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

Reference Number: PA.CP.PHAR.202
Effective Date: 01/18
Last Review Date: 03/17

Coding Implications
Revision Log

Description
The intent of the criteria is to ensure that patients follow selection elements established by Pennsylvania Health and Wellness® clinical policy for C1 esterase inhibitor (human – Berinert®, Cinryze®; recombinant – Ruconest®).

Policy/Criteria
It is the policy of health plans affiliated with Pennsylvania Health and Wellness that Berinert, Cinryze, and Ruconest are **medically necessary** when one of 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 all of the following (i - iii):
      i. History of recurrent angioedema;
      ii. Family history of angioedema;
      iii. Other types of angioedema have been ruled out (e.g., ACE-I/ARB-associated or other drug-induced angioedema, allergic angioedema, nonhistaminergic angioedema);
2. Member meets one of the following (a, b, or c):
   a. Berinert: prescribed to treat acute abdominal, facial, or laryngeal attacks;
   b. Ruconest: prescribed to treat acute attacks, not including laryngeal attacks;
   c. Cinryze: prescribed to for routine prophylaxis against angioedema attacks of HAE;
3. Prescribed dose does not exceed:
   a. Berinert: 20 IU/kg per single dose, up to 2 doses administered in a 24 hour period;
   b. Ruconest: 4200 IU per single dose, up to 2 doses administered in a 24 hour period;
   c. Cinryze: 1000 units (2 vials) every 3-4 days.

Approval duration:
***Berinert or Ruconest* – 12 months (no more than 4 doses per month)**
***Cinryze* – 6 months**

B. Other diagnoses/indications: Refer to PA.CP.PHAR.57 - Global Biopharm Policy.

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. Documentation of positive response to therapy (if Cinryze is requested, member has demonstrated reduction in attacks from baseline, or request is for a dose increase);
3. Prescribed dose does not exceed:
   a. Berinert: 20 IU/kg per single dose, up to 2 doses administered in a 24 hour period;
   b. Ruconest: 4200 IU per single dose, up to 2 doses administered in a 24 hour period;
   c. Cinryze: 2500 units (5 vials) every 3-4 days.

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.PHAR.57 - Global Biopharm Policy**.**

Background
Description/Mechanism of Action:
Berinert is a human plasma-derived, purified, pasteurized, lyophilized concentrate of C1 esterase inhibitor. Berinert is prepared from large pools of human plasma from US donors.

Ruconest is a recombinant analogue of human complement C1 esterase inhibitor. Ruconest is purified from the milk of transgenic rabbits.

Cinryze is a sterile, stable, lyophilized preparation of C1 esterase inhibitor derived from human plasma.

Increased vascular permeability and the clinical manifestation of HAE attacks may be primarily mediated through contact system activation. Suppression of contact system activation by C1 esterase inhibitor through the inactivation of plasma kallikrein and factor XIIa is thought to modulate this vascular permeability by preventing the generation of bradykinin.

Formulations:
Berinert is supplied as single-use vials containing 500 IU of lyophilized concentrate for reconstitution.
Ruconest is supplied as single-use vials containing 2100 IU of lyophilized powder for reconstitution.
Cinryze is supplied as single-use vials containing 500 units of lyophilized powder for reconstitution.

FDA Approved Indications:
Berinert is a C1 esterase inhibitor (human)/intravenous product indicated for:

- Treatment of acute abdominal, facial, or laryngeal attacks of HAE in adult and adolescent patients.

Limitations of use: The safety and efficacy of Berinert for prophylactic therapy have not been established.

Ruconest is a C1 esterase inhibitor (recombinant)/intravenous product indicated for:

- Treatment of acute attacks in adult and adolescent patients with HAE.

Limitations of use: Effectiveness was not established in HAE patients with laryngeal attacks.

Cinryze is a C1 esterase inhibitor (human)/intravenous product indicated for:

- Routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE.

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

References
1. Berinert Prescribing Information. Marburg, Germany: CSL Behring GmbH; September 2016. Available at: www.berinert.com. Accessed February 8, 2017.
2. Cinryze Prescribing Information. Lexington, MA: Shire ViroPharma, Inc.; December 2016. Available at: www.cinryze.com. Accessed February 8, 2017.
3. Ruconest Prescribing Information. Raleigh, NC: Santarus Inc.; February 2015. Available at: www.ruconest.com. Accessed February 8, 2017.
4. 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.
5. 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.
6. Craig T, Pursun E, Bork K, et al. WAO guideline for the management of hereditary angioedema. WAO Journal. 2012; 5: 182-199.
7. 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.
8. 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.