(C1 Inhibitor (Cinryze®, Berinert®)	**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)] **Berinert HCPCS**: **J0597** per 10 units **Cinryze HCPCS**: **J0598** per 10 units

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

- Hereditary angioedema (HAE), prophylaxis
- Hereditary angioedema (HAE), treatment

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, 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 <u>continues to experience moderate to severe adverse events</u> 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.

<u>Hereditary angioedema (HAE), prophylaxis</u>

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. 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**
3. Not used in the combination with other HAE therapies for the prophylaxis of HAE attacks (e.g. Haegarda, Orladeyo, Takhzyro)

Covered Doses
Up to 1,000 units infused every 3 to 4 days

Coverage Period
Indefinite

ICD-10:
D84.1

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

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.

<u>Hereditary angioedema (HAE), treatment</u>

- Being used to treat acute attacks

Covered Doses
Up to 20 units/kg infusion per attack

Coverage Period
Cover once per attack

ICD-10:
D84.1

(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
Berinert: 500 units lyophilized concentrate in a single-use vial for reconstitution with 10 mL of diluent (sterile water)

HAE Diagnosis: [1,2]

- HAE is an inherited autosomal disorder.
- ≥ 75% of patients with HAE report a family history of attacks.
  - A diagnosis of HAE (C1 INH deficiency) is suggested by a history of recurrent attacks of angioedema and abdominal pain. Swelling may affect the extremities, face, upper respiratory tract and gastrointestinal tract.
  - Typically swelling develops gradually over hours, increasing slowly for 12 – 36 hours and subsiding after 2 – 5 days. Urticaria is not a feature of HAE.
  - The onset of HAE attacks is in childhood or young adulthood and worsens around the time of puberty.
  - Attacks do not respond to antihistamines or corticosteroids.
  - Laboratory complement tests are used to confirm the diagnosis of HAE.
  - Virtually all patients with hereditary angioedema have a persistently low antigenic C4 level with normal antigenic C1 and C3 levels.
  - Measurement of C4 levels can rule out hereditary angioedema, although in rare cases, the C4 level is normal between attacks. Subsequent measurement of antigenic and functional C1-inhibitor levels confirms the diagnosis of hereditary angioedema and distinguishes between type I (low antigenic and functional C1-inhibitor levels) and type II (normal antigenic C1-inhibitor level but low functional C1-inhibitor activity).
  - In rare cases, patients with inherited angioedema have normal functional C1-inhibitor levels; some but not all of these patients are found to have a factor XII mutation.

Table 2. Diagnostic criteria for HAE [1,2]

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

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.[3]

(6) References

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(7) Policy Update

Date of last review: 1Q2021
Date of next review: 1Q2022
Changes from previous policy version:

- Section (2): Hereditary angioedema (HAE), prophylaxis - Expanded authorization period to indefinite duration and removed reauthorization requirement for continued response to therapy.
  Rationale: Low potential for inappropriate use