

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

Reference Number: HIM.PA. 170

Effective Date: 01.01.24

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Line of Business: HIM

[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<sup>®</sup>, Cinryze<sup>®</sup>, Haegarda<sup>®</sup>) and recombinant C1 esterase inhibitor (Ruconest<sup>®</sup>).

### **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<sup>®</sup> 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. Member meets one of the following (a, b, or c):
    - a. Age  $\geq$  5 years for Berinert;
    - b. Age  $\geq$  6 years for Cinryze or Haegarda;
    - c. Age  $\geq$  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  $\geq$  18 years, failure of icatibant\* (generic Firazyr<sup>®</sup>), unless contraindicated or clinically significant adverse effects are experienced;  
*\*Prior authorization may be required for icatibant*
  6. If request is for Cinryze for long-term prophylaxis of HAE attacks, failure of all the following (a, b, and c)\*, unless clinically significant adverse effects are experienced or all are contraindicated:
    - a. Haegarda;
    - b. Takhzyro<sup>®</sup>;
    - c. If age  $\geq$  12 years: Orladeyo<sup>®</sup>;*\*Prior authorization may be required for Haegarda, Orladeyo, and Takhzyro*
  7. Member is not using the requested product in combination with another FDA-approved product for the same indication (e.g., using a combination of Berinert, Firazyr, Kalbitor, or Ruconest 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 one of the following (a, b, c, or d):
    - a. Berinert: 20 IU/kg of body weight per single dose, up to 2 doses administered in a 24-hour period;
    - b. Cinryze: 2,000 units (4 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 (must meet 1 or 2):**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
  - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: HIM.PA.33 for health insurance marketplace; or
  - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: HIM.PA.103 for health insurance marketplace; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: HIM.PA.154 for health insurance marketplace.

**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. Member meets one of the following (a or b):
  - a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
  - b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B*);
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 a combination of Berinert, Firazyr, Kalbitor, or Ruconest 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 one of the following (a, b, c, or d):
  - a. Berinert: 20 IU/kg of body weight per single dose, up to 2 doses administered in a 24-hour period;
  - b. Cinryze: 2,000 units (4 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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
  - a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: HIM.PA.33 for health insurance marketplace; or
  - b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: HIM.PA.103 for health insurance marketplace; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: HIM.PA.154 for health insurance marketplace.

**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 – HIM.PA.154 for health insurance marketplace 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 ( <i>off-label</i> ) Typical dosing range (mg/day): 10 mg/day <i>US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema</i>	40 mg/day ( <i>off-label</i> )
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.	90 mg/24 hours

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	Do not administer more than 3 injections in 24 hours.	
Orladeyo (berotralstat)	HAE attack prophylaxis: 150 mg PO QD	150 mg/day
Takhzyro (lanadelumab- fylo)	HAE attack prophylaxis: <u>Adult and pediatric patients ≥ 12 years of age</u> 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  <u>Pediatric patients 6 to &lt; 12 years of age</u> 150 mg SC every 2 weeks A dosing interval of 150 mg every 4 weeks may be considered if the patient is well-controlled (e.g., attack free) for more than 6 months  <u>Pediatric patients 2 to &lt; 6 years of age</u> 150 mg SC every 4 weeks	See dosing regimen

Therapeutic alternatives are listed as Brand name<sup>®</sup> (generic) when the drug is available by brand name only and generic (Brand name<sup>®</sup>) 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)	10-38 mg/dL (age- and gender-specific ranges)
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 6 genes causing HAE-nl-C1INH have been identified:

Identified Genes Associated with Mutations in HAE-nl-C1INH
<i>F12</i>
<i>ANGPT1</i>
<i>PLG</i>
<i>KNG1</i>
<i>MYOF</i>
<i>HS3ST6</i>

- 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: 2,000 units (not exceeding 80 units/kg) every 3-4 days

Drug Name	Indication	Dosing Regimen	Maximum Dose
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, 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. Kankakee, IL: CSL Behring LLC; September 2021. Available at: [www.berinert.com](http://www.berinert.com). Accessed May 8, 2024.
2. Cinryze Prescribing Information. Lexington, MA: Takeda Pharmaceuticals U.S.A., Inc.; February 2023. Available at: [www.cinryze.com](http://www.cinryze.com). Accessed May 8, 2024.
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9. Maurer M, Magerl M, Betschel S, et al. The international WAO/EAACI guideline for the management of hereditary angioedema-The 2021 revision and update. *Allergy*. 2022;77(7):1961-1990.



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11. Quest Diagnostics® [internet database]. Updated periodically. Accessed May 8, 2024.
12. LabCorp [internet database]. Burlington, North Carolina: Laboratory Corporation of America. Updated periodically. Accessed May 8, 2024.

**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
J0599	Injection, C-1 esterase inhibitor (human), Haegarda, 10 units

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy created per August SDC (adapted from CP.PHAR.202).	08.22.23	12.23
3Q 2024 annual review: no significant changes; references reviewed and updated.	05.08.24	08.24

**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.

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