Drug Coverage Policy

Effective Date……01/01/2026
Coverage Policy Number……IP0315
Policy Title….. C1 Esterase Inhibitors (Intravenous)

Hereditary Angioedema – C1 Esterase Inhibitors (Intravenous)

- Berinert® (C1 esterase inhibitor [human] intravenous infusion - CSL Behring)
- Cinryze® (C1 esterase inhibitor [human] intravenous infusion - Takeda)
- Ruconest® (C1 esterase inhibitor [recombinant] intravenous infusion – Pharming)

INSTRUCTIONS FOR USE
The following Coverage Policy applies to health benefit plans administered by Cigna Companies. Certain Cigna Companies and/or lines of business only provide utilization review services to clients and do not make coverage determinations. References to standard benefit plan language and coverage determinations do not apply to those clients. Coverage Policies are intended to provide guidance in interpreting certain standard benefit plans administered by Cigna Companies. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement, Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document always supersedes the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Each coverage request should be reviewed on its own merits. Medical directors are expected to exercise clinical judgment where appropriate and have discretion in making individual coverage determinations. Where coverage for care or services does not depend on specific circumstances, reimbursement will only be provided if a requested service(s) is submitted in accordance with the relevant criteria outlined in the applicable Coverage Policy, including covered diagnosis and/or procedure code(s). Reimbursement is not allowed for services when billed for conditions or diagnoses that are not covered under this Coverage Policy (see "Coding Information" below). When billing, providers must use the most appropriate codes as of the effective date of the submission. Claims submitted for services that are not accompanied by covered code(s) under the applicable Coverage Policy will be denied as not covered. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations.

Overview

Berinert, Cinryze, and Ruconest are C1 esterase inhibitor (C1-INH) replacement therapies for hereditary angioedema (HAE).[1-3] Cinryze and Berinert are human plasma-derived C1-INH; Ruconest is a recombinant C1-INH purified from milk of transgenic rabbits. Labeled indications are as follows:

- Berinert is indicated for the **treatment of acute abdominal, facial, or laryngeal HAE attacks** in adults and pediatric patients.[1]
- Cinryze is indicated for routine **prophylaxis against HAE attacks** in patients ≥ 6 years of age.[2]
- Ruconest is indicated for the **treatment of acute HAE attacks** in adults and adolescent patients.[3]

Of note, although Cinryze is labeled for use in the prophylactic setting and Berinert is labeled for use in the acute treatment setting, use of Cinryze in the acute setting and Berinert in the prophylactic setting has been reported in the literature.[4,5]

Guidelines

Acute Treatment of HAE Attacks

According to US HAE Association Medical Advisory Board Guidelines (2020), when HAE is suspected based on clinical presentation, appropriate testing includes measurement of the serum C4 level, C1-INH antigenic level, and C1-INH functional level.[6] Low C4 plus low C1-INH antigenic or functional level is consistent with a diagnosis of HAE types I/II. The goal of acute therapy is to minimize morbidity and prevent mortality from an ongoing HAE attack. Patients must have ready access to effective on-demand medication to administer at the onset of an HAE attack. All HAE attacks are eligible for treatment, irrespective of the location of swelling or severity of the attack. First-line treatments include plasma-derived C1-INH, Ruconest, Kalbitor® (ecallantide subcutaneous [SC] injection), and icatibant (Firazyr®, generic).

The guidelines note that HAE with normal C1-INH (HAE-nC1INH) is challenging to diagnose due to the lack of validated biochemical test.[6] Genetic testing could be helpful in confirming diagnosis.[6] The most common mutation linked to HAE-nC1INH is in the F12 gene. These guidelines note the following criteria for diagnosis of HAE-nC1INH: a history of recurrent angioedema without hives and no concomitant use of medication-related angioedema; documented normal or near normal C4, C1-INH antigen, and C1-INH function; and either a mutation associated with the disease or a positive family history of recurrent angioedema and documented lack of efficacy of high-dose antihistamine therapy (i.e., cetirizine at 40 mg/day or the equivalent) for at least 1 month or an interval expected to be associated with three or more angioedema attacks, whichever is longer. Supportive evidence includes a history of rapid and durable response to a bradykinin-targeted medication and predominant documented visible angioedema or in patients with abdominal symptoms, evidence of bowel wall edema documented by imaging. With regards to on-demand treatment of HAE-nC1INH, the guidelines note the lack of randomized controlled studies. However, it notes that there are numerous open-label reports with successful responses to on-demand treatments used for HAE type I/II. There are no data on short-term prophylaxis for HAE-nC1INH. Use of C1INH replacement for long-term prophylaxis is noted to be complex and controversial.

In guidelines from the World Allergy Organization (WAO)/European Academy of Allergy and Clinical Immunology (EAACI) [2021], it is recommended that all attacks be treated with either IV

C1-INH, Kalbitor, or icatibant (evidence level A for all).[7] Regarding IV C1-INH, it is noted that Berinert and Cinryze are both plasma-derived products available for this use, although indications vary globally. It is essential that patients have on-demand medication to treat all attacks; thus, the guidelines recommend that patients have and carry medication for treatment of at least two attacks.

Long-Term Prophylaxis
US HAE Association Medical Advisory Board Guidelines (2020) note the decision on when to use long-term prophylaxis cannot be made on rigid criteria but should reflect the needs of the individual patient.[6] First-line medications for HAE I/II include intravenous (IV) C1-INH, Haegarda® (C1-INH [human] SC injection), or Takhzyro® (landelumab-flyo SC injection). The guideline was written prior to approval of Orladeyo® (berotralstat capsules).

According to WAO/EAACI guidelines (2021), it is recommended to evaluate for long-term prophylaxis at every visit, taking disease activity, burden, and control as well as patient preference into consideration.[7] The following therapies are supported as first-line options for long-term prophylaxis: plasma-derived C1-INH (87% agreement), Takhzyro (89% agreement), and Orladeyo (81% agreement). With regard to plasma-derived C1-INH, it is noted that Haegarda provided very good and dose-dependent preventative effects on the occurrence of HAE attacks; the subcutaneous route may provide more convenient administration and maintain improved steady-state plasma concentrations compared with the IV route. Of note, androgens are not recommended in the first-line setting for long-term prophylaxis. Recommendations are not made regarding long-term prophylaxis in HAE with normal C1-INH.

An international consensus paper was published on the diagnosis, pathophysiology, and treatment of HAE-nl-C1INH.[9] The paper notes there is a paucity of high-level evidence in HAE-nC1INH and that all recommendations are based on expert opinion. Mutations in six different genes have been linked to HAE-nC1INH; however, the paper also specifies that many patients still lack an identified pathogenic variant for HAE-nC1INH. The six known gene variants are the following: the genes for coagulation factor XII (*F12 or FXII*), plasminogen (*PLG*), angiopoietin-1 (*ANGPT1*), kininogen-1 (*KNG1*), myoferlin (*MYOF*), and heparan sulfate glucosamine 3-O-sulfotransferase-6 (*HS3OST6*). Two more additional genes have been identified in the past year that have been linked to HAE-nC1INH in families that also experienced hives, the gene for carboxypeptidase N (*CPN*) and disabled homolog 2 interacting protein (*DAB2IP*). HAE-FXII and HAE-PLG appear to be bradykinin-mediated; the underlying mechanism of the other types have not been clearly identified. HAE-nC1INH patients have either a family history of recurrent angioedema or a genetic pathogenic variant in one of the known genes. Patients with HAE-unknown (HAE-UNK) have the phenotype indicative of HAE-nC1INH (recurrent angioedema that is not mast cell-mediated, normal C1INH function, and a positive family history of angioedema), but do not have an identified pathogenic variant. The diagnosis is based on exclusion of other causes such as HAE type I/II, mast-cell mediated angioedema, and medication-associated angioedema. Compared to mast-cell mediated angioedema, HAE-nC1INH attacks tend to progress slower, last longer, and are more likely to involve the abdomen or require intubation. Patients with HAE-nC1INH show no response to high-dose H1 antihistamines, corticosteroids, epinephrine, leukotriene receptor antagonists, or Xolair® (omalizumab for subcutaneous use). For management of HAE-nC1INH attacks, treatment with a plasma-derived C1 INH concentrate, bradykinin B2 receptor antagonist (icatibant), or plasma kallikrein inhibitor (Kalbitor) are noted to be generally effective. The consensus paper also notes there are limitations to diagnosing HAE-nC1INH on clinical signs and symptoms alone due to much variability even with a family with the same pathogenic variant. The paper notes that inclusion of family history as a required criterion for HAE might be problematic since this could be unreliable. The presence of a family history of angioedema may be considered strongly supportive of an HAE diagnosis, but cannot be an absolute requirement for

diagnosis. There are very limited data on the use of short-term or long-term prophylaxis for HAE-nC1INH. Long-term prophylaxis with antifibrinolytics, such as tranexamic acid, appear to benefit some subtypes of HAE-nC1INH (e.g., HAE-PLG). Data on Takhzyro (lanadelumab-flyo injection) use for prophylaxis are also very limited; a Phase III trial failed to demonstrate a difference, compared with placebo, in reducing the number of HAE-nC1INH attacks.[10]

Laboratory Diagnosis of Hereditary Angioedema.[6,7,9]

Laboratory Test	HAE Type I	HAE Type II	HAE - nC1INH (Formerly HAE Type III)
C4 Level	Low	Low	Normal
C1-INH protein/antigenic level	Low	Normal or high	Normal
C1-INH functional level	Low	Low	Normal
Genetic mutations	Mutation in SERPING1 gene	Mutation in SERPING1 gene	Mutations in other genes (e.g., F12, PLG)

HAE – Hereditary angioedema; HAE-nC1INH – Hereditary angioedema with normal C1 inhibitor; F12 – Gene for factor XII; PLG – Gene for plasminogen.

Dosing Information for Plasma-Derived C1-INH (Berinert, Cinryze)
For prophylaxis (Berinert or Cinryze), the maximum allowable dose in the policy comes from the Cinryze prescribing information and is applied to both Berinert and Cinryze prophylactic use requests. For the acute setting (Berinert or Cinryze), dosing recommendations come from the Berinert prescribing information and are applied to both Berinert and Cinryze requests for acute use. Of note, in the pivotal study of Berinert, a maximum of 20 IU/kg of Berinert was administered, and response was assessed for up to 24 hours. For the treatment of acute attacks, the prescribing information states that doses of Berinert lower than 20 IU/kg should not be administered.

Coverage Policy

POLICY STATEMENT
Prior Authorization is required for benefit coverage of Berinert, Cinryze, and Ruconest. Approval is recommended for those who meet the **Criteria** and **Dosing** for the listed indications. Extended approvals are allowed if the patient continues to meet the Criteria and Dosing. Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by a clinician (i.e., Medical Director or Pharmacist). All approvals are provided for the duration noted below. Because of the specialized skills required for evaluation and diagnosis of patients treated with Berinert, Cinryze, and Ruconest, as well as monitoring required for adverse events and long-term efficacy, approval requires the medication to be prescribed by or in consultation with a physician who specializes in the condition being treated. A patient who has previously met initial therapy criteria for Berinert, Cinryze, and Ruconest for the requested indication under the Coverage Review Department and is currently receiving the requested therapy is only required to meet the continuation therapy criteria (i.e., currently receiving Berinert, Cinryze, or Ruconest). If past criteria have not been met under the Coverage Review Department and the patient is currently receiving Berinert, Cinryze, or Ruconest, initial therapy criteria must be met.

Documentation: Documentation will be required where noted in the criteria as **[documentation required]**. Documentation may include, but is not limited to, chart notes, laboratory records, and prescription claims records. All documentation must include patient-specific identifying information.

Intravenous C1 Esterase Inhibitors (Berinert, Cinryze, or Ruconest) are considered medically necessary when the following are met:

I. Berinert or Cinryze. Patient meets **ONE** of the following (1, 2, or 3):

FDA-Approved Indications

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1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis.** Approve Berinert or Cinryze for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial therapy. Approve if the patient meets BOTH of the following (i and ii):
     - **i.** Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels **at baseline**, as defined by the laboratory reference values **[documentation required]**; AND
     - **ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders; OR
   - **B)** Patient is currently receiving Berinert or Cinryze prophylaxis. Approve if the patient meets ALL of the following (i, ii, and iii):
     Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Berinert or Cinryze for this indication through the Coverage Review Department, review under criteria for Initial Therapy.
     - **i.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
     - **ii.** According to the prescriber, the patient has had a favorable clinical response since initiating Berinert or Cinryze prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND
       Note: Examples of a favorable clinical response include decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks.
     - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

Dosing. Approve **ONE** of the following dosing regimens (A or B):
- **A)** Patient is ≥ 12 years of age: Approve up to a maximum dose of 2,500 units (not exceeding 100 units/kg), administered intravenously no more frequently than twice weekly with doses separated by at least 3 days; OR
- **B)** Patient is < 12 years of age: Approve up to a maximum dose of 1,000 units, administered intravenously no more frequently than twice weekly with doses separated by at least 3 days.

2. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks.** Approve Berinert or Cinryze for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial therapy. Approve if the patient meets ALL of the following (i, ii, and iii):
     - **i.** Patient has HAE type I or type II as confirmed by following (a and b):
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND
     - **ii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.
     - **iii.** Preferred product criteria is met for the product(s) as listed in the below table [for Berinert ONLY]; OR
   - **B)** Patient who has treated previous acute HAE attacks with Berinert or Cinryze. Approve if the patient meets ALL of the following (i, ii, and iii):
     Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Berinert or Cinryze for this indication through the Coverage Review Department, review under criteria for Initial Therapy.
     - **i.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
     - **ii.** According to the prescriber, the patient has had a favorable clinical response with Berinert or Cinryze treatment; AND
       Note: Examples of a favorable clinical response include decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity.
     - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

Dosing. Approve 20 IU/kg, administered intravenously no more frequently than once daily.

Other Uses with Supportive Evidence

3. **Hereditary Angioedema (HAE) With Normal C1 Inhibitor (C1-INH) – Treatment of Acute Attacks**.
   Note: This is also known as HAE type III.
   Approve Berinert or Cinryze for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial Therapy. Approve if the patient meets ALL of the following (i, ii, iii, and iv):
     - **i.** Patient meets BOTH of the following (a and b):
       - **a)** Patient has normal levels of C1-INH (protein level and/or functional activity), as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has normal serum C4 levels, as defined by the laboratory reference values **[documentation required]**; AND
     - **ii.** According to the prescriber, the recurrent angioedema attacks are not responsive to high-dose oral H_1 antihistamine therapy; AND
       Note: High dose oral H_1 antihistamine therapy is the highest dose tolerated by the patient and can be up to four times the FDA-approved dose.

iii. Patient meets ONE of the following (a or b):
- **a)** Patient has a confirmed pathogenic variant in ONE of the following: factor XII (*F12*), plasminogen (*PLG*), angiopoietin-1 (*ANGPT1*), kininogen-1 (*KNG1*), myoferlin (*MYOF*), and heparan sulfate glucosamine 3-*O*-sulfotransferase-6 (*HS3OST6)* **[documentation required]**; OR
- **b)** Patient meets BOTH of the following (1 and 2):
  (1)A pathogenic variant has not been identified [**documentation required]**; AND
  (2) Patient meets ONE of the following (a or b):
  - **a.** Patient has a known family history of HAE with normal C1 inhibitor; OR
  - **b.** Patient has a family history of recurrent angioedema without hives; AND

iv. The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders; OR

B) Patient has treated previous acute HAE attacks with Berinert or Cinryze. Approve if the patient meets ALL of the following (i, ii, and iii):
Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Berinert or Cinryze for this indication through the Coverage Review Department, review under criteria for Initial Therapy.

i. Patient has a diagnosis of HAE with normal C1-INH **[documentation required]**; AND

ii. According to the prescriber, the patient has had a favorable clinical response with Berinert or Cinryze treatment; AND
Note: Examples of a favorable clinical response include decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity.

iii. The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

Dosing. Approve 20 IU/kg, administered intravenously no more frequently than once daily.

Employer Plans and Individual and Family Plans:

Product	Criteria
Berinert	**1. Hereditary Angioedema Due to C1 Inhibitor Deficiency (Type I or II), Treatment of Acute Attacks.** **A)** Patient meets BOTH of the following (i and ii): **i.** Patient meets the above prior authorization criteria for Berinert; AND **ii.** Patient meets ONE of the following (a, b, c, or d): **a)** Patient has tried the Preferred Product, Ruconest **[documentation required]**; OR **b)** According to the prescriber, the patient has had a history of at least one laryngeal attack; OR **c)** Patient has an allergy to rabbits or rabbit-derived products; OR **d)** Patient is less than 13 years of age. **2. Other Conditions.** Approve if the patient meets the above prior authorization criteria for Berinert.

II. Ruconest. Patient meets the following:

FDA-Approved Indication

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1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Treatment of Acute Attacks.** Approve Ruconest for 1 year if the patient meets ONE of the following (A or B):
   - **A)** Initial therapy. Approve if the patient meets BOTH of the following (i and ii):
     - **i.** Patient has HAE type I or type II as confirmed by the following (a and b):
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
       - **a)** Patient has low levels of functional C1-INH protein (< 50% of normal) at baseline, as defined by the laboratory reference values **[documentation required]**; AND
       - **b)** Patient has lower than normal serum C4 levels at baseline, as defined by the laboratory reference values **[documentation required]**; AND
     - **ii.** The medication is prescribed by, or in consultation with, an allergist/immunologist
   - **B)** Patient who has treated previous acute HAE attacks with Ruconest. Approve if the patient meets ALL of the following (i, ii, and iii):
     Note: If the patient is currently receiving the requested therapy, but has not previously received approval of Ruconest for this indication through the Coverage Review Department, review under criteria for Initial Therapy.
     - **i.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
       Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement.
     - **ii.** According to the prescriber, the patient has had a favorable clinical response with Ruconest treatment; AND
       Note: Examples of a favorable clinical response include decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, or decrease in HAE acute attack frequency or severity.
     - **iii.** The medication is prescribed by or in consultation with an allergist/immunologist or a physician who specializes in the treatment of HAE or related disorders.

Dosing. Approve up to a maximum dose of 4,200 units (not exceeding 50 units/kg), administered intravenously no more frequently than twice daily.

Conditions Not Covered

Intravenous C1 Esterase Inhibitors (Berinert, Cinryze, or Ruconest) for any other use are considered not medically necessary, including the following (this list may not be all inclusive; criteria will be updated as new published data are available):

1. **Hereditary Angioedema (HAE) Prophylaxis (Ruconest ONLY).** Ruconest is not FDA-approved for prophylaxis of HAE attacks. A small (n = 32) Phase II, randomized, double-blind, placebo-controlled trial in adults and adolescents ≥ 13 years of age showed efficacy of Ruconest over placebo for reducing mean monthly rate of HAE attacks ($P < 0.0001$).[8] At this time, evidence is not sufficient to support Ruconest use for HAE prophylaxis.
   Note: This Condition Not Covered does not apply to Berinert or Cinryze.

Coding Information

Note: 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

HCPCS Codes	Description
J0596	Injection, C1 esterase inhibitor (recombinant), Ruconest, 10 units
J0597	Injection, C1 esterase inhibitor (human), Berinert, 10 units
J0598	Injection, C1 esterase inhibitor (human), Cinryze, 10 units

References

1. Berinert® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; September 2021.
2. Cinryze® intravenous infusion [prescribing information]. Lexington, MA: Takeda; January 2021.
3. Ruconest® intravenous infusion [prescribing information]. Warren, NJ: Pharming; April 2020.
4. Zuraw BL. Hereditary angioedema. *N Engl J Med*. 2008;359:1027-1036.
5. Craig T, Shapiro R, Vegh A, et al. Efficacy and safety of an intravenous C1-inhibitor concentrate for long-term prophylaxis in hereditary angioedema. *Allergy Rhinol (Providence)*. 2017;8(1):13-19.
6. 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(1):132-150.e3.
7. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema: the 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.
8. Riedl MA, Grivcheva-Panovska V, Moldovan D, et al. Recombinant human C1 esterase inhibitor for prophylaxis of hereditary angio-oedema: a phase 2, multicentre, randomised, double-blind, placebo-controlled crossover trial. *Lancet.* 2017;390:1595-1602.
9. Zuraw BL, Bork K, Bouillet L, et al. Hereditary angioedema with normal C1 inhibitor: an updated international consensus paper on diagnosis, pathophysiology, and treatment. *Clin Rev Allergy Immunol.* 2025;68:24.
10. Riedl MA, Staubach P, Farkas H, et al. Lanadelumab for prevention of attacks of non-histaminergic normal C1 inhibitor angioedema: results from the randomized, double-blind CASPIAN study and CASPIAN open-label extension. *Front. Immunol*. 2025 May 21;16:1502325.

Revision Details

Type of Revision	Summary of Changes	Date
Annual Revision	No criteria changes.	01/15/2025
Annual Revision	**Policy Title.** **Updated** from "Hereditary Angioedema – C1 Esterase Inhibitors (IV)" **to** "Hereditary Angioedema – C1 Esterase Inhibitors (Intravenous)"	01/01/2026

	Updated documentation requirements throughout the policy where required. **Updated** preferred product requirements for Employer Plans and Individual and Family Plans. **Conditions Not Covered** **Removed** C1-Inhibitor normal (levels and function) episodes of angioedema not related to a documented pathogenic variant in the *F12, ANGPT1, PLG,* or *KNG1* gene. **<u>For Berinert and Cinryze</u>** **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency – Prophylaxis.** **Added** "Due to C1 Inhibitor (C1-INH) Deficiency" to indication name **Added** "Patient has HAE type I or type II as confirmed by the following diagnostic criteria and **added** "Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement." **Removed** "Confirmed pathogenic variant in the *SERPING1, F12, ANGPT1*, *PLG* or *KNG1* gene" **Removed** "Berinert or Cinryze will not be concomitantly administered with other FDA approved prophylactic treatments for HAE (for example Haegarda, Takhzyro, or Orladeyo)" **Added** "a physician who specializes in the treatment of HAE or related disorders" to specialist requirement. **Added** criteria for "<u>Patient is currently receiving Berinert or Cinryze prophylaxis"</u> **<u>Berinert and Cinryze</u> Hereditary Angioedema (HAE) With Normal C1 Inhibitor (C1-INH) – Treatment of Acute Attacks**. Added new approval condition and requirements under "Other Uses with Supportive Evidence". **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency - Treatment of Acute Attacks** **Added** "Due to C1 Inhibitor (C1-INH) Deficiency" to indication name **Added** "Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b): Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement."	

	Removed "Confirmed pathogenic variant in the *SERPING1, F12, ANGPT1*, *PLG* or *KNG1* gene" **Removed** "Berinert or Cinryze will not be concomitantly administered with other FDA-approved treatments for acute HAE attacks (for example Firazyr, icatibant, Kalbitor, Ruconest, or Sajazir)" **Added** "a physician who specializes in the treatment of HAE or related disorders" to specialist requirement. **Added** criteria for "Patient who has treated previous acute HAE attacks with Berinert or Cinryze" **For Ruconest** **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency - Treatment of Acute Attacks** **Added** "Due to C1 Inhibitor (C1-INH) Deficiency" to indication name **Added** "Patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b): Note: A diagnosis of HAE with normal C1-INH (also known as HAE type III) does NOT satisfy this requirement." **Removed** "Confirmed pathogenic variant in the *SERPING1, F12, ANGPT1*, *PLG* or *KNG1* gene" **Removed** "Ruconest will not be concomitantly administered with other FDA-approved treatments for acute HAE attacks (for example, Berinert, Cinryze, Firazyr, icatibant, Kalbitor, or Sajazir)" **Added** "a physician who specializes in the treatment of HAE or related disorders" to specialist requirement. **Added** criteria for "Patient who has treated previous acute HAE attacks with Ruconest"	

The policy effective date is in force until updated or retired.