Clinical Policy: C1 Esterase Inhibitors (Berinert, Cinryze, Haegarda, Ruconest)
Reference Number: CP.PHAR.202
Effective Date: 03.01.16
Last Review Date: 02.21
Line of Business: Commercial, HIM*, Medicaid

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 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 both of the following (i and ii):
            i. History of recurrent angioedema;
            ii. Family history of angioedema;
      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 $\geq$ 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, 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 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, member requires major dental work or surgical procedure;
5. 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 Takhyzyro® for long-term prophylaxis of HAE attacks);
6. 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: 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
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.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. 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. 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. 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.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
Appendix B: Therapeutic Alternatives
Not applicable

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 (further broken down into Type I and Type II) and HAE of unknown origin (also known as Type III).
  - In both Type I (~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.

<table>
<thead>
<tr>
<th>Laboratory Test &amp; Reference Range</th>
<th>Mayo Clinic</th>
<th>Quest Diagnostics</th>
<th>LabCorp</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4</td>
<td>14-40 mg/dL</td>
<td>16-47 mg/dL</td>
<td>13-44 mg/dL</td>
</tr>
<tr>
<td>C1-INH, antigenic</td>
<td>19-37 mg/dL</td>
<td>21-39 mg/dL</td>
<td>21-39 mg/dL</td>
</tr>
<tr>
<td>C1-INH, functional</td>
<td>Normal: &gt; 67%</td>
<td>Normal: ≥ 68%</td>
<td>Normal: &gt; 67%</td>
</tr>
<tr>
<td></td>
<td>Equivocal: 41-67%</td>
<td>Equivocal: 41-67%</td>
<td>Equivocal: 41-67%</td>
</tr>
<tr>
<td></td>
<td>Abnormal: &lt; 41%</td>
<td>Abnormal: ≤ 40%</td>
<td>Abnormal: &lt; 41%</td>
</tr>
</tbody>
</table>

- 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.
- HAE attack triggers may include minor trauma (such as dental procedures), oral contraceptives, and ACE inhibitors.
- 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.

V. Dosage and Administration

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>human C1 esterase inhibitor (Berinert)</td>
<td>Treatment of acute HAE attacks</td>
<td>20 IU/kg body weight IV</td>
<td>Based on weight, 20 IU/kg/dose</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Indication</td>
<td>Dosing Regimen</td>
<td>Maximum Dose</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
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</tr>
<tr>
<td>human C1 esterase inhibitor (Haegarda)</td>
<td>Prophylaxis against HAE attacks</td>
<td>60 IU/kg body weight SC twice weekly (every 3 or 4 days)</td>
<td>Based on weight, 60 IU/kg/dose</td>
</tr>
<tr>
<td>human C1 esterase inhibitor (Cinryze)</td>
<td>Prophylaxis against HAE attacks</td>
<td>Age 6-11 years: 500 units IV every 3-4 days</td>
<td>2,500 units (not exceeding 100 units/kg) every 3-4 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Age ≥ 12 years: 1,000 units IV every 3-4 days</td>
<td></td>
</tr>
<tr>
<td>recombinant C1 esterase inhibitor (Ruconest)</td>
<td>Treatment of acute HAE attacks</td>
<td>Weight &lt; 84 kg: 50 units/kg IV</td>
<td>4,200 units/dose; up to 2 doses within a 24-hour period</td>
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<tr>
<td></td>
<td></td>
<td>Weight ≥ 84 kg: 4,200 units IV</td>
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<td>May administer a second dose if symptoms persist.</td>
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</tbody>
</table>

VI. Product Availability

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>human C1 esterase inhibitor (Berinert)</td>
<td>Vial with powder for reconstitution: 500 IU</td>
</tr>
<tr>
<td>human C1 esterase inhibitor (Haegarda)</td>
<td>Vial with powder for reconstitution: 2,000 IU, 3000 IU</td>
</tr>
<tr>
<td>human C1 esterase inhibitor (Cinryze)</td>
<td>Vial with powder for reconstitution: 500 units</td>
</tr>
<tr>
<td>recombinant C1 esterase inhibitor (Ruconest)</td>
<td>Vial with powder for reconstitution: 2,100 units</td>
</tr>
</tbody>
</table>

VII. References

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.

<table>
<thead>
<tr>
<th>HCPSC Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0599</td>
<td>Injection, C-1 esterase inhibitor (human), Haegarda, 10 units</td>
</tr>
<tr>
<td>J0597</td>
<td>Injection, C-1 esterase inhibitor (human), Berinert, 10 units</td>
</tr>
<tr>
<td>J0598</td>
<td>Injection, C-1 esterase inhibitor (human), Cinryze, 10 units</td>
</tr>
<tr>
<td>J0596</td>
<td>Injection, C-1 esterase inhibitor (recombinant), Ruconest, 10 units</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicaid: Added criteria to confirm diagnosis. Removed age requirement. Increased approval duration to 12 months for Berinert/Ruconest and incorporated recommended dosing from PI. Added criteria for continued approval. Removed warnings against hypersensitivity reactions. For Cinryze, modified initial approval duration for long-term prophylaxis to 6 months and for renewal to 12 months. For continued therapy, added max dose criteria and reasons to discontinue.</td>
<td>02.17</td>
<td>03.17</td>
</tr>
<tr>
<td>1Q18 annual review: policies combined for commercial and Medicaid; Added Haegarda into the policy; Medicaid: added specialist requirement, removed “Other types of angioedema have</td>
<td>11.15.17</td>
<td>02.18</td>
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</tbody>
</table>
## Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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<tbody>
<tr>
<td>11.06.18</td>
<td>02.19</td>
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</tbody>
</table>

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.

1Q19 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; 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.

Added HIM line of business due to addition of agent(s) to the HIM formulary with PA

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.

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.

## 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
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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.

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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.

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