Policy Number	**RX504.013**
Policy Effective Date	**11/15/2024**
Policy End Date	**12/31/2025**

Management of Hereditary Angioedema (HAE) with C1 Esterase Inhibitor, Human and Ecallantide

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-

reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

NOTE 1: C1 esterase inhibitor, human (Cinryze®) may be self-administered. Refer to the applicable pharmacy benefit plan when self-administered.

Cinryze® (C1 esterase inhibitor, human)
Cinryze **may be considered medically necessary** for routine prophylaxis against angioedema attacks in adults, adolescents and pediatric Individuals (6 years of age and older) diagnosed with hereditary angioedema (HAE) when:

Diagnosis of HAE Type I/II confirmed by ONE of the following:

- Laboratory testing that includes C4, C1 inhibitor (C1INH) protein, and C1INH function (**SEE Table 1. Testing Profiles for Diagnosis of Different Types of Hereditary Angioedema**):
  - Type 1 HAE: Decreased quantities of C4 level, C1-INH protein level, and C1-INH function level or;
  - Type 2 HAE: Decreased quantities of C4 level and C1-INH function level (C1-INH protein level may be normal or elevated).

Diagnosis of HAE Type III (diagnosis of HAE with a normal C1INH):

- History of recurrent angioedema in the absence of concomitant urticaria or use of a medication known to cause angioedema; and
- Documented normal or near normal C4, C1INH protein, and C1INH function; and
- One of the following:
  - A genetic mutation associated with the disease (mutation in Coagulation factor FXII/12, plasminogen, angiopoietin-1 or kininogen 1); or
  - A positive family history of angioedema and documented evidence of a lack of efficacy of chronic high-dose antihistamine therapy (e.g., cetirizine).

Cinryze **is considered experimental, investigational and/or unproven** for all other treatments including but not limited to:

- Treatment of an acute HAE attack;
- As dual therapy with another agent for routine prophylaxis against HAE (e.g., Haegarda, Orladeyo, Takhzyro).

NOTE 2: Safety and efficacy of Cinryze have not been established in neonates, infants, or children under the age of six years old. Cinryze is contraindicated for individuals who have

manifested life-threatening immediate hypersensitivity reactions, including anaphylaxis to the product.

Kalbitor® (ecallantide)
Kalbitor **may be considered medically necessary** in individuals 12 years of age or older for the treatment of acute attacks of hereditary angioedema (HAE) when administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema (See **NOTE 3**) when the following criteria are met.

Diagnosis of HAE Type I/II confirmed by ONE of the following:

- Laboratory testing that includes C4, C1INH protein, and C1INH function **(See Table 1. Testing Profiles for Diagnosis of Different Types of Hereditary Angioedema)**:
  - Type 1 HAE: Decreased quantities of C4 level, C1-INH protein level, and C1-INH function level or
  - Type 2 HAE: Decreased quantities of C4 level and C1-INH function level (C1-INH protein level may be normal or elevated).

Diagnosis of HAE Type III (diagnosis of HAE with a normal C1INH):

- History of recurrent angioedema in the absence of concomitant urticaria or use of a medication known to cause angioedema; and
- Documented normal or near normal C4, C1INH protein, and C1INH function; and
- One of the following:
  - A genetic mutation associated with the disease (mutation in Coagulation factor FXII/12, plasminogen, angiopoietin-1 or kininogen 1); or
  - A positive family history of angioedema and documented evidence of a lack of efficacy of chronic high-dose antihistamine therapy (e.g., cetirizine).

Kalbitor **is considered experimental, investigational and/or unproven** for all other treatments including but not limited to:

- Individuals with HAE who are under age 12;
- Treatment for prophylactic therapy for HAE;
- As dual therapy with another agent for treating acute attacks of HAE; or
- Individuals without a diagnosis of HAE.

NOTE 3: HAE guidelines recommend that individuals with HAE should have a quantity of acute therapy medications sufficient to treat 2 acute attacks per month (in addition to their prophylactic therapy if needed).

NOTE 4: Inidividuals with HAE are often managed by an expert in the management of HAE and/or work closely with an HAE expert (usually an allergist/immunologist).

NOTE 5: Generally, medications administered by medical personnel in a professional setting are covered under the individuals medical benefit while those medications that are self-administered are covered under the pharmacy benefit.

Please refer to the applicable pharmacy benefit plan for the following medications:

- Berinert® (C1 Esterase Inhibitor [Human])
- Firazyr® (icatibant)
- Haegarda® (C1 Esterase Inhibitor Subcutaneous [Human])
- Orladeyo™ (berotralstat)
- Ruconest® (C1 Esterase Inhibitor [Recombinant])
- Takhzyro™ (lanadelumab-flyo)

Policy Guidelines

Testing profiles for the diagnosis of the different types of hereditary angioedema are outlined in Table 1 below.

Table 1. Testing Profiles for Diagnosis of Different Types of Hereditary Angioedema

	C1INH Protein Level	C1INH Function	C4 level
HAE Type I	Low	Low	Low
HAE Type II	Normal-High	Low	Low
HAE Type III (Diagnosis of HAE with normal C1INH levels)	Normal	Normal	Normal

C1INH: C1 inhibitor; HAE: hereditary angioedema

Description

Hereditary Angioedema

Hereditary angioedema (HAE) is the result of a defect in the gene controlling the synthesis of C1 inhibitor. C1 inhibitor (C1INH) maintains the natural regulation of the contact, complement, and fibrinolytic systems, that when left unrestricted, can initiate or perpetuate an attack by consuming the already low levels of endogenous C1 inhibitor in HAE patients. C1 inhibitors have been used in Europe for over ten years for the prophylaxis and acute treatment of HAE.

HAE affects an estimated 1 in 50,000 individuals in the United States. HAE is caused by having insufficient amounts of a plasma protein called C1 esterase inhibitor. People with HAE can develop rapid swelling of the hands, feet, limbs, face, intestinal tract, or airway. These acute attacks of swelling can occur spontaneously, or can be triggered by stress, surgery, or infection. Swelling of the airway is potentially fatal without immediate treatment.

There are several types of angioedema: this medical policy will focus on HAE. HAE includes type I, type II, and HAE-normal C1INH (nC1INH) (previously referred to as type III). Two forms of HAE

(type I and II) are not distinguishable clinically but can be diagnosed by laboratory findings. Zuraw et al. (2013) noted the following: Type I HAE presents with low C1INH antigenic and functional levels, whereas type II HAE presents with normal C1INH antigenic levels but decreased C1INH functional levels. Diagnosis of type I or type II HAE requires evidence of a low C1INH antigenic or functional level, as well as decreased C4 levels and generally normal C1q levels. (6) Zuraw et al. also noted in the 2013 practice parameter "At least 95% of patients with C1INH deficiency will have a reduced C4 level, even between attacks, and this number increases to virtually 100% during angioedema attacks." For those individuals with recurrent angioedema and normal C4 and C1INH levels, the possibility of HAE with normal C1INH levels should be considered. Furthermore Zuraw et al. notes "At the current time, there is no screening test to rule in a diagnosis of HAE with normal C1INH levels. Therefore, the diagnosis is one of exclusion and rests on the history of recurrent angioedema with a strong family history of angioedema." Unlike allergic angioedema, HAE attacks are usually of a longer duration and lack a response to antihistamines, corticosteroids, or epinephrine. (6)

Maurer et al. (2022) notes HAE with normal C1-INH (HAE-nC1-INH) is a group of very rare diseases. Six types of HAE-nC1-INH are currently recognized, based on underlying mutations of 1) factor XII (FXII), 2) angiopoietin-1 (ANGPT1), 3) plasminogen (PLG), 4) kininogen 1 (KNG1), 5) myoferlin (MYOF), and 6) heparan sulfate-glucosamine 3-O-sulfotransferase 6 (HS3ST6). However, in many patients with HAE-nC1-INH, no gene mutation can be found. (8)

Regulatory Status

Cinryze® (C1 esterase inhibitor, human)

In 2008, the U.S. Food and Drug Administration (FDA) provided a biologics license application (BLA) for Cinryze. Cinryze is a C1 esterase inhibitor used for the treatment of routine prophylaxis against angioedema attacks with HAE. Cinryze, includes the following indications: for routine prophylaxis against angioedema attacks in adults, adolescents, and pediatric patients (6 years of age and older) with HAE. (5) Cinryze is intended to increase the level of functional C1 esterase inhibitor in a patient's plasma, thereby preventing the acute attack of swelling (1-2). Cinryze is administered intravenously and can be given every three or four days for routine prevention of HAE attacks.

Kalbitor® (ecallantide)

In 2009, the FDA approved Kalbitor to be manufactured under the BLA for the indication of the treatment of acute attacks of HAE. Kalbitor is indicated for the treatment of acute attacks of HAE in patients 12 years of age and older. (4) The label includes a black box warning for anaphylaxis and notes: "Kalbitor should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema." (4) Kalbitor is a plasma kallikrein inhibitor and is administered subcutaneously.

Rationale

This policy was originally developed in 2009 and has been updated with searches of scientific literature through May 22, 2024. The following is a summary of the key literature to date.

Cinryze®

As indicated in the U.S. Food and Drug Administration (FDA) Highlights of Prescribing Information for Cinryze, the safety and efficacy of Cinryze prophylaxis therapy to reduce the incidence, severity, and duration of hereditary angioedema (HAE) attacks was demonstrated in a single randomized, double blind, placebo controlled multi-center cross-over study of 24 subjects. (5) Subjects were screened to confirm a diagnosis of HAE and a history of at least two HAE attacks per month. The subjects (mean age 38.1 years with a range of 9 to 73 years) were randomized to one of two treatment groups: either Cinryze prophylaxis for 12 weeks followed by 12 weeks of placebo prophylaxis; or randomized to placebo prophylaxis for 12 weeks followed by 12 weeks of Cinryze prophylaxis. Two subjects dropped out (one in each arm); 22 subjects crossed over into period 2 and were included in the efficacy analysis. Subjects were given either Cinryze or placebo injections every 3 to 4 days, approximately 2 times per week. Subjects recorded all angioedema symptoms daily. An attack was defined as the subject-reported indication of swelling at any location following a report of no swelling on the previous day.

The efficacy determination was based on the number of attacks during the 12-week period while receiving Cinryze as compared to the number of attacks during the placebo treatment period. The effectiveness of C1 esterase inhibitor prophylaxis in reducing the number of HAE attacks was variable among the subjects.

Table 2. Summary Statistics on Number of HAE Attacks in the Randomized, Placebo-Controlled, Crossover, Routine Prophylaxis Trial.

Statistics	**Cinryze N=22**	**Placebo N=22**
Mean	6.1	12.7
SD	5.4	4.8
Median	6	13.5
Min	0	6
Max	17	22

SD: standard deviation

Subjects treated with Cinryze had a 66% reduction in days of swelling ($p<0.0001$) and decreases in the average severity of attacks ($p=0.0006$) and the average duration of attacks ($p=0.0023$).

Pediatric Patients

The safety and efficacy of Cinryze (500 U and 1,000 U) for the prevention of HAE attacks and the reduction of the severity and requirement for acute treatment was demonstrated in a randomized, single-blind, multi-center, dose-ranging cross-over study of 12 pediatric subjects aged 7 to 11 years. (5)

During the 12-week study period, a greater reduction in the normalized number of angioedema attacks per month was observed with 1,000 U Cinryze compared to 500 U Cinryze (p=0.03). When compared to the baseline observational period, a reduction in the normalized number of angioedema attacks was observed for both Cinryze 500 U and Cinryze 1,000 U (mean absolute reduction in number of HAE attacks: 2.6, 3.0 respectively; mean percent reduction in HAE attacks: 71.1% and 84.5%, respectively). In addition, both doses lessened the severity of attacks and reduced the use of acute treatment compared with baseline.

Kalbitor®
As indicated in the FDA Highlights of Prescribing Information for Kalbitor, the safety and efficacy of Kalbitor to treat acute attacks of HAE in adolescents and adults were evaluated in 2 randomized, double-blind, placebo-controlled trials (EDEMA4 and EDEMA3) in 168 patients with HAE. (4) Patients having an attack of HAE, at any anatomic location, with at least 1 moderate or severe symptom, was treated with 30 mg subcutaneous Kalbitor or placebo. Because patients could participate in both trials, a total of 143 unique patients participated. Of the 143 patients, 94 were female, 123 were Caucasian, and the mean age was 36 years (range 11-77). There were 64 patients with abdominal attacks, 55 with peripheral attacks, and 24 with laryngeal attacks.

In both trials, the effects of Kalbitor were evaluated using the Mean Symptom Complex Severity (MSCS) score and the Treatment Outcome Score (TOS). These endpoints evaluated attack severity using the MSCS score and patient response to treatment (TOS) for an acute HAE attack.

MSCS score is a point-in-time measure of symptom severity. At baseline, and post-dosing at 4 hours and 24 hours, patients rated the severity of each affected symptom on a categorical scale (0 = normal, 1 = mild, 2 = moderate, 3 = severe). Patient-reported severity was based on each patient's assessment of symptom impact on their ability to perform routine activities. Ratings were averaged to obtain the MSCS score. The endpoint was reported as the change in MSCS score from baseline. A decrease in MSCS score reflected an improvement in symptom severity; the maximum possible change toward improvement was -3.

TOS is a measure of symptom response to treatment. At 4 hours and 24 hours post-dosing, patient assessment of response for each anatomic site of attack involvement was recorded on a categorical scale (significant improvement [100], improvement [50], same [0], worsening [-50], significant worsening [-100]). The response at each anatomic site was weighted by baseline severity and then the weighted scores across all involved sites were averaged to calculate the TOS. A TOS value >0 reflected an improvement in symptoms from baseline. The maximum possible score was +100.

EDEMA4 was a randomized, double-blind, placebo-controlled trial in which 96 patients were randomized 1:1 to receive Kalbitor 30 mg subcutaneous or placebo for acute attacks of HAE. (4) The primary endpoint was the change from baseline in MSCS score at 4 hours, and the TOS at 4 hours was a key secondary endpoint. Patients treated with Kalbitor demonstrated a greater decrease from baseline in the MSCS than placebo and a greater TOS than patients with placebo

and the results were statistically significant. At 24 hours, patients treated with Kalbitor also demonstrated a greater decrease from baseline in the MSCS than placebo (-1.5 vs. -1.1; p = 0.04) and a greater TOS (89 vs. 55, p = 0.03). More patients in the placebo group (24/48, 50%) required medical intervention to treat unresolved symptoms within 24 hours compared to the Kalbitor-treated group (16/48, 33%). Some patients reported improvement following a second 30 mg subcutaneous dose of Kalbitor, administered within 24 hours following the initial dose for symptom persistence or relapse, but efficacy was not systematically assessed for the second dose.

As with the EDEMA4 trial, the EDEMA3 was a randomized, double-blind, placebo-controlled trial in which 72 patients were randomized 1:1 to receive Kalbitor or placebo for acute attacks of HAE. (4) EDEMA3 was similar in design to EDEMA4 with the exception of the order of the prespecified efficacy endpoints. In EDEMA3, the primary endpoint was the TOS at 4 hours, and the key secondary efficacy endpoint was the change from baseline in MSCS at 4 hours. As in EDEMA4, patients treated with Kalbitor demonstrated a greater decrease from baseline in the MSCS than placebo and a greater TOS than patients treated with placebo and the results were statistically significant. In addition, more patients in the placebo group (13/36, 36%) required medical intervention to treat unresolved symptoms within 24 hours compared to the Kalbitor-treated group (5/36, 14%).

Summary of Evidence

For individuals who have hereditary angioedema (HAE) who receive Cinryze (C1 esterase inhibitor, human) for routine prophylaxis against angioedema attacks, the evidence includes clinical information noted on the U.S. Food and Drug Administration's (FDA) product label for Cinryze. In a randomized, double blind, placebo controlled multi-center cross-over study, participants treated with Cinryze had a 66% reduction in days of swelling ($p<0.0001$) and decreases in the average severity of attacks ($p=0.0006$) and the average duration of attacks ($p=0.0023$). The use of Cinryze is considered medically necessary when used according to the FDA's indications for use and when criteria outlined in Coverage is met. The use of Cinryze is considered experimental, investigational and/or unproven for all other treatments.

For individuals who have HAE who received Kalbitor (ecallantide) for the treatment of acute attacks of HAE, the evidence includes clinical information noted on the FDA product label for Kalbitor. In 2 randomized, double-blind, placebo-controlled trials (EDEMA4 and EDEMA3); on the safety and efficacy of Kalbitor attack severity and patient response to treatment was evaluated using the Mean Symptom Complex Severity (MSCS) score and the Treatment Outcome Score (TOS). A decrease in MSCS score reflected an improvement in symptom severity. Patients treated with Kalbitor demonstrated a greater decrease from baseline in the MSCS than placebo and a greater TOS than patients with placebo and the results were statistically significant. The use of Kalbitor is considered medically necessary when used according to the FDA's indications for use and when criteria outlined in Coverage is met. The use of Kalbitor is considered experimental, investigational and/or unproven for all other treatments.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	J0598, J1290

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
11/15/2024	Document updated with literature review. The following Coverage changes were made: 1) NOTE 1 was added, other NOTEs were renumbered; 2) Changed the criteria noted under Diagnosis of HAE Type I/II under the laboratory testing criteria for both Cinryze® (C1 esterase inhibitor, human) and Kalbitor® (ecallantide); 3) Information addressing Table 1. Testing Profiles for Diagnosis of Different Types of Hereditary Angioedema moved from "Coverage" section to the "Policy Guidelines" section; 4) Other editorial changes made for clarity. No new references added.
02/01/2024	Document updated with literature review. Coverage unchanged. References updated.
02/01/2023	Document updated with literature review. The following changes were made to Coverage: Removed from criterion under HAE Type III on both Cinryze® (C1 esterase inhibitor, human) and Kalbitor® (ecallantide) sections "A demonstrated F12 mutation associated with the disease (Factor XII/12)" and replaced with "A genetic mutation associated with the disease (mutation in Coagulation factor FXII/12, plasminogen, angiopoietin-1 or kininogen1)". Reference 8 added, and other references updated.
09/01/2021	Document updated with literature review. The following changes were made to Coverage: 1) Added "As dual therapy with another agent for routine prophylaxis against HAE (e.g., Haegarda, Orladeyo, Takhzyro)" to the Cinryze statement addressing experimental, investigational and/or unproven indications. 2) Added "Orladeyo™ (berotralstat)" to the list of medications listed under NOTE 5 referring the user to the applicable pharmacy benefit plan. No new references added.
08/15/2020	Document updated with literature review. The following changes were made to Coverage: 1) Criteria to confirm the diagnosis of Hereditary Angioedema has changed, 2) NOTEs 2-5 have been added, 3) NOTE 5 referring to the applicable pharmacy benefit plan has additional drugs listed. Title changed from: Management of Hereditary Angioedema (HAE) with Cinryze or Kalbitor. References added: 6 and 7; some references removed.

10/01/2018	Document updated with literature review. The following FDA change was made to the age requirement for Cinryze® (C1 esterase inhibitor, human): changed from age 9 and older to 6 and older. Reference 8 added.
12/01/2017	Reviewed. No changes.
07/15/2017	Document partially updated with literature review. The following coverage clarification was added concerning hereditary angioedema (HAE) testing: When diagnosis confirmed by C4 and C1 Inhibitor laboratory testing for HAE type I or II OR for HAE III when testing is normal for C4 and C1 and patient has a known HAE-causing C1-INH mutation (i.e. mutation of coagulation factor XII gene), or a family history of HAE. Added the following statement regarding Haegarda® (C1 Esterase Inhibitor Subcutaneous [Human]): "This drug is self-administered. Please refer to applicable pharmacy benefit plan."
08/15/2016	Document updated with literature review. The following was added to the coverage section: 1) Kalbitor may be considered medically necessary in patients 12 years of age or older for the treatment of acute attacks of hereditary angioedema (HAE) when administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema, and 2) Kalbitor is considered experimental, investigational and/or unproven for all other treatments including but not limited to: patients with HAE who are under age 12, treatment for prophylactic therapy for HAE, As dual therapy with another agent for treating acute attacks of HAE, or patients without a diagnosis of HAE. Title changed from: Cinryze [C1 Esterase Inhibitor (Human)] for Routine Prophylaxis of Hereditary Angioedema (HAE).
04/01/2015	Document updated with literature review. Coverage unchanged.
06/15/2011	Document updated with literature review. No change in coverage. Title changed to CINRYZE [C1 Esterase Inhibitor (Human)] for Routine Prophylaxis of Hereditary Angioedema (HAE).
09/15/2009	New medical document with coverage criteria based on approved labeled FDA indications.