

UTILIZATION MANAGEMENT MEDICAL POLICY

POLICY: Hereditary Angioedema – C1 Esterase Inhibitors (Intravenous) Utilization Management Medical Policy

- 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)

REVIEW DATE: 08/25/2021; selected revision 06/01/2022

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 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 International/Canadian HAE guideline (2019) and the World Allergy Organization and European Academy of Allergy and Clinical Immunology updated guidelines (2017) have similar recommendations.^{7,8}

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). The International/Canadian HAE Guideline (2019) notes that plasma-derived C1-INH and Takhzyro are effective therapies for long-term prophylaxis in patients with HAE I/II (high level of evidence, strong recommendation).⁷

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 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.

POLICY STATEMENT

Prior Authorization is recommended for medical 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.

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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Berinert or Cinryze is recommended in those who meet one of the following criteria:

FDA-Approved Indications

-
1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis.** Approve Berinert or Cinryze for the duration noted if the patient meets one of the following criteria (A or B):
 - A) **Initial therapy.** Approve for 1 year if the patient meets both of the following criteria (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.
 - B) **Patient is currently receiving Berinert or Cinryze prophylaxis.** Approve for 1 year if the patient meets all of the following criteria (i, ii, and iii):
 - i. Patient has a diagnosis of HAE type I or 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 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 regimens (A or B):

- A) Patient is \geq 12 years of age: Approve up to a maximum dose of 2,500 units (not exceeding 100 units/kg) intravenously, no more frequently than once every 3 days; OR
- B) Patient is $<$ 12 years of age: Approve up to a maximum dose of 1,000 units intravenously, no more frequently than once every 3 days.

2. Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Treatment of Acute Attacks. Approve Berinert or Cinryze for the duration noted if the patient meets one of the following criteria (A or B):

- A) Initial therapy. Approve for 1 year if the patient meets both of the following criteria (i and ii):

- i. Patient has HAE type I or type II as confirmed by following 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.

- B) Patient who has treated previous acute HAE attacks with Berinert or Cinryze. Approve for 1 year if the patient meets all of the following criteria (i, ii, and iii):

- 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 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 intravenously, no more frequently than once daily.

II. Coverage of Ruconest is recommended in those who meet the following criteria:

FDA-Approved Indication

1. **Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Treatment of Acute Attacks.** Approve Ruconest for the duration noted if the patient meets one of the following criteria (A or B):

A) Initial therapy. Approve for 1 year if the patient meets both of the following criteria (i and ii):

i. Patient has HAE type I or type II as confirmed by following 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.

B) Patient who has treated previous acute HAE attacks with Ruconest. Approve for 1 year if the patient meets all of the following criteria (i, ii, and iii):

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 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) intravenously, no more frequently than twice daily.

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Coverage of Berinert, Cinryze, or Ruconest is not recommended in the following situations:

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 ($P < 0.0001$).⁹ 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. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

REFERENCES

1. Berinert® intravenous infusion [prescribing information]. Kankakee, IL: CSL Behring; March 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 Mar 1;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 Jan;9(1):132-150.e3.
7. Betschel S, Badiou J, Binkley K, et al. The International/Canadian Hereditary Angioedema Guideline [published correction appears in *Allergy Asthma Clin Immunol*. 2020 May 6;16:33]. *Allergy Asthma Clin Immunol*. 2019;15:72.
8. Mauer 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;73(8):1575-1596.
9. 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.

HISTORY

Type of Revision	Summary of Changes	Review Date
Annual Revision	All indications: Examples of response to therapy moved to a note (previously these were listed in criteria).	08/26/2020
Annual Revision	Dosing: In dosing for the Berinert and Cinryze approval condition of “Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis”, the phrase “adults and adolescents ≥ 12 years of age” was revised to “patient is ≥ 12 years of age”. The phrase “pediatric patients 6 to 11 years of age” was revised to “patient is < 12 years of age”.	08/25/2021
Selected Revision	<p><u>Berinert and Cinryze</u> Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Prophylaxis: A Note was added to the initial and continuation criteria that a diagnosis of HAE with normal C1-INH (also known as HAE type III) does not satisfy the requirement for a diagnosis of HAE type I or type II.</p> <p>Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Treatment of Acute Attacks: A Note was added to the initial and continuation criteria that a diagnosis of HAE with normal C1-INH (also known as HAE type III) does not satisfy the requirement for a diagnosis of HAE type I or type II.</p> <p><u>Ruconest</u> Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Treatment of Acute Attacks: A Note was added to the initial and continuation criteria that a diagnosis of HAE with normal C1-INH (also known as HAE type III) does not satisfy the requirement for a diagnosis of HAE type I or type II.</p>	06/01/2022