

## c1 esterase inhibitor (human) (Cinryze)

### Commercial Medical Benefit Drug Policy

#### Place of Service

Home Infusion Administration

Infusion Center Administration

Office Administration

Outpatient Facility Infusion Administration

Self-administration (*covered under the Medical Benefit*)

### Drug Details

**USP Category:** IMMUNOLOGICAL AGENTS

**Mechanism of Action:** C1 inhibitor (human) is a sterile, stable, lyophilized preparation of C1 inhibitor derived from human plasma.

#### **HCPCS:**

J0598:Injection, c-1 esterase inhibitor (human), cinryze, 10 units

#### **How Supplied:**

500 units lyophilized powder in an 5 mL vial with 5 mL sterile water (single use)

### Condition(s) listed in policy (*see coverage criteria for details*)

- Hereditary Angioedema (HAE), prophylaxis

Any condition not listed in this policy requires a review to confirm it is medically necessary. For conditions that have not been approved for intended use by the Food and Drug Administration (i.e., off-label use), the criteria outlined in the Health and Safety Code section 1367.21 must be met.

### Special Instructions and Pertinent Information

Provider must submit documentation (such as office chart notes, lab results or other clinical information) to ensure the member has met all medical necessity requirements.

The member's specific benefit may impact drug coverage. Other utilization management processes, and/or legal restrictions may take precedence over the application of this clinical criteria.

For billing purposes, drugs must be submitted with the drug's assigned HCPCS code (as listed in the drug policy) and the corresponding NDC (national drug code). An unlisted, unspecified, or miscellaneous code should not be used if there is a specific code assigned to the drug.

### Coverage Criteria

**The following condition(s) require Prior Authorization/Preservice.**

#### **Hereditary Angioedema (HAE), prophylaxis**

**Meets medical necessity if all the following are met:**

#### Initial

1. Lab documentation shows serum C4 and C1-INH (antigenic and functional) levels consistent with HAE type I or II
2. Either of the following:
  - a. Long term prophylaxis and meets the following:

- i. Patient has a history of frequent or severe attacks (i.e., an HAE attack at least once per month, a history of serious attacks with laryngeal/ upper airway involvement or attacks resulting in impaired daily living)
- ii. Not being used in combination with other HAE preventative therapies (e.g., Andembry, Dawnzera, Haegarda, Orladeyo, Takhzyro)
- b. Short term prophylaxis and being used for pre-procedural prophylaxis (i.e., dental/oral surgeries, intubation, endoscopies, any angioedema attack- inducing events)
- 3. Dose does not exceed the FDA-approved or compendium-supported maximum

#### Reauthorization for long term prophylaxis

1. **Effective 6/1/2026**, will require the following:
  - a. Patient is responding to therapy (e.g., decrease in frequency of attacks, decrease in severity of attacks)
  - b. Not being used in combination with other HAE preventive therapies (e.g., Andembry, Dawnzera, Haegarda, Orladeyo, Takhzyro)
2. Dose does not exceed the FDA-approved or compendium-supported maximum

#### **Covered Doses:**

Long term prophylaxis: Not to exceed 1,000 units given intravenously every 3 to 4 days

Short term prophylaxis: Not to exceed 1000-2000 units given intravenously 1-6 hours prior to procedure for 1 dose

#### **Coverage Period:**

Long term prophylaxis: 1 year

Short term prophylaxis: 1 dose

#### **ICD-10:**

D84.1

### **Additional Information**

HAE Diagnosis:

- Suspicion of HAE-1/2 should prompt laboratory investigations to support a diagnosis
  - Measurements of serum/plasma levels of C1-INH function, C1- INH protein, and C4 are used to diagnose HAE-1/2
  - HAE-1: Both concentration and function of C1-INH are low (<50% of normal).
  - HAE-2:
    - C1-INH concentrations are normal or elevated
    - C1-INH function is low (<50% of normal)
  - C4 levels are usually low in HAE-1/2 patients, but the sensitivity and specificity of C4 as a marker for HAE are limited.
  - Sequencing of the SERPING1 gene can be supportive in the diagnostic workup of some HAE-1/2 patients (including prenatal diagnosis); however, bio-chemical C1-INH testing is effective and less expensive than genetic testing
- HAE with normal C1 inhibitor (HAE-nC1-INH)
  - The different forms of HAE share some clinical features and, possibly, therapeutic options with HAE-1/2

- Can only be diagnosed by genetic testing, which is becoming increasingly available
- Genetic testing should be performed and include testing for the 6 recognized HAE types:
  - HAE with mutation in the factor XII gene (HAE-FXII)
  - HAE with mutation in the angiotensin-converting enzyme 1 gene (HAE-ANGPT1)
  - HAE with mutation in the plasminogen gene (HAE-PLG)
  - HAE with mutation in the kininogen 1 gene (HAE-KNG1)
  - HAE with mutation in the myoferlin gene (HAE-MYOF)
  - HAE with mutation in the heparan sulfate 3-O- sulfotransferase 6 gene (HAE-HS3ST6).
- Additional mutations are likely to be identified in the future and should be included in the genetic diagnostic workup for HAE.

Type of Angioedema	Laboratory Findings		
	C4 Level	Antigenic C1 INH Level	Functional C1 INH Level
HAE – Type I	↓	↓	↓
HAE – Type II	↓	↔ or ↑	↓

**Key:** ↓ - decreased, ↑ - increased, ↔ - normal

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: 1961–1990.

### Plasma-derived C1 inhibitors

- Cinryze and Berinert are both plasma-derived C1 inhibitors
- In the US, Cinryze and Berinert are approved for different indications:
  - Cinryze is FDA-approved for prophylaxis of HAE attacks
  - Berinert is FDA-approved for treatment of acute HAE attacks. Berinert may be self-administered after proper training.
- In Europe, plasma-derived C1 inhibitor products, including Cinryze and Berinert, have been in use for more than 35 years; these agents have been used for treatment of acute attacks and prophylaxis.
- A small, published German clinical study (n=22) studied doses of Berinert ranging from 500u to 1,000u up to twice a week for HAE prophylaxis.

Kreuz W, Martinez-Saguer I, Avgoren-Pursun E, et al. C1-inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. *Transfusion* 2009;49:1987–1995.

### References

1. AHFS. Available by subscription at <http://www.lexi.com>
2. 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*. 2020;S2213–2198(20)30878–3. doi:10.1016/j.jaip.2020.08.046
3. Cinryze (C1 esterase Inhibitor [human]) Prescribing Information. Takeda Pharmaceuticals U.S.A., Lexington, MA: 11/2024.
4. DrugDex. Available by subscription at <http://www.micromedexsolutions.com/home/dispatch>
5. 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: 1961–1990.

6. Zuraw BL, Bernstein JA, Lang DM, et al. A focused parameter update: Hereditary angioedema, acquired C1 inhibitor deficiency, and angiotensin-converting enzyme inhibitor-associated angioedema. *J Allergy Clin Immunol*. 2013 Jun;131(6):1491 - 3. DOI: <https://doi.org/10.1016/j.jaci.2013.03.034>

### Review History

Date of Last Annual Review: 1Q2026

Changes from previous policy version:

- **Effective 6/1/2026**, reauthorization criteria will need to be met for continuation of treatment

*Blue Shield of California Medication Policy to Determine Medical Necessity  
Reviewed by P&T Committee*