Clinical Policy Title:	c1 esterase Inhibitors
Policy Number:	RxA.070
Drug(s) Applied:	Berinert®, Cinryze®, Haegarda®, Ruconest®
Original Policy Date:	02/07/2020
Last Review Date:	01/17/2023
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 hereditary angioedema (HAE) [Cinryze®].
- For routine prophylaxis to prevent hereditary angioedema (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 International Units per kg body weight intravenously	20 International Units/kg intravenously
human C1 esterase inhibitor (Haegarda®)	Prophylaxis against HAE attacks	60 International Units per kg body weight subcutaneously twice weekly (every 3 or 4 days)	60 International Units/kg subcutaneously twice weekly (no sooner than every 3 days)
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 (not exceeding 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 may administer a second dose if symptoms persist.	4,200 International Units/dose; up to 2 doses within a 24-hour period

Dosage Forms

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

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. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Hereditary Angioedema (must meet all):

1. Diagnosis of HAE confirmed by a history of recurrent angioedema and 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 at least one of the following (i or ii):
      i. Presence of a mutation associated with the disease (see Appendix D);
      ii. Family history of angioedema and documented failure of high-dose antihistamine therapy (i.e., cetirizine 40 mg/day or equivalent) for at least 1 month or an interval expected to be associated with 3 or more attacks of angioedema, whichever is longer;
2. Prescribed by or in consultation with a hematologist, allergist, or immunologist;
3. Members meet on of the following (a, b, or c):
   a. Age ≥ 5 years for Berinert®;
   b. Age ≥ 6 years for Cinryze® and Haegarda®;
   c. Age ≥ 13 years for Ruconest®;
4. Member meets one of the following (a,b or c):
   a. For treatment of acute HAE attacks, request does not exceed 4 doses per month and 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, both of the following (i and ii):

i. Member requires major dental work or surgical procedure;
ii. Request does not exceed 2 doses per 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;
   b. Cinryze®: 2,500 units (5 vials) every 3 to 4 days;
   c. Haegarda®: 60 IU/kg of body weight per single dose, twice weekly;
   d. Ruconest®: 4,200 U per single dose, up to 2 doses administered in a 24-hour period.

Approval Duration:
Short-term prophylaxis: 4 weeks (no more than 2 doses per procedure)
Treatment of acute attacks: Up to 4 doses per month
Commercial: 6 months
Medicaid: 6 months
Long-term prophylaxis:
Commercial: 6 months
Medicaid: 6 months

II. Continued Therapy Approval

A. All 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. For treatment of acute attacks, request does not exceed 4 doses per month;
5. 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, 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

Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Maximum Dose
cetirizine	40 mg/day (off-label) Typical dosing range (mg/day): 10 mg/day US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema	40 mg/day (off-label)
icatibant (Firazyr®)	30 mg subcutaneously in the abdominal area; if response is inadequate or symptoms recur, additional injections of 30 mg may be administered at intervals of at least 6 hours. Do not administer more than 3 injections in 24 hours.	90 mg/24 hours

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

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.

  *Contraindications listed reflect direct statements made in the manufacturer's package insert; for additional uses, warnings, and precautions, please refer to clinical guidelines.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- Diagnosis of HAE:
  - There are two classifications of HAE: HAE with C1-INH deficiency (HAE-C1INH, further broken down into Type 1 and Type II) and HAE with normal C1-INH (also known as HAE-nl-C1INH). HAE-nl-C1INH was previously referred to as type III HAE, but this term is obsolete and should not be used.
  - 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%

  - HAE-nl-C1INH, on the other hand, presents with normal C4 and C1-INH levels. Some patients have an associated mutation , while others have no identified genetic indicators. HAE-nl-C1INH is very rare, 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).
- Short-term prophylaxis may be indicated before invasive medical, surgical, or dental procedures. Busse et al recommend that a single dose of 20 units/kg of plasma-derived C1 inhibitor can be given 1 to 12 hours before the stressor. On-demand treatment should also be available in the event of delayed swelling in the wake of the procedure.

References

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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 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.	01/20/2021	03/09/2021
Policy was reviewed: 1) Dosing Information, Maximum Dose, Berinert®:	11/22/2021	01/17/2022

Updated to include maximum dosing information for indication Treatment of acute HAE attacks. 2) Dosing Information, Maximum Dose, Haegarda®: Updated to include maximum dosing information for indication Prophylaxis against acute HAE attacks. 3) Initial Approval Criteria I.A.4.c was removed. 4) I.a.6.a,I.A.6.c , II.B.4.a and II.B.4.c was updated to remove" up to 2 administered in a 24-hour period". 5) Initial and continued therapy approval duration updated to remove short term prophylaxis. 6) Statement about provider sample ''The provision of provider samples does not guarantee coverage…" was added to Clinical Policy. 7) References were reviewed and updated.		
Policy was reviewed: 1. Dosing Information, Dosing Regimen, recombinant C1 esterase inhibitor (Ruconest®): Updated dosing information from Weight ≥ 84 kg: 4,200 units intravenous (2 vials) may administer a second dose if symptoms persist to Weight ≥ 84 kg: 4,200 units intravenous may administer a second dose if symptoms persist for indication Treatment of acute HAE attacks. 2. Initial Approval Criteria, I.A.1: Updated diagnostic criteria from Diagnosis of HAE confirmed by one of the following to Diagnosis of HAE confirmed by a history of recurrent angioedema and one of the following. 3. Initial Approval Criteria, I.A.1.b.i: Updated diagnostic criteria from History of recurrent angioedema to Presence of a mutation associated with the disease (see Appendix D). 4. Initial Approval Criteria, I.A.1.b.ii: Updated diagnostic criteria from Family history of angioedema to Family history of angioedema and documented failure of high-dose antihistamine therapy (i.e., cetirizine 40 mg/day or equivalent) for at least 1 month or an interval expected to be associated with 3 or more attacks of angioedema, whichever is longer. 5. Initial Approval Criteria, I.A.4.a: Updated dosing criteria from For treatment of acute HAE attacks, meets one of the following to For treatment of acute HAE attacks, request does not exceed 4 doses per month and meets one of the following.	09/30/2022	01/17/2023

6. Initial Approval Criteria, I.A.4.b: Updated diagnostic criteria from For prophylaxis of HAE attacks, meets all of the following to For long-term prophylaxis of HAE attacks, meets all of the following. 7. Initial Approval Criteria, I.A.4.c: Updated to include new diagnostic criteria For short-term prophylaxis of HAE attacks, both of the following (i and ii): i. Member requires major dental work or surgical procedure; ii. Request does not exceed 2 doses per procedure. 8. Intitial Therapy Approval Crtieria, I.A: Updated to include new approval criteria Short-term prophylaxis: 4 weeks (no more than 2 doses per procedure). 9. Intitial Therapy Approval Crtieria, I.A: Updated approval duration criteria for Treatment of HAE attacks: from Medicaid: 12 months to Medicaid: 6 months. 10. Initial Therapy Approval Crtieria, I.A: Updated approval duration criteria for Prophylaxis: Commercial: 6 months Medicaid: 12 months to Long-term prophylaxis: Commercial: 6 months Medicaid: 6 months. 11. Continued Therapy Approval, II.A.4: Updated to include new dosing criteria For treatment of acute attacks, request does not exceed 4 doses per month. 12. Continued Therapy Approval, II.A.5.a: Updated dosing criteria from Berinert®: 20 IU/kg of body weight per single dose to Berinert®: 20 IU/kg of body weight per single dose, up to 2 doses administered in a 24-hour period. 13. Continued Therapy Approval, II.A.5.d: Updated dosing criteria from Ruconest®: 4,200 U per single dose, up to 2 doses administered in a 24-hour period to Ruconest®: 4,200 U per single dose, up to 2 doses administered in a 24-hour period, up to 2 doses administered in a 24-hour period. 14. Continued Therapy Approval, II.A: Updated approval duration criteria Prophylaxis to Long-term Prophylaxis. 15. Appendix B, Drug Name: Updated to include therapeutic alternatives: a. cetirizine;		

b. icatibant (Firazyr®). 16. Disclaimer about contraindications," Contraindications listed reflect statements made in the manufacturer's package insert.." was added to Appendix C. 17. Appendix D, General Information: Updated information available from 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) to There are two classifications of HAE: HAE with C1-INH deficiency (HAE-C1INH, further broken down into Type 1 and Type II) and HAE with normal C1-INH (also known as HAE-nl-C1INH). HAE-nl-C1INH was previously referred to as type III HAE, but this term is obsolete and should not be used. 18. Appendix D, General Information: Updated information available from 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 to HAE-nl-C1INH, on the other hand, presents with normal C4 and C1-INH levels. Some patients have an associated mutation , while others have no identified genetic indicators. HAE-nl-C1INH is very rare, 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. 19. Appendix D, General Information: Updated information available from HAE attack triggers may include minor trauma (such as dental procedures), oral contraceptives, and ACE inhibitors to HAE attack triggers may include minor trauma (such as dental procedures). 20. Appendix D, General Information: "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" was repaced with Short-term prophylaxis may be indicated before invasive medical, surgical, or dental procedures. Busse et al recommend that a single dose of 20 units/kg of plasma-derived C1 inhibitor can be given 1 to 12 hours before the stressor. On-demand treatment should also be available in the event of delayed swelling in the wake of the procedure. 21. References were reviewed and updated.		