

## Clinical Policy: C1 Esterase Inhibitors

Reference Number: ERX.SPA.28

Effective Date: 07.01.16

Last Review Date: 02.19

[Revision Log](#)

See **Important Reminder** at the end of this policy for important regulatory and legal information.

### Description

The following are C1 esterase inhibitors requiring prior authorization: human C1 esterase inhibitor (Berinert<sup>®</sup>, Cinryze<sup>®</sup>, Haegarda<sup>®</sup>) and recombinant C1 esterase inhibitor (Ruconest<sup>®</sup>).

### FDA Approved Indication(s)

C1 esterase inhibitors are indicated:

- For the treatment of acute attacks of hereditary angioedema (HAE) in adolescent and adult patients [Berinert and Ruconest only]
- For the routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE [Cinryze and Haegarda only]

Limitation(s) of use:

- The safety and efficacy of Berinert for prophylactic therapy have not been established.
- Effectiveness of Ruconest was not established in HAE patients with laryngeal attacks.

### Policy/Criteria

*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

*Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.*

It is the policy of health plans affiliated with Envolve Pharmacy Solutions<sup>™</sup> that Berinert, Cinryze, Haegarda, and Ruconest are **medically necessary** when the following criteria are met:

#### I. Initial Approval Criteria

##### A. Hereditary Angioedema (must meet all):

1. Diagnosis of HAE confirmed by one of the following (a or b):
  - a. Low C4 level and low C1-INH antigenic or functional level (*see Appendix D*);
  - b. Normal C4 level and normal C1-INH levels, and both of the following (i and ii):
    - i. History of recurrent angioedema;
    - ii. Family history of angioedema;
2. Prescribed by or in consultation with a/an hematologist, allergist, or immunologist;
3. Member meets one of the following (a, b, c, or d):
  - a. Age ≥ 5 years for Berinert;
  - b. Age ≥ 6 years for Cinryze;
  - c. Age ≥ 12 years for Haegarda;
  - d. Age ≥ 13 years for Ruconest;
4. Member meets one of the following (a, b, or c):
  - a. For treatment of acute HAE attacks, meets one of the following (i or ii):
    - i. Request is for Berinert;
    - ii. Request is for Ruconest and member does not experience laryngeal attacks;
  - b. For long-term prophylaxis of HAE attacks, meets all of the following (i and ii):
    - i. Request is for Cinryze or Haegarda;
    - ii. Member experiences more than one severe event per month OR is disabled more than five days per month OR has a history of previous airway compromise;
  - c. For short-term prophylaxis of HAE attacks, meets both of the following (i and ii):

- i. Request is for a plasma-derived C1 esterase inhibitor (i.e., Ruconest, Cinryze, or Haegarda);
  - ii. Member requires major dental work or surgical procedure;
5. Member is not using the requested product in combination with another FDA-approved product for the same indication (e.g., using both Berinert and Firazyr® for acute HAE attacks);
6. Dose does not exceed:
  - a. Berinert: 20 IU/kg of body weight per single dose, up to 2 doses administered in a 24-hour period;
  - b. Cinryze: 2,500 units (5 vials) every 3 to 4 days;
  - c. Haegarda: 60 IU/kg of body weight per dose twice weekly;
  - d. Ruconest: 4,200 IU per single dose, up to 2 doses administered in a 24-hour period.

**Approval duration:**

**Short-term prophylaxis: 2 doses per procedure**

**Treatment of acute attacks: 12 months (up to 4 doses per month)**

**Long-term prophylaxis: 12 months**

**B. Other diagnoses/indications**

1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**II. Continued Therapy**

**A. Short Term Prophylaxis of Hereditary Angioedema Attacks**

1. Re-authorization is not permitted. Members must meet the initial approval criteria.

**Approval duration: Not applicable**

**B. All Other Indications in Section I (must meet all):**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy (e.g., if Cinryze or Haegarda is requested, member has demonstrated reduction in attacks from baseline, or request is for a dose increase);
3. Member is not using the requested product in combination with another FDA-approved product for the same indication (e.g., both Berinert and Firazyr for acute HAE attacks);
4. If request is for a dose increase, new dose does not exceed:
  - a. Berinert: 20 IU/kg of body weight per single dose, up to 2 doses administered in a 24-hour period;
  - b. Cinryze: 2,500 units (5 vials) every 3 to 4 days;
  - c. Haegarda: 60 IU/kg of body weight per dose twice weekly;
  - d. Ruconest: 4,200 IU per single dose, up to 2 doses administered in a 24-hour period.

**Approval duration:**

**Treatment of acute attacks: 12 months (up to 4 doses per month)**

**Long-term prophylaxis: 12 months**

**C. Other diagnoses/indications (must meet 1 or 2):**

1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.

**Approval duration: Duration of request or 6 months (whichever is less); or**

2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

**III. Diagnoses/Indications for which coverage is NOT authorized:**

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.**

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

C1-INH: C1 esterase inhibitor  
 FDA: Food and Drug Administration  
 HAE: hereditary angioedema

*Appendix B: Therapeutic Alternatives*

Not applicable

*Appendix C: Contraindications/Boxed Warnings*

- Contraindication(s):
  - Ruconest: known or suspected allergy to rabbits and rabbit derived products
  - Ruconest, Berinert, Cinryze, Haegarda: history of immediate/life-threatening hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations
- Boxed warning(s): none reported

*Appendix D: General Information*

- Diagnosis of HAE:
  - There are two classifications of HAE: HAE with C1-INH deficiency (further broken down into Type 1 and Type II) and HAE of unknown origin (also known as Type III).
  - In both Type 1 (~85% of cases) and Type II (~15% of cases), C4 levels are low. C1-INH antigenic levels are low in Type I while C1-INH functional levels are low in Type II. Diagnosis of Type I and II can be confirmed with laboratory tests. Reference ranges for C4 and C1-INH levels can vary across laboratories (see below for examples); low values confirming diagnosis are those which are below the lower end of normal.

Laboratory Test & Reference Range	Mayo Clinic	Quest Diagnostics	LabCorp
C4	14-40 mg/dL	16-47 mg/dL	9-36 mg/dL
C1-INH, antigenic	19-37 mg/dL	21-39 mg/dL	21-39 mg/dL
C1-INH, functional	Normal: > 67% Equivocal: 41-67% Abnormal: < 41%	Normal: ≥ 68% Equivocal: 41-67% Abnormal: ≤ 40%	Normal: > 67% Equivocal: 41-67% Abnormal: < 41%

- Type III, on the other hand, presents with normal C4 and C1-INH levels. Some patients have an associated mutation in the FXII gene, while others have no identified genetic indicators. Type III is very rare (number of cases unknown), and there are no laboratory tests to confirm the diagnosis. Instead, the diagnosis is clinical and supported by recurrent episodes of angioedema with a strong family history of angioedema.
- HAE attack triggers may include minor trauma (such as dental procedures), oral contraceptives, and ACE inhibitors.
- Bowen T, Cicardi M, Farkas, H., et al. recommend plasma-derived C1 inhibitors for short-term prophylaxis: 10 to 20 units per kg one dose 1 hour before surgery or less than 6 hours before procedures (must be given before endotracheal intubation/manipulations) with a second dose of equal amount available during surgery.

**V. Dosage and Administration**

Drug Name	Indication	Dosing Regimen	Maximum Dose
Human C1 esterase inhibitor (Berinert)	Treatment of acute HAE attacks	20 IU/kg body weight IV	20 IU/kg/dose
Human C1 esterase inhibitor (Haegarda)	Prophylaxis against HAE attacks	60 IU/kg body weight SC twice weekly (every 3 or 4 days)	60 IU/kg/dose
Human C1 esterase inhibitor (Cinryze)	Prophylaxis against HAE attacks	1,000 units IV every 3-4 days	2,500 units (not exceeding 100)

Drug Name	Indication	Dosing Regimen	Maximum Dose
			units/kg) every 3-4 days
Recombinant C1 esterase inhibitor (Ruconest)	Treatment of acute HAE attacks	Weight < 84 kg: 50 units/kg IV Weight ≥ 84 kg: 4,200 units IV  May administer a second dose if symptoms persist.	4,200 units/dose; up to 2 doses within a 24 hour period

## VI. Product Availability

Drug Name	Availability
Human C1 esterase inhibitor (Berinert)	Vial with powder for reconstitution: 500 IU
Human C1 esterase inhibitor (Haegarda)	Vial with powder for reconstitution: 2,000 IU, 3,000 IU
Human C1 esterase inhibitor (Cinryze)	Vial with powder for reconstitution: 500 units
Recombinant C1 esterase inhibitor (Ruconest)	Vial with powder for reconstitution: 2,100 units

## VII. References

1. Berinert Prescribing Information. Marburg, Germany: CSL Behring GmbH; September 2017. Available at: [www.berinert.com](http://www.berinert.com). Accessed October 30, 2018.
2. Cinryze Prescribing Information. Lexington, MA: Shire ViroPharma, Inc.; June 2018. Available at: [www.cinryze.com](http://www.cinryze.com). Accessed October 30, 2018.
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4. Haegarda Prescribing Information. Kankakee, IL: CSL Behring LLC; October 2017. Available at: [www.haegarda.com](http://www.haegarda.com). Accessed October 30, 2018.
5. Bowen T, Cicardi M, Farkas H, et al. Canadian 2003 International Consensus Algorithm For the Diagnosis, Therapy, and Management of Hereditary Angioedema. *J Allergy Clin Immunol*. 2004 Sep;114(3):629-37
6. Cicardi M, Bork K, Caballero T, et al. Evidence-based recommendations for the therapeutic management of angioedema owing to hereditary C1 inhibitor deficiency: consensus report of an International Working Group. *Allergy*. 2012; 67(2): 147-157.
7. Cicardi M, Aberer W, Banerji A, et al. Classification, diagnosis, and approach to treatment for angioedema: consensus report from the Hereditary Angioedema International Working Group. *Allergy*. 2014; 69(5): 602-616.
8. Craig T, Pursun E, Bork K, et al. WAO guideline for the management of hereditary angioedema. *WAO Journal*. 2012; 5: 182-199.
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10. 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; 131(6): 1491-1493.
11. Maurer M, Magerl M, Ansotegui I, et al. The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update. *Allergy*. 2018; 73(8):1575-1596.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created	05.16	06.16
Added criteria to confirm diagnosis. Removed age requirement as it is not an absolute contraindication per PI. Increased approval duration to 12 months for Berinert/Ruconest and incorporated recommended dosing from PI. Added criteria for continued approval.	04.17	05.17

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Removed warnings against hypersensitivity reactions. For Cinryze, modified initial approval duration for long-term prophylaxis to 6 months and for renewal to 12 months. For continued therapy, added max dose criteria.		
1Q18 annual review: Added specialist requirement. Removed “Other types of angioedema have been ruled out” from part of diagnosis due to its subjective nature, while specialist has been added. Removed qualifying descriptions of “abdominal, facial, or laryngeal attacks” for Berinert as there is no evidence that there is lack of efficacy in other forms of HAE. Added short-term prophylaxis criteria for plasma-derived C1 esterase inhibitors according to AOW treatment guidelines. Added trial of danazol for long-term prophylaxis in adults.	11.27.17	02.18
1Q 2019 annual review: added age requirements for all C1 esterase inhibitors; removed trial of danazol for long-term prophylaxis per WHO/EAACI 2017 guidelines; added requirement that member is not using requested product in combination with other approved treatments for the same indication; added quantity limit of 4 doses per month for treatment of acute attacks; added requirement that members requesting continued therapy for short term prophylaxis must meet initial criteria; references reviewed and updated.	10.30.18	02.19

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.

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