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

Reference Number: CP.PHAR.202
Effective Date: 03.01.16
Last Review Date: 02.23
Line of Business: Commercial, HIM*, 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®).

**For Health Insurance Marketplace (HIM), if request is through pharmacy benefit, Berinert is non-formulary and should not be approved using these criteria; refer to the formulary exception policy, HIM.PA.103.*

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 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, failure of Haegarda, 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: Up to 4 doses per month
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer
Long-term prophylaxis:
Medicaid/HIM – 6 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; 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: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; 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: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and 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. 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 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/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer
Long-term prophylaxis:
Medicaid/HIM – 12 months
Commercial – 6 months or to the member's renewal date, whichever is longer

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: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; 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: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; 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: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and 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.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and 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*) Typical dosing range (mg/day): 10 mg/day	40 mg/day (*off-label*)

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
	US HAEA Medical Advisory Board 2020 Guidelines for the Management of Hereditary Angioedema	
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

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)	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
F12
ANGPT1
PLG
KNG1
MYOF
HS3ST6

- 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

Drug Name	Availability
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 November 3, 2022.
2. Cinryze Prescribing Information. Lexington, MA: ViroPharma, Inc.; January 2021. Available at: www.cinryze.com. Accessed November 3, 2022.
3. Ruconest Prescribing Information. Warren, NJ: Pharming Healthcare Inc.; April 2020. Available at: www.ruconest.com. Accessed November 3, 2022.
4. Haegarda Prescribing Information. Kankakee, IL: CSL Behring LLC; January 2022. Available at: www.haegarda.com. Accessed November 3, 2022.
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, 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..
10. Mayo Clinic Laboratories [internet database]. Rochester, Minnesota: Mayo Foundation for Medical Education and Research. Updated periodically. Accessed November 3, 2022.
11. Quest Diagnostics® [internet database]. Updated periodically. Accessed November 3, 2022.
12. LabCorp [internet database]. Burlington, North Carolina: Laboratory Corporation of America. Updated periodically. Accessed November 3, 2022.

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

HCPCS Codes	Description
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
1Q18 annual review: policies combined for commercial and Medicaid; Added Haegarda into the policy; Medicaid: 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 for plasma-derived C1 esterase inhibitors according to AOW treatment guidelines; references reviewed and updated.	11.15.17	02.18
1Q19 annual review: added age requirements for all C1 esterase inhibitors; removed trial of danazol for long-term prophylaxis per WAO/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; revised approval duration for acute attacks and long-term prophylaxis to 6 months or member's renewal date for Commercial; added requirement that members requesting continued therapy for short term prophylaxis must meet initial criteria; references reviewed and updated.	11.06.18	02.19
Added HIM line of business due to addition of agent(s) to the HIM formulary with PA	03.14.19	
1Q 2020 annual review: initial auth duration for Medicaid & HIM LOBs revised to 6 months for alignment; removed specific C1 esterase inhibitor options for short-term prophylaxis; HAE lab reference range updated; references reviewed and updated.	11.27.19	02.20
1Q 2021 annual review: no significant changes; reconciled FDA indication language; RT4: pediatric extension for Haegarda, ≥ 6 years, updated age restriction criteria; updated Haegarda HCPCS code; references reviewed and updated.	10.02.20	02.21
Per June SDC and prior clinical guidance, added redirection to generic Firazyr for treatment of acute HAE attacks, added redirection to Haegarda for HAE prophylaxis.	06.02.21	08.21
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 criterion for age ≥ 18 years	11.03.21	02.22

Reviews, Revisions, and Approvals	Date	P&T Approval Date
for Firazyr redirection; 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.		
Template changes applied to other diagnoses/indications and continued therapy section.	10.03.22	
1Q 2023 annual review: no significant changes; updated Appendix D lab reference range and mutations associated with HAE; references reviewed and updated.	11.03.22	02.23

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.