PRIOR AUTHORIZATION POLICY

POLICY: Hereditary Angioedema – C1 Esterase Inhibitors (Intravenous) Prior Authorization Policy
- Berinert® (C1 esterase inhibitor [human] for IV use – CSL Behring)
- Cinryze® (C1 esterase inhibitor [human] for intravenous [IV] use – Shire/Takeda)
- Ruconest® (recombinant C1 esterase inhibitor for IV use – Pharming Healthcare, Inc.)

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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. Berinert is indicated for the treatment of acute abdominal, laryngeal, or facial attacks of HAE in adult and pediatric patients.[2] Cinryze is indicated for routine prophylaxis against angioedema attacks in pediatric, adolescent, and adult patients with HAE.[1] 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 called HAE with normal C1-INH (HAE nC1-INH), previously referred to as HAE type III, have normal C4 and C1-INH antigenic protein levels.[4] HAE nC1-INH is much less prevalent than HAE types I/II, and the exact cause of HAE nC1-INH has not been determined.[4,6] Pathogenic variants in the genes encoding for Factor XII (regulates bradykinin generation), angiopoietin-1 (involved in vascular permeability), and plasminogen have been associated with HAE nC1-INH; however, the majority of cases have unknown etiology. There are no randomized or controlled clinical trial data available with any therapy for use in HAE nC1-INH.[6-8]

Guidelines

Per the World Allergy Organization/European Academy of Allergy and Clinical Immunology guidelines (2017), all HAE type I/II attacks should be considered for acute treatment; treatment is mandatory for any attack potentially affecting the upper airway (HAE nC1-INH is not addressed within the scope of the guideline).[5] Attacks should be treated as early as possible. Self-administration at home facilitates earlier response. The guidelines recommend C1-INH products (Berinert, Cinryze, or Ruconest), Kalbitor® (ecallantide injection), or icatibant injection (Firazyr®, generics) as first-line treatment options. Androgens and anti-fibrinolytics 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), a practice parameter update from

a Joint Task Force (2013), and an international and Canadian guideline (2019) have similar recommendations for acute treatment of HAE type I/II attacks.[6,9,11]

The decision to initiate long-term prophylaxis is individualized based on multiple factors and should be made by the patient and an HAE specialist.[6] C1-INH concentrate and Takhzyro™ (lanadelumab-flyo injection) are recognized as treatment options for long-term prophylaxis of HAE type I/II attacks.[5,6] Androgens are not considered first-line and are contraindicated in certain groups (e.g., pregnancy, prepubescent children, androgen-dependent malignancy).[6] 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, guidelines note that 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 or Takhzyro therapy.[6,9]

POLICY STATEMENT

Prior authorization is recommended for prescription benefit coverage of Berinert, Cinryze, and Ruconest. Because of the specialized skills required for evaluation and diagnosis of patients treated with these products, approval requires Berinert, Cinryze, or Ruconest to be prescribed by or in consultation with a physician who specializes in the condition being treated. 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.

Automation: None.

RECOMMENDED AUTHORIZATION CRITERIA

I. Coverage of Berinert or Cinryze 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.** 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 has a diagnosis of HAE type I or II **[documentation required]**; AND
     - **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.

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):
       - **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.** Patient has a diagnosis of HAE type I or II **[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 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.

II. Coverage of Ruconest 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] – 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):
       - **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.** Patient has a diagnosis of HAE type I or type II **[documentation required]**; AND
     - **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.

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 ($P < 0.0001$).[12] 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

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2. Berinert® [prescribing information]. Kankakee, IL: CSL Behring LLC; April 2019.
3. Ruconest® [prescribing information]. Bridgewater, NJ: Pharming Healthcare, Inc.; December 2019.
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6. 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. Available at: https://aacijournal.biomedcentral.com/articles/10.1186/s13223-019-0376-8. Accessed on August 4, 2020.
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12. 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.