Clinical Policy Title:	c **esterase Inhibitors**
Policy Number:	RxA.70
Drug(s) Applied:	Berinert®, Cinryze®, Haegarda®, Ruconest®
Original Policy Date:	02/07/2020
Last Review Date:	03/09/2021
Line of Business Policy Applies to:	All lines of business

Background

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

C1 esterase inhibitors are indicated:

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

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.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
human C1 esterase inhibitor (Berinert®)	Treatment of acute HAE attacks	20 IU/kg body weight Intravenous	Based on weight
human C1 esterase inhibitor (Haegarda®)	Prophylaxis against HAE attacks	60 IU/kg body weight Subcutaneous twice weekly (every 3 or 4 days)	Based on weight
human C1 esterase inhibitor (Cinryze®)	Prophylaxis against HAE attacks	Adults and adolescents (12 years old and above): 1,000 units Intravenous every 3-4 days. Pediatrics (6 to 11 years old): 500 units Intravenous every 3-4 days.	2,500 units (notexceeding 100 units/kg) every 3-4 days 1,000 units every 3 to 4 days.

Dosing Information

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

Dosage Forms

- human C1 esterase inhibitor (Berinert®): Vial with powder for reconstitution: 500 IU
- human C1 esterase inhibitor (Haegarda®): Vial with powder for reconstitution: 2000 IU, 3000 IU
- human C1 esterase inhibitor (Cinryze®): Vial (8 mL) with powder for reconstitution: 500 units
- recombinant C1 esterase inhibitor (Ruconest®): Vial with powder for reconstitution: 2100 U

Clinical Policy

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

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. Members meet on of the following (a, b, c, or d):
   a. Age ≥ 5 years for Berinert®;
   b. Age ≥ 6 years for Cinryze® and Haegarda®;
   c. Age ≥ 12 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 all of the following (i and ii):
      i. Request is for plasma-derived C1 esterase inhibitor (i.e., Ruconest®, Cinryze®, or Haegarda®);
      ii. Member requires major dental work or surgical procedure;
5. Member is not concomitantly using the requested product 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 single dose, up to 2 doses administered in a 24-hour period;
d. Ruconest®: 4,200 U 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: Up to 4 doses per month
Commercial: 6 months
Medicaid: 12 months
Long-term prophylaxis:
Commercial: 6 months
Medicaid: 12 months

II. Continued Therapy 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. Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy;
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 concomitantly 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 U per single dose, up to 2 doses administered in a 24-hour period.

Approval Duration
Treatment of acute attacks: Up to 4 doses per month
Medicaid: 12 months
Commercial: 6 months
Long-term prophylaxis
Medicaid: 12 months
Commercial: 6 months

III. Appendices

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 or its excipients.

- 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 andsupported 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.

References

1. Berinert Prescribing Information. Kankakee, IL: CSL Behring LLC; April 2019. Available at: www.berinert.com. Accessed January 20, 2021.
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3. Ruconest Prescribing Information. Raleigh, NC: Santarus Inc.; April 2020. Available at: www.ruconest.com. Accessed January 20, 2021.
4. Haegarda Prescribing Information. Kankakee, IL: CSL Behring LLC; September 2020. Available at: www.haegarda.com. Accessed January 20, 2021.
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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. Accessed January 20, 2021.
8. Craig T, Pursun E, Bork K, et al. WAO guideline for the management of hereditary angioedema. WAO Journal. 2012; 5: 182-199. Accessed January 20, 2021.
9. 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. Accessed January 20, 2021.
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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. Accessed January 20, 2021.

Review/Revision History	Review/Revised Date	P&T Approval Date
Policy established.	01/2020	02/07/2020
1. Updated References 2. Update to Ruconest dosing to IU 3. Update Ruconest dosage form to IU	05/2020	05/21/2020
Policy was reviewed: 1) Background updated added separate line item for Berinert®: "For the treatment of acute abdominal, facial, or laryngeal hereditary angioedema (HAE)…." 2) Under background Cinryze® was updated added "pediatric patients (6 years of age and older)". 3) Indication updated for drug Haegarda® 4) Dosing information was updated: added pediatric	01/20/2021	03/09/2021

dosing criteria for Cinryze®. 5) Dosing information SCand IV abbreviated forms changed to Subcutaneous & Intravenous respectively 6) Initial Therapy Criteria I.A.3.c was removed and clubbed with A.3.b. and age for Ruconest® was updated from age ≥ 13 to age ≥ 12. 7) Continuation therapy criteria II.A.1. rephrased to "Member is currently receiving medication that has been authorized by RxAdvance or the member has met initial approval criteria listed in this policy 8) Initial therapy and continued therapy approval duration updated from Duration of request or 3 months (Whichever is less) to "3 months" 9) Deleted HIM from Approval duration 10) References were updated		