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

Reference Number: MDN.CP.PHAR.202
Effective Date: 04.01.22
Last Review Date: 04.22
Line of Business: Meridian IL Medicaid

Coding Implications
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.*

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** (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 long-term prophylaxis of HAE attacks, failure of Haegarda, unless contraindicated or clinically significant adverse effects are experienced;
6. 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);
7. 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: Up to 4 doses per month**
**Medicaid** – 6 months
**Long-term prophylaxis**:
**Medicaid** – 6 months

**B. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid.

**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 Centene benefit or member has previously met initial approval criteria;
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 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: Up to 4 doses per month**
**Medicaid –** 12 months
**Long-term prophylaxis:**
**Medicaid –** 12 months

**C. Other diagnoses/indications** (must meet 1 or 2)**:**

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.
   **Approval duration: Duration of request or 6 months (whichever is less)**; or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid.

**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 policies – CP.PMN.53 for Medicaid 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 for all relevant lines of business and may require prior authorization.*

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| cetirizine | 40 mg/day (*off-label*)<br>Typical dosing range (mg/day): 10 mg/day<br>*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:<br>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.<br><br>Do not administer more than 3 injections in 24 hours. | 90 mg/24 hours |

*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%<br>Equivocal: 41-67%<br>Abnormal: < 41% | Normal: ≥ 68%<br>Equivocal: 41-67%<br>Abnormal: ≤ 40% | Normal: > 67%<br>Equivocal: 41-67%<br>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<br>Age ≥ 12 years: 1,000 units IV every 3-4 days | Age 6-11 years: 1,000 units every 3-4 days<br>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 | 4,200 units/dose; up to 2 doses within a 24-hour period |

| Drug Name | Indication | Dosing Regimen | Maximum Dose |
|---|---|---|---|
| | | Weight ≥ 84 kg: 4,200 units IV<br><br>May administer a second dose if symptoms persist. | |

## 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, 3000 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.
2. Cinryze Prescribing Information. Lexington, MA: ViroPharma, Inc.; January 2021. Available at: www.cinryze.com. Accessed October 20, 2021.
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4. Haegarda Prescribing Information. Kankakee, IL: CSL Behring LLC; September 2020. Available at: www.haegarda.com. Accessed October 20, 2021.
5. 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.
6. 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.
7. Busse PJ, Christiansen SC, Reidl MA, et al. US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema. *J Allergy Clin Immunol*. 2021; 9(1): 132-150.e3.
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.
9. 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.
10. Mayo Clinic Laboratories [internet database]. Rochester, Minnesota: Mayo Foundation for Medical Education and Research. Updated periodically. Accessed November 8, 2021.

11. Quest Diagnostics ® [internet database]. Updated periodically. Accessed November 8, 2021.
12. LabCorp [internet database]. Burlington, North Carolina: Laboratory Corporation of America. Updated periodically. Accessed November 8, 2021.

**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 |
|---|---|
| J0599 | Injection, C-1 esterase inhibitor (human), Haegarda, 10 units |
| J0597 | Injection, C-1 esterase inhibitor (human), Berinert, 10 units |
| J0598 | Injection, C-1 esterase inhibitor (human), Cinryze, 10 units |
| J0596 | Injection, C-1 esterase inhibitor (recombinant), Ruconest, 10 units |

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Policy created, adapted from CP.PHAR.202 | 04.01.22 | 04.22 |

**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. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or

regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. 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. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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**Note:**
**For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.