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

Reference Number: PA.CP.PHAR.202
Effective Date: 01/18
Last Review Date: 07/18

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 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*]

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 B*);
   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 hematologist, allergist, or immunologist;
3. 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, ii, and iii):
      i. Request is for Cinryze or Haegarda;

ii. Patient experiences more than one severe event per month OR is disabled more than five days per month OR the patient has a history of previous airway compromise;
iii. For postpubertal adolescent and adults: failure of a trial of danazol unless contraindicated or clinically significant adverse effects are experienced;

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;

4. Dose does not exceed:
a. Berinert: 20 IU/kg of body weight IV per dose, up to 2 doses administered in a 24 hour period;
b. Cinryze: 2500 units (5 vials) IV every 3-4 days;
c. Haegarda: 60 IU/kg of body weight SC 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. Hereditary Angioedema (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, member has demonstrated reduction in attacks from baseline, or request is for a dose increase);
3. If request is for a dose increase, new dose does not exceed:
e. Berinert: 20 IU/kg of body weight IV per dose, up to 2 doses administered in a 24 hour period;
f. Cinryze: 2500 units (5 vials) IV every 3-4 days;
g. Haegarda: 60 IU/kg of body weight SC per dose twice weekly;
h. Ruconest: 4200 IU per single dose, up to 2 doses administered in a 24 hour period.

Approval duration:
***Berinert or Ruconest* – 12 months (no more than 4 doses per month)**
***Cinryze* – 12 months**

B. 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

Appendices

Appendix A: Abbreviation Key

ACE-I: angiotensin-converting enzyme inhibitor
ARB: angiotensin receptor blocker
CI-INH: C1 esterase inhibitor
HAE: hereditary angioedema
IU: international units

Appendix B: 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.

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	

References

1. Berinert Prescribing Information. Marburg, Germany: CSL Behring GmbH; September 2016. Available at: www.berinert.com. Accessed November 15, 2017.
2. Cinryze Prescribing Information. Lexington, MA: Shire ViroPharma, Inc.; December 2016. Available at: www.cinryze.com. Accessed November 15, 2017.
3. Ruconest Prescribing Information. Raleigh, NC: Santarus Inc.; February 2015. Available at: www.ruconest.com. Accessed November 15, 2017.
4. Haegarda Prescribing Information. Kankakee, IL: CSL Behring LLC; July 2017. Available at: www.haegarda.com. Accessed November 15, 2017.
5. Danocrine Prescribing Information. Bridgewater, NJ: Sanofi-Aventis U.S. LLC.; December 2011. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/017557s033s039s040s041s042lbl.pdf. Accessed November 16, 2017.
6. 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
7. 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.
8. 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.
9. Craig T, Pursun E, Bork K, et al. WAO guideline for the management of hereditary angioedema. WAO Journal. 2012; 5: 182-199.
10. Zuraw BL, Banerji A, Bernstein JA, et al. US Hereditary Association Medical Advisory Board 2013 recommendations for the management of hereditary angioedema due to C1 inhibitor deficiency. J Allergy Clin Immunol. 2013; 1(5): 458-467.

11. 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.