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Coverage Policy Number IP0315

Hereditary Angioedema – C1 Esterase Inhibitors (IV)

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Related Coverage Resources

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. 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

This policy supports medical necessity review for the following intravenous (IV) C1 Esterase Inhibitors:

- **Berinert®** (C1 esterase inhibitor [human] intravenous infusion)
- **Cinryze®** (C1 esterase inhibitor [human] intravenous infusion)
- **Ruconest®** (C1 esterase inhibitor [recombinant] intravenous infusion)

Additional criteria that support the review for medical necessity exceptions of non-covered products are located in the Non-Covered Product Table by the respective plan type and drug list where applicable.

Receipt of sample product does not satisfy any criteria requirements for coverage.

Medical Necessity Criteria

Intravenous (IV) C1 Esterase Inhibitors are considered medically necessary when the following are met:

I. Berinert or Cinryze. Individual meets **ONE** of the following**:**

1. **Hereditary Angioedema (HAE) – Prophylaxis.** Individual meets **ALL** of the following criteria:
   A. Diagnosis of HAE confirmed by documentation of **ONE** of the following:
      i. Confirmed pathogenic variant in the *SERPING1*, *F12*, *ANGPT1*, *PLG* or *KNG1* gene.
      ii. One C4 level below the lower limit of normal as defined by the laboratory performing the test and **ONE** of the following:
         1. Has low levels of functional C1-INH protein (less than 50% of normal) at baseline, as documented by laboratory reference values
         2. Has low C1-INH antigenic levels (less than 50% of normal) at baseline, as documented by laboratory reference values
   B. Berinert or Cinryze will not be concomitantly administered with other FDA-approved prophylactic treatments for HAE (for example Haegarda®, Takhzyro®, or Orladeyo®)
   C. Medication is prescribed by, or in consultation with, an allergist/immunologist

   Dosing. ONE of the following dosing regimens:
   1. 12 years of age and older: The dose is 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
   2. Less than 12 years of age: The dose is 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) – Treatment of Acute Attacks. Individual meets ALL of the following criteria:**
   A. Diagnosis of HAE confirmed by documentation of **ONE** of the following:
      i. Confirmed pathogenic variant in the *SERPING1*, *F12*, *ANGPT1*, *PLG* or *KNG1* gene.
      ii. One C4 level below the lower limit of normal as defined by the laboratory performing the test and **ONE** of the following:
         1. Has low levels of functional C1-INH protein (less than 50% of normal) at baseline, as documented by laboratory reference values
         2. Has low C1-INH antigenic levels (less than 50% of normal) at baseline, as documented by laboratory reference values
   B. Berinert or Cinryze will not be concomitantly administered with other FDA-approved prophylactic treatments for HAE (for example Firazyr®, icatibant, Kalbitor®, Ruconest, or Sajazir™)
   C. Medication is prescribed by, or in consultation with, an allergist/immunologist
   D. Non-Covered Product Criteria is met, refer to below table(s)

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

II. Ruconest.

1. **Hereditary Angioedema (HAE) – Treatment of Acute Attacks.** Individual meets **ALL** of the following criteria:
   A. Diagnosis of HAE confirmed by documentation of **ONE** of the following:
      i. Confirmed pathogenic variant in the *SERPING1*, *F12*, *ANGPT1*, *PLG* or *KNG1* gene.
      ii. One C4 level below the lower limit of normal as defined by the laboratory performing the test and **ONE** of the following:
         1. Has low levels of functional C1-INH protein (less than 50% of normal) at baseline, as documented by laboratory reference values

2. Has low C1-INH antigenic levels (less than 50% of normal) at baseline, as documented by laboratory reference values

B. Ruconest will not be concomitantly administered with other FDA-approved prophylactic treatments for HAE (for example, Berinert, Cinryze, Firazyr®, icatibant, Kalbitor®, or Sajazir™)
C. Medication is prescribed by, or in consultation with, an allergist/immunologist
D. Non-Covered Product Criteria is met, refer to below table(s)

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

Employer Group Non-Covered Products and Criteria:

Non-Covered Product	Criteria
Berinert (C1 esterase inhibitor [human] intravenous infusion)	**ONE** of the following: 1. Less than age 18 years 2. Individual is currently receiving Berinert 3. Documentation of failure, contraindication or intolerance to icatibant (Sajazir)
Cinryze (C1 esterase inhibitor [human] intravenous infusion)	**ONE** of the following: 1. Less than age 18 years 2. Individual is currently receiving Cinryze 3. Documentation of failure, contraindication or intolerance to icatibant (Sajazir)
Ruconest (C1 esterase inhibitor [recombinant] intravenous infusion)	**ONE** of the following: 1. Less than age 18 years 2. Individual is currently receiving Ruconest 3. Documentation of failure, contraindication or intolerance to icatibant (Sajazir)

Individual and Family Plan Non-Covered Products and Criteria:

Non-Covered Product	Criteria
Berinert (C1 esterase inhibitor [human] intravenous infusion)	**ONE** of the following: 1. Less than age 18 years 2. Individual is currently receiving Berinert 3. Documentation of failure, contraindication or intolerance to icatibant (Sajazir)
Cinryze (C1 esterase inhibitor [human] intravenous infusion)	**ONE** of the following: 1. Less than age 18 years 2. Individual is currently receiving Cinryze 3. Documentation of failure, contraindication or intolerance to icatibant (Sajazir)
Ruconest (C1 esterase inhibitor [recombinant] intravenous infusion)	**ONE of the following:** 1. Less than age 18 years 2. Individual is currently receiving Ruconest 3. Documentation of failure, contraindication or intolerance to icatibant (Sajazir)

When coverage is available and medically necessary, the dosage, frequency, duration of therapy, and site of care should be reasonable, clinically appropriate, and supported by evidence-based literature and adjusted based upon severity, alternative available treatments, and previous response to therapy.

Reauthorization Criteria

I. Berinert or Cinryze.
Continuation of Berinert or Cinryze is considered medically necessary for continued use when **ONE** of the following is met:

1. **Hereditary Angioedema (HAE) – Prophylaxis.** Individual meets **ALL** of the following criteria:
   A. The above medical necessity criteria have been met prior to the start of Berinert or Cinryze therapy
   B. There is documentation of beneficial response since initiating Berinert or Cinryze prophylactic therapy compared with baseline (for example, decrease in HAE acute attack frequency, decrease in HAE attack severity, or decrease in duration of HAE attacks)
   C. Medication continues to be prescribed by, or in consultation with, an allergist/immunologist

2. **Hereditary Angioedema (HAE) – Treatment of Acute Attacks.** Individual meets **ALL** of the following criteria:
   A. The above medical necessity criteria have been met prior to the start of Berinert or Cinryze therapy
   B. There is documentation of beneficial response since initiating Berinert or Cinryze therapy (for example, 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.)
   C. Medication continues to be prescribed by, or in consultation with, an allergist/immunologist

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II. Ruconest.
Continuation of Ruconest is considered medically necessary for the treatment of acute hereditary angioedema attacks when **ALL** of the following are met:

1. The above medical necessity criteria have been met prior to the start of Ruconest therapy
2. There is documentation of beneficial response since initiating Ruconest therapy (for example, 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.)
3. Medication continues to be prescribed by, or in consultation with, an allergist/immunologist

Authorization Duration

Initial approval duration: up to 12 months
Reauthorization approval duration: up to 12 months

Conditions Not Covered

Any other use is considered experimental, investigational or unproven, including the following (this list may not be all inclusive):

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 Recommended for Approval does not apply to Berinert or Cinryze.

2. **C1-Inhibitor normal (levels and function) episodes of angioedema not related to a documented pathogenic variant mutation in the *F12*, *ANGPT1*, *PLG*, or *KNG1* gene.**

Coding Information

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

Background

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).

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.

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.

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.