Clinical Policy: C1 Esterase Inhibitors (Berinert, Cinryze, Haegarda, Ruconest)

Reference Number: PA.CP.PHAR.202
Effective Date: 01/18
Last Review Date: 01/19

Coding Implications

Revision Log

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

FDA Approved Indication(s)
C1 esterase inhibitors are indicated:

- For the treatment of acute attacks of hereditary angioedema (HAE) in adult and pediatric patients [*Berinert only*]
- For the treatment of acute attacks in adolescent and adult patients with HAE [*Ruconest only*]
- For the routine prophylaxis against angioedema attacks in adults, adolescents and pediatric patients (6 years of age and older) with HAE [*Cinryze only*]
- For the routine prophylaxis to prevent HAE attacks in adolescent and adult patients [*Haegarda only*]

Limitations 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
It is the policy of health plans affiliated with Centene Corporation® that Berinert, Cinryze, Haegarda, and Ruconest are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Hereditary Angioedema (HAE) (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 hematologist, an allergist, or an immunologist;
3. Members 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 (iand 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., 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: 2500 units (5 vials) every 3 to4 days;
c. Haegarda: 60 IU/kg of body weight per dose twice weekly;
d. Ruconest: 4200 IU per single dose, up to 2 doses administered in a 24 hour period.

Approval duration:
Acute attacks & long-term prophylaxis: 12 months
Short-term prophylaxis: 2 doses per procedure

B. Other diagnoses/indications: Refer to PA.CP.PMN.53

II. Continued Approval

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 Pennsylvania Health and Wellness benefit or member has previously met all initial approval criteria or Continuity of Care Policy (PA.LTSS.PHAR.01) applies;
2. Member is responding positively to therapy (e.g., if Cinryze or Haegarda are requested for long-term prophylaxis, member has demonstrated a 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:
e. Berinert: 20 IU/kg of body weight per single dose, up to 2 doses administered in a 24 hour period;

f. Cinryze: 2500 units (5 vials) every 3 to 4 days;
g. Haegarda: 60 IU/kg of body weight per dose twice weekly;
h. Ruconest: 4200 IU per single dose, up to 2 doses administered in a 24-hour period.

Approval duration: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy or Continuity of Care Policy (PA.LTSS.PHAR.01) applies; or
2. Refer to PA.CP.PMN.53

III. 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.

IV. 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	Based on weight
human C1 esterase inhibitor (Haegarda)	Prophylaxis against HAE attacks	60 IU/kg body weight SC twice weekly (every 3 or 4 days)	Based on weight
human C1 esterase inhibitor (Cinryze)	Prophylaxis against HAE attacks	1,000 units IV every 3-4 days	2,500 units (not exceeding 100 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

V. 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, 3000 IU
human C1 esterase inhibitor (Cinryze)	Vial with powder for reconstitution: 500 units

Drug Name	Availability
recombinant C1 esterase inhibitor (Ruconest)	Vial with powder for reconstitution: 2,100 units

Coding Implications
Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J0596	Injection, C-1 esterase inhibitor (recombinant), Ruconest, 10 units
J0597	Injection, C-1 esterase inhibitor (human), Berinert, 10 units
J0598	Injection, C-1 esterase inhibitor (human), Cinryze, 10 units

Reviews, Revisions, and Approvals	Date	Approval Date
Added Haegarda into the policy. 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 for plasma-derived C1 esterase inhibitors according to AOW treatment guidelines. References reviewed and updated.	02/18	
1Q19 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 requirement that members requesting continued therapy for short term prophylaxis must meet initial criteria; references reviewed and updated.	01/19	

References
1. Berinert Prescribing Information. Marburg, Germany: CSL Behring GmbH; September 2017. Available at: www.berinert.com. Accessed October 15, 2018.
2. Cinryze Prescribing Information. Lexington, MA: Shire ViroPharma, Inc.; June 2018. Available at: www.cinryze.com. Accessed October 15, 2018.
3. Ruconest Prescribing Information. Raleigh, NC: Santarus Inc.; March 2018. Available at: www.ruconest.com. Accessed October 15, 2018.
4. Haegarda Prescribing Information. Kankakee, IL: CSL Behring LLC; October 2017. Available at: www.haegarda.com. Accessed October 15, 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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