation that the member has tried and failed 1 syringe per 28 days dosing (i.e. experiences an attack).	

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

HCPCS	
J0596	Injection, C-1 esterase inhibitor (recombinant), Ruconest, 10 units
J0597	Injection, C-1 esterase inhibitor (human), Berinert, 10 units
J0598	Injection, C-1 esterase inhibitor (human), Cinryze, 10 units
J0599	Injection, c-1 esterase inhibitor (human), Haegarda, 10 units
J1290	Injection, ecallantide, 1 mg [Kalbitor]
J1744	Injection, icatibant, 1 mg [Firazyr] [Sajazir]
J0593	Inj., lanadelumab-flyo, 1 mg [Takhzyro]
ICD-10 Diagnosis	
D84.1	Defects in the complement system

Document History

Revised: 08/18/2023
Document History:

- 08/18/2023 - Annual Review: Adjusted quantity limits on acute treatment agents icatibant (Firazyr, Sajazir) and Kalbitor. Wording and formatting changes. Coding Reviewed: No changes.
- 03/13/2023 - Select Review: Takhzyro age update. Added new strength of Takhzyro with quantity limits and with override criteria for those 6 years of age and older. Coding Reviewed: No changes.
- 03/27/2023 - Step therapy table updates.
- 08/19/2022- Annual Review: Added rabbit allergy in MNA section for Ruconest. Coding reviewed: No changes.
- 09/13/2021- Select Review: Add Berinert Kit, remove Berinert Vial, add branded generic Sajazir. Coding reviewed: Added Sajazir to HCPCS J1744.
- 08/20/2021- Annual Review: Takhzyro administrative update, Add do not approve criteria in Acute Attacks Agents. Coding reviewed: No changes.
- 08/01/2021 – Administrative update to add documentation.
- 02/19/2021– Select Review: Update quantity limit for Takhzyro and add override criteria. Update may not be approved section in the PA for HAE prophylaxis agents. Update approval duration limits for the HAE prophylaxis agents Coding Reviewed: No changes.
- 11/20/2020– Select Review: Update Haegarda clinical criteria and HAE agents for prophylaxis step therapy for Haegarda's use in children 6 years of age and older. Added initial and continuation of use criteria to the agents used in HAE prophylaxis. Coding Reviewed: No changes.
- 08/21/2020 – Annual Review: No changes. Coding reviewed: No changes.
- 11/15/2019 – Select review. Update with new maximum Quantity Limits for treatment of HAE acute attack agents, Berinert, Firazyr, Ruconest, and Kalbitor. Coding Reviewed: No Changes.
- 08/16/2019 – Annual review. Discuss Quantity Limits for HAE acute attack agents. Minor wording and formatting changes. Coding Reviewed: Added HCPCS J0593 Effective 10/1/19, DELETE J3490, J3590, C9399 –Effective 10/1/19
- 02/22/2019 – Update NP ST for Prophylaxis of Acute Angioedema Attacks to include Takhzyro as a potential preferred agent.
- 08/17/2018 – Annual Review: New NP ST for HAE agents for Prophylaxis of Acute Angioedema Attacks. Update HAE for Prophylaxis of Acute Attacks PA with pediatric age criteria for Cinryze. Review new preliminary PA for lanadelumab as part of PA for HAE agents for Prophylaxis of Acute Angioedema Attacks. Also review lanadelumab as part of new NP ST for HAE agents for Prophylaxis of Acute Angioedema Attacks. – Updated HCPCS (J3590, C9399) and ICD-10-CM (D84.1) coding. Update clinical criteria due to FDA approval for Takhzyro on 8-24-18. Revised language for HCPCS (J3590, C9399). Added J3490 with revised language.

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Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

CC-0034 Agents for Hereditary Angioedema

Commercial Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
8/1/2019	Haegarda Takhzyro	Cinryze

Medicaid Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
03/01/2020: GA, IN, KY, NY, NJ, NV, SC, WNY 03/15/2020: IN 06/01/2020: CA 04/01/2023: DC	Haegarda Takhzyro	Cinryze

Medicare Medical Benefit

Effective Date	Preferred Agents	Non-Preferred Agents
N/A	N/A	N/A