**POLICY:** Hereditary Angioedema – C1 Esterase Inhibitors (Intravenous)

- Cinryze® (C1 esterase inhibitor [human] for intravenous [IV] use – Shire/Takeda)
- Berinert® (C1 esterase inhibitor [human] for IV use – CSL Behring)
- Ruconest® (recombinant C1 esterase inhibitor for IV use – Pharming Healthcare, Inc.)

**APPROVAL DATE:** 08/07/2019

## OVERVIEW

Cinryze, Berinert, 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. Cinryze is indicated for routine prophylaxis against angioedema attacks in pediatric, adolescent, and adult patients with HAE.[1] Berinert is indicated for the treatment of acute abdominal, laryngeal, or facial attacks of HAE in adult and pediatric patients.[2] Ruconest is indicated for the treatment of acute HAE attacks in adult 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, guidelines do not differentiate between these products. Plasma-derived C1-INH therapy is supported for both acute treatment and prophylactic therapy.[4,5,8,9] Additionally, use of Cinryze for acute treatment of acute HAE attacks has been reported in literature.[10]

### Disease Overview

HAE due to C1-INH deficiency has two subtypes: HAE type I and HAE type II. HAE diagnosis can be confirmed by measuring functional C1-INH protein levels (usually < 50% of normal in patients with HAE), C4 levels, and C1-INH antigenic levels.[4,5] Patients with HAE type I have low C4 and C1-INH antigenic protein levels, along with low levels of functional C1-INH protein. Patients with HAE type II have low C4 and functional C1-INH protein level, with a normal or elevated C1-INH antigenic protein level. C1-INH replacement therapies are appropriate for both HAE type I and type II.

Patients with the third type of HAE, currently called HAE with normal C1-INH (previously referred to as HAE type III), have normal C4 and C1-INH antigenic protein levels.[4] The exact cause of HAE with normal C1-INH has not been determined. There are no randomized or controlled clinical trial data available with any therapy for use in HAE with normal C1-INH.[6,7] Until data from randomized controlled studies become available, no firm recommendations regarding the treatment of HAE with normal C1-INH can be made.[6]

### Dosing Information for Plasma-Derived C1-INH (Berinert, Cinryze)

Potency of Berinert and Cinryze are both expressed in standard units of C1 inhibitor (equal to the mean C1 inhibitor quantity in 1 mL of normal human plasma). For prophylaxis of HAE attacks, the dosing provided in the policy is taken from Cinryze prescribing information. For treatment of acute HAE attacks, the dosing provided in this policy is taken from Berinert prescribing information. 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.

### Guidelines

Per the World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines (2017), all attacks should be considered for acute treatment; treatment is mandatory for any attack potentially affecting the upper airway.[5] Attacks should be treated as early as possible. Self-administration at home facilitates earlier response. The guidelines recommend C1-INH products (Cinryze, Berinert, or

Ruconest), Kalbitor® (ecallantide injection), or icatibant injection (Firazyr®, generics) as first-line treatment options. Androgens and antifibrinolytics are not effective as acute treatment. Patients should carry acute treatment with them at all times and should have enough supply on hand for treatment of two attacks. Other guidelines from the US Hereditary Angioedema Association Medical Advisory Board (2013) and a practice parameter update from a Joint Task Force (2013) have similar recommendations for acute treatment.[8,9]

C1-INH concentrate is first-line for long-term prophylaxis. Androgens should not be used in pregnant or breastfeeding women, or in children < 16 years of age. In other populations, the use of androgens for long-term prophylaxis may be considered as second-line but should be considered critically due to potential for adverse events. Therefore, the US Hereditary Angioedema Association Medical Advisory Board's position is that anabolic androgens should not be used in patients who have a preference for alternative therapy and that patients should not be required to fail anabolic androgen therapy as a prerequisite to receiving prophylactic C1-INH therapy.[8] Plasma-derived C1-INH therapy has been proven to be effective and safe for long-term prophylactic therapy. Of note, these guidelines have not been updated to include Takhzyro™ (lanadelumab-flyo injection).

## 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 indication(s). 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.

**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.

## RECOMMENDED AUTHORIZATION CRITERIA

**I.** Coverage of Cinryze or Berinert is recommended in those who meet 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.** The patient has HAE type I or type II as confirmed by the following diagnostic criteria (a and b):
       - **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)** Patients 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 is currently receiving Cinryze or Berinert for HAE type I or type II prophylaxis [documentation required to confirm HAE type I or type II diagnosis]; AND

**ii.** According to the prescriber, the patient has had a favorable clinical response (e.g., decrease in number of HAE acute attack frequency, decrease in HAE attack severity, decrease in duration of HAE attacks) since initiating Cinryze or Berinert prophylactic therapy compared with baseline (i.e., prior to initiating prophylactic therapy); AND

**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.**[1] Approve one of the following regimens (A or B):

**A)** In adults and adolescents ≥ 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)** In pediatric patients 6 to 11 years of age, approve up to a maximum dose of 1,000 units intravenously, no more frequently than once every 3 days.

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**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.** The patient has HAE type I or type II as confirmed by following criteria (a and b):

**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)** Patients who have 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.** The patient has treated previous acute HAE type I or type II attacks with Cinryze or Berinert [documentation required to confirm HAE type I or type II diagnosis]; AND

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

**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.**[2] 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 Indications**

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**1. Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Treatment of Acute Attacks.** Approve Ruconest for 1 year 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.** The patient has HAE type I or type II as confirmed by following criteria (a and b):

**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)** Patients who have 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.** The patient has treated previous acute HAE type I or type II attacks with Ruconest [documentation required to confirm HAE type I or type II diagnosis]; AND

**ii.** According to the prescriber, the patient has had a favorable clinical response (e.g., decrease in the duration of HAE attacks, quick onset of symptom relief, complete resolution of symptoms, decrease in HAE acute attack frequency or severity) with Ruconest treatment; AND

**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.**[3] 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

Berinert, Cinryze, or Ruconest have not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval.)

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 ($P < 0.0001$).[11] 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. Cinryze® [prescribing information]. Lexington, MA: Shire/Takeda; June 2018.
2. Berinert® [prescribing information]. Kankakee, IL: CSL Behring LLC; September 2017.
3. Ruconest® [prescribing information]. Bridgewater, NJ: Pharming Healthcare, Inc.; March 2018.
4. Bowen T, Cicardi M, Farkas H, et al. 2010 international consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Ann Allergy Asthma Immunol*. 2010;6:24.
5. 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. Available at: https://onlinelibrary.wiley.com/doi/epdf/10.1111/all.13384. Accessed on August 1, 2019.
6. Zuraw BL, Bork K, Binkley KE, et al. Hereditary angioedema with normal C1 inhibitor function: consensus of an international expert panel. *Allergy Asthma Proc.* 2012;33:S145-S156.
7. Magerl M, Germenis AE, Maas C, et al. Hereditary angioedema with normal C1 inhibitor. Update on evaluation and treatment. *Immunol Allergy Clin N Am.* 2017;37:571-584.
8. Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Angioedema Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. *J Allergy Clin Immunol: In Practice*. 2013;1:458-467. Available at: https://haei.org/wp-content/uploads/2015/04/Zuraw-B-L-US-HAEA-MAB-2013-Recommendations.pdf. Accessed on August 1, 2019.
9. Zuraw BL, Bernstein JA, Lang DM. A focused parameter update: Hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol.* 2013;131(6):1491-1493.e25.
10. Zuraw BL. Hereditary angioedema. *N Engl J Med*. 2008;359:1027-1036.

11. 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 | Approval Date |
|---|---|---|
| New policy | -- | 10/03/2018 |
| Annual revision | **All indications:** "Prescribing physician" changed to "prescriber" throughout criteria. Dosing clarified to reflect maximum approvable dosing.<br><br>**Hereditary Angioedema (HAE) Due to C1 Inhibitor (C1-INH) Deficiency [Type I or Type II] – Treatment of Acute Attacks (Berinert and Cinryze)**: An interval of "no more frequently than once daily" was added to dosing. | 08/07/2019 |