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

Reference Number: ERX.SPA.28
Effective Date: 07.01.16
Last Review Date: 02.22
Line of Business: Commercial, Medicaid

Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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

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.

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

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Berinert, Cinryze, Haegarda, and Ruconest are **medically necessary** when the following criteria are met:

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 meets one of the following (a, b, or c):
   a. Age ≥ 5 years for Berinert;
   b. Age ≥ 6 years for Cinryze or 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, both 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. If request is for treatment of acute HAE attacks and member is age ≥ 18 years, failure of icatibant (generic Firazyr®), unless contraindicated or clinically significant adverse effects are experienced;
6. If request is for long-term prophylaxis of HAE attacks and member is age ≥ 12 years, failure of Takhzyro™, unless contraindicated or clinically significant adverse effects are experienced;
7. 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 or using a combination of Cinryze, Haegarda, Orladeyo™, and/or Takhzyro for long-term prophylaxis of HAE attacks);
8. 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 IU 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: 6 months (up to 4 doses per month)
Long-term prophylaxis: 6 months

B. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

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 a health plan affiliated with Envolve Pharmacy Solutions or member has previously met initial approval criteria;
2. Member is responding positively to therapy (e.g., if Cinryze or Haegarda is requested, member has demonstrated 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., using both Berinert and Firazyr for acute HAE attacks or using a combination of Cinryze, Haegarda, Orladeyo, and/or Takhzyro for long-term prophylaxis of 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 IU per single dose, up to 2 doses administered in a 24-hour period.

Approval duration:
Treatment of acute attacks: 12 months (up to 4 doses per month)
Long-term prophylaxis: 12 months

C. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off-label use policy – ERX.PA.01 or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

C1-INH: C1 esterase inhibitor
C4: complement component 4
FDA: Food and Drug Administration
HAE: hereditary angioedema
HAE-nl-C1INH: hereditary angioedema with normal C1 inhibitor

Appendix B: Therapeutic Alternatives
This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ 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®)	Treatment of acute HAE attacks: 30 mg SC 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
Takhzyro™ (lanadelumab-fylo)	300 mg SC every 2 weeks A dosing interval of 300 mg every 4 weeks may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months	300 mg SC every 2 weeks

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

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 (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	13-57 mg/dL (age- and gender-specific ranges)	14-44 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 a known 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; mutations in 4 genes causing HAE-nl-C1INH have been identified:

Identified Genes Associated with Mutations in HAE-nl-C1INH
F12
ANGPT1
PLG
KNG1

- 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.

V. 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, 20 IU/kg/dose
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, 60 IU/kg/dose
Human C1 esterase inhibitor (Cinryze)	Prophylaxis against HAE attacks	Age 6-11 years: 500 units IV every 3-4 days Age ≥ 12 years: 1,000 units IV every 3-4 days	Age 6-11 years: 1,000 units every 3-4 days Age ≥ 12 years: 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

VI. 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, 3,000 IU
Human C1 esterase inhibitor (Cinryze)	Vial with powder for reconstitution: 500 units
Recombinant C1 esterase inhibitor (Ruconest)	Vial with powder for reconstitution: 2,100 units

VII. References

1. Berinert Prescribing Information. Marburg, Germany: CSL Behring GmbH; September 2021. Available at: www.berinert.com. Accessed October 20, 2021.
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10. Mayo Clinic Laboratories [internet database]. Rochester, Minnesota: Mayo Foundation for Medical Education and Research. Updated periodically. Accessed November 4, 2021.
11. Quest Diagnostics ® [internet database]. Updated periodically. Accessed November 4, 2021.
12. LabCorp [internet database]. Burlington, North Carolina: Laboratory Corporation of America. Updated periodically. Accessed November 4, 2021.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
1Q18 annual review: 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 criteria for plasma-derived C1 esterase inhibitors according to AOW treatment guidelines. Added trial of danazol for long-term prophylaxis in adults.	11.27.17	02.18
1Q 2019 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 quantity limit of 4 doses per month for treatment of acute attacks; added requirement that members requesting	10.30.18	02.19

Reviews, Revisions, and Approvals	Date	P&T Approval Date
continued therapy for short term prophylaxis must meet initial criteria; references reviewed and updated.		
1Q 2020 annual review: initial auth durations for treatment of acute attacks and long-term prophylaxis revised from 12 to 6 months; removed specific C1 esterase inhibitor options for short-term prophylaxis; HAE lab reference range updated; references reviewed and updated.	11.04.19	02.20
1Q 2021 annual review: no significant changes; reconciled FDA indication language; RT4: pediatric extension for Haegarda ≥ 6 years, updated age restriction criteria; references reviewed and updated.	10.02.20	02.21
1Q 2022 annual review: updated diagnosis criteria to include a recurrent history of angioedema and either an associated mutation or family history of angioedema with failure of high-dose antihistamines for HAE-nl-C1INH; added redirections to Firazyr for the treatment of acute HAE attacks and to Takhzyro for long-term prophylaxis of HAE attacks; clarified the number of doses for treatment of acute attacks and short-term prophylaxis within criteria; added auth duration of 4 weeks for short-term prophylaxis; references reviewed and updated.	11.11.21	02.22

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members.