C1 Inhibitor (Cinryze®)	Place of Service Office Administration Home Infusion Administration Infusion Center Administration Self-Administration *(covered under Medical Benefit)* Outpatient Facility Administration* [*Prior authorization required – see section (1)] HCPCS: J0598 per 10 units

Conditions listed in policy *(see criteria for details)*:

- Hereditary angioedema (HAE), prophylaxis

AHFS therapeutic class: Blood product derivative

Mechanism of action: C1 inhibitor (human) is a sterile, stable, lyophilized preparation of C1inhibitor derived from human plasma. C1 inhibitor therapy in patients with C1 deficiency is believed to suppress contact system activation via inactivation of plasma kallikrein and factor XIIa, preventing bradykinin angioedema.

(1) Special Instructions and Pertinent Information

Covered under the medical benefit, please submit clinical information for prior authorization review via fax.

**CRITERIA FOR HOSPITAL OUTPATIENT FACILITY ADMINISTRATION **

AAAAI Guidelines 2011, MCG™ Care Guidelines, 19th edition, 2015

Members with the following plans: **PPO, Direct Contract HMO, and when applicable, Medi-Cal, ASO/Shared Advantage, HMO (non-direct contract),** may be required to have their medication administered at a preferred site of service, including the home, a physician's office, or an independent infusion center not associated with a hospital.

For members that cannot receive infusions in the preferred home or ambulatory setting AND meet one of the following criteria points, drug administration may be performed at a hospital outpatient facility infusion center.

ADMINISTRATION OF CINRYZE IN THE HOSPITAL OUTPATIENT FACILITY SITE OF CARE REQUIRES ONE OF THE FOLLOWING: (*Supporting Documentation must be submitted)*

1. **Patient is receiving their first infusion of Cinryze® or is being re-initiated on Cinryze® after at least 6 months off therapy.** *Subsequent doses will require medical necessity for continued use in the hospital outpatient facility site of care.*

Or

Additional clinical monitoring is required during administration as evidenced by one of the following:

2. **Patient has experienced a previous severe adverse event on Cinryze® based on documentation submitted.**

3. **Patient continues to experience moderate to severe adverse events on Cinryze® based on documentation submitted, despite receiving premedication such as acetaminophen, steroids, diphenhydramine, fluids, etc.**

4. **Patient is clinically unstable based on documentation submitted.**

5. **Patient is physically or cognitively unstable based on documentation submitted.**

(2) Prior Authorization/Medical Review is required for the following condition(s)

All requests for C1 inhibitor for conditions NOT LISTED in section 3 must be sent for clinical review and receive authorization prior to drug administration or claim payment.

Hereditary angioedema (HAE), prophylaxis

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 meets the following:
        i. Being used for pre-procedural prophylaxis (i.e., dental/oral surgeries, intubation, endoscopies, any angioedema attack- inducing events)

Covered Doses and Coverage Period

Long term prophylaxis: Up to 1,000 units infused every 3 to 4 days indefinitely
Short term prophylaxis: 1000-2000 units given 1-6 hours prior to procedure for 1 dose

ICD-10:

D84.1

(3) The following condition(s) DO NOT require Prior Authorization/Preservice

All requests for C1 inhibitor must be sent for clinical review and receive authorization prior to drug administration or claim payment.

(4) This Medication is NOT medically necessary for the following condition(s)

Coverage for a Non-FDA approved indication, requires that criteria outlined in Health and Safety Code § 1367.21, including objective evidence of efficacy and safety are met for the proposed indication.

Please refer to the Provider Manual and User Guide for more information.

(5) Additional Information

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

HAE Diagnosis[1]:

- 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).
    - 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 1	↓	↓	↓
HAE – Type 2	↓	↔ or ↑	↓

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

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.[2]

(6) References

- AHFS®. Available by subscription at http://www.lexi.com
- 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
- Cinryze® (C1 esterase Inhibitor [human]) [Prescribing information]. Lexington, MA: Takeda Pharmaceuticals U.S.A.; 1/2021.
- DrugDex®. Available by subscription at http://www.micromedexsolutions.com/home/dispatch
- 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.
- 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

1. 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.
2. 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.

(7) Policy Update

Date of last review: 1Q2023
Date of next review: 1Q2024
Changes from previous policy version:

- No clinical change to policy following routine annual review.

BSC Drug Coverage Criteria to Determine Medical Necessity
Reviewed by P&T Committee