

Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Hereditary Angioedema Agents: Cinryze, Haegarda, Berinert, Firazyr, Kalbitor, Ruconest, Takhzyro, Orladeyo	MP-RX-FP-36-23	<input checked="" type="checkbox"/> MMM MA <input checked="" type="checkbox"/> MMM Multihealth

Service Category

- | | |
|--|---|
| <input type="checkbox"/> Anesthesia | <input type="checkbox"/> Medicine Services and Procedures |
| <input type="checkbox"/> Surgery | <input type="checkbox"/> Evaluation and Management Services |
| <input type="checkbox"/> Radiology Procedures | <input type="checkbox"/> DME/Prosthetics or Supplies |
| <input type="checkbox"/> Pathology and Laboratory Procedures | <input checked="" type="checkbox"/> Part B Drugs |

Service Description

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 pts	Intravenous infusion	- Risk of serious anaphylactic reactions
Haegarda (C1 Esterase Inhibitor, Human)	Prophylaxis	Routine prophylaxis against HAE attacks (≥ 6 years)	Subcutaneous	-Serious arterial and venous Thromboembolic events
Berinert (C1 Esterase Inhibitor, Human)	Treatment	Treatment of acute abdominal, facial, or laryngeal attacks of HAE in adult and pediatric pts (≥ 5 years)	Intravenous infusion	-Made from human plasma and may contain infectious agents
Firazyr (icatibant)	Treatment	Treatment of acute attacks of HAE in adults pts (≥ 18 years)	Subcutaneous	-Laryngeal attacks
Kalbitor (ecallantide)	Treatment	Treatment of acute attacks of HAE in adult and pediatric pts (≥ 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 pts (≥ 13 years) Note: Effectiveness not established in pts 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

Policy Name	Policy Number	Scope
Hereditary Angioedema Agents: Cinryze, Haegarda, Berinert, Firazyr, Kalbitor, Ruconest, Takhzyro, Orladeyo	MP-RX-FP-36-23	<input checked="" type="checkbox"/> MMM MA <input checked="" type="checkbox"/> MMM Multihealth

Background Information

Hereditary Angioedema (HAE) is a chronic autosomal dominant disorder associated with recurrent, unpredictable, and potentially lifethreatening 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 (Icanadelumab) 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.

Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Hereditary Angioedema Agents: Cinryze, Haegarda, Berinert, Firazyr, Kalbitor, Ruconest, Takhzyro, Orladeyo	MP-RX-FP-36-23	<input checked="" type="checkbox"/> MMM MA <input checked="" type="checkbox"/> MMM Multihealth

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 attack.

Clinical Criteria:

B vs D Criteria: Takhzyro included in this PA is subject to B vs D evaluation. Medication must be furnished “incident to” physician service provided and usually not self-administered to be covered by Medicare and to be eligible to be evaluated through part B. If not, medication must be evaluated through part D.

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 confirmed 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. All other indications not included above; **OR**

Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Hereditary Angioedema Agents: Cinryze, Haegarda, Berinert, Firazyr, Kalbitor, Ruconest, Takhzyro, Orladeyo	MP-RX-FP-36-23	<input checked="" type="checkbox"/> MMM MA <input checked="" type="checkbox"/> MMM Multihealth

II. In combination with other HAE agents for prophylaxis of acute attacks (including but not limited to Cinryze, Haegarda, Orladeyo, or Takhzyro).

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. Confirmation of 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 confirmed 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. All other indications not included above; **OR**
- II. Individuals using to treat laryngeal attacks; **OR**
- III. In combination with other HAE agents for acute attacks (including but not limited to Berinert, Icatibant (Firazyr, Sajazir), or Kalbitor); **OR**

Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Hereditary Angioedema Agents: Cinryze, Haegarda, Berinert, Firazyr, Kalbitor, Ruconest, Takhzyro, Orladeyo	MP-RX-FP-36-23	<input checked="" type="checkbox"/> MMM MA <input checked="" type="checkbox"/> MMM Multihealth

IV. Individual has a known or suspected allergy to rabbits or rabbit-derived products.

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

- I. All other indications not included above; **OR**
- II. In combination with other HAE agents for acute attacks (including but not limited to Berinert, Icatibant (Firazyr, Sajazir, Kalbitor, or Ruconest).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J0593	Inj., lanadelumab-flyo, 1 mg [Takhzyro]
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]

ICD-10	Description
D84.1	Defects in the complement system

Policy Name	Policy Number	Scope	
Hereditary Angioedema Agents: Cinryze, Haegarda, Berinert, Firazyr, Kalbitor, Ruconest, Takhzyro, Orladeyo	MP-RX-FP-36-23	<input checked="" type="checkbox"/> MMM MA	<input checked="" type="checkbox"/> MMM Multihealth

Limits or Restrictions

A. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Hereditary Angioedema (HAE) Acute Attack Agents

Drug	Limit
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)
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)
Berinert (C1 esterase inhibitor [human]) 500 IU kit	Up to 20 IU/kg once per attack (Max: 24 kits/30 days)
Exceptions	
N/A	

Hereditary Angioedema (HAE) for Prophylaxis of Acute Attacks Agents

Drug	Limit
Takhzyro (lanadelumab-flyo) 300 mg	1 syringe/vial per 28 days*
Takhzyro (lanadelumab-flyo) 150 mg	1 syringe per 28 days*
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*
Exceptions	

*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

Policy Name	Policy Number	Scope
Hereditary Angioedema Agents: Cinryze, Haegarda, Berinert, Firazyf, Kalbitor, Ruconest, Takhzyro, Orladeyo	MP-RX-FP-36-23	<input checked="" type="checkbox"/> MMM MA <input checked="" type="checkbox"/> MMM Multihealth

documentation that the member has tried and failed 1 syringe per 28 days dosing (i.e. experiences an attack).

Reference Information

1. Bork, K., Anderson, J.T., Caballero, T. et al. Assessment and management of disease burden and quality of life in patients with hereditary angioedema: a consensus report. *Allergy Asthma Clin Immunol* 17, 40 (2021). <https://doi.org/10.1186/s13223-021-00537-2>. Accessed on July 9, 2022.
2. Busse, PJ, Christiansen SC, Riedl MA et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol Pract*. 2021;9:132-50.
3. *Clinical Pharmacology* [database online]. Tampa, FL: Gold Standard, Inc.: 2022. URL: <http://www.clinicalpharmacology.com>. Updated periodically.
4. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. <http://dailymed.nlm.nih.gov/dailymed/about.cfm>. Accessed: July 9, 2022.
5. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
6. Efficacy and Safety Study of DX-2930 to Prevent Acute Angioedema Attacks in Patients with Type I and Type II HAE. NCT02586805 (HELP Study). Available at <https://www.clinicaltrials.gov/ct2/show/study/NCT02586805>.
7. Haegarda [Package Insert]. Marburg, Germany. CSL Behring, GmbH.; 2017.
8. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2022; Updated periodically.
9. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema The 2017 revision and update. *Allergy*. 2018 Jan 10.
10. Riedl MA, Bernstein JA, Craig T, et al. An open-label study to evaluate the long-term safety and efficacy of lanadelumab for prevention of attacks in hereditary angioedema: design of the HELP study extension. *Clin Transl Allergy*. 2017;7:36.
11. Riedl MA. Creating a Comprehensive Treatment Plan for Hereditary Angioedema. *Immunol Allergy Clin N Am*. 2013; 33 (4): 471-485. doi:10.1016/j.iac.2013.07.003.
12. Takhzyro [Package Insert]. Lexington, MA. Dyax Corp, Shire; 2018.
13. Zuraw B, 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.
14. Zuraw BL, Banerji A, Bernstein JA, 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. doi:10.1016/j.jaip.2013.07.002.
15. Zuraw BL, Bernstein JA, Lang DM, et al. A focused parameter update: Hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol*. 2013; 131(6):1491-1493.e1-e25. Available from: [http://www.jacionline.org/article/S0091-6749\(13\)00523-X/pdf](http://www.jacionline.org/article/S0091-6749(13)00523-X/pdf).

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

Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Hereditary Angioedema Agents: Cinryze, Haegarda, Berinert, Firazyr, Kalbitor, Ruconest, Takhzyro, Orladeyo	MP-RX-FP-36-23	<input checked="" type="checkbox"/> MMM MA <input checked="" type="checkbox"/> MMM Multihealth

No part of this publication may be reproduced, stored in a retrieval system or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from the health plan.

© CPT Only – American Medical Association

Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Policy Inception	Elevance Health’s Medical Policy adoption.	N/A	11/30/2023

Revised: 08/18/2023