blue california
Promise Health Plan

c1 esterase inhibitor (human) (Cinryze)

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 C1inhibitor 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, 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 California Code of Regulations (CCR), Title 22, Section 51303 and 51313 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.

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

Hereditary angioedema, prophylaxis
Meets medical necessity if all the following are met:
1. Chart documentation for the clinical diagnosis of Type I or Type II Hereditary Angioedema (HAE), including serum C4 and C1-INH (antigenic or functional level) that are below the limits of the laboratory's normal reference range, AND
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), AND
ii. Not used in the combination with other HAE therapies for the prophylaxis of HAE attacks (e.g., Haegarda, Orladeyo, Takhzyro), OR

b. Short term prophylaxis and being used for pre-procedural prophylaxis (i.e., dental/oral surgeries, intubation, endoscopies, any angioedema attack- inducing events)

Covered Doses:
Long term prophylaxis: Up to 1,000 units given intravenously every 3 to 4 days
Short term prophylaxis: 1000-2000 units given intravenously 1-6 hours prior to procedure

Coverage Period:
Long term prophylaxis: Indefinitely
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 angiopoietin-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).

o 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

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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: 2/2023.
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: 1Q2025
Changes from previous policy version:

- No clinical change to policy following annual review.

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