Pharmacy Policies

Hereditary Angioedema

Policy Number: 9.021
Version Number: 10.0
Version Effective Date: 07/01/2016

Product Applicability

☑ All Plan+ Products

Well Sense Health Plan
☒ New Hampshire Medicaid
☒ NH Health Protection Program
☐ __________________________

Boston Medical Center HealthNet Plan
☒ MassHealth
☒ Qualified Health Plans/ConnectorCare/Employer Choice Direct
☐ Senior Care Options
☐ __________________________

Note: Disclaimer and audit information is located at the end of this document.

Summary

The Plan will authorize coverage of Berinert®, Cinryze™, Firazyr®, Kalbitor®, and Ruconest® when appropriate criteria are met.

Description of Item or Service

Hereditary Angioedema (HAE) is a rare genetic disorder resulting from either low levels of C1-esterase inhibitor or dysfunctional C1-esterase inhibitor (C1-INH). C1-INH is an important regulator in bradykinin production via the Factor XII/kallikrein proteolytic cascade. Low levels of C1-INH causes excess bradykinin that leads to leaky blood vessels and fluid accumulation in body tissues resulting in HAE symptoms. Clinical implications of HAE include recurrent angioedema affecting the upper gastrointestinal and respiratory tracts. Laryngeal edema can be fatal if symptoms are not recognized and treated promptly.

Approaches to treatment of HAE include acute treatment of angioedema attacks, short-term prophylaxis (i.e. dental procedures, surgery, intubation), and long term prophylaxis for patients that experience more than one

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severe event per month or are disabled more than 5 days per month. All patients with HAE should receive education on trigger avoidance (e.g. facial trauma, avoidance of certain medications) and a written plan for treatment of acute attacks that can be used in emergency department care.

There are currently four medications FDA approved for the treatment of HAE: Berinert®, Firazyr®, Kalbitor®, and Ruconest®. Cinryze™ is indicated for the prevention of HAE attacks. Berinert®, Cinryze™, and Ruconest® are C1-esterase inhibitors. Ruconest® is the only C1-esterase inhibitor that is plasma-free. Firazyr® and Kalbitor® both modulate bradykinin activity; Firazyr® is a selective bradykinin B2 receptor antagonist and Kalbitor® inhibits plasma kallikrein activity. Cinryze™, Berinert®, and Ruconest® are administered by intravenous infusion, while Kalbitor® and Firazyr® are administered subcutaneously. Berinert®, Cinryze™, Firazyr®, and Ruconest® can be self-administered; Kalbitor® requires administration by a healthcare provider.

Specifically, product labeling for Kalbitor® contains a black box warning stating that due to the risk of anaphylaxis, Kalbitor® should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema.

Ruconest® is purified from the milk of transgenic rabbits. It is therefore contraindicated in patients with a known or suspected allergy to rabbits and rabbit-derived products due to the risk of an anaphylactic reaction. Its efficacy has not been established in laryngeal HAE attacks, and it should therefore be avoided in these instances.

Other medications used for treatment and prophylaxis of HAE include attenuated androgens (danazol, oxandrolone, methyltestosterone), antifibrinolytic therapy (oral tranexamic acid, oral aminocaproic acid), and fresh frozen plasma (only useful in short term prophylaxis). Oral tranexamic acid, the preferred antifibrinolytic therapy in Europe, was approved for use in the United States under the brand name Lysteda® in November 2009 for the treatment of heavy menstrual bleeding.

Attenuated androgens have been shown to be effective for treatment and prophylaxis of HAE, and are a reasonable first line option given their widespread availability and low cost relative to C1 esterase inhibitor. According to the World Allergy Organization guideline for management of HAE, antifibrinolytic agents are not recommended for treatment or long term prophylaxis for HAE.

### Policy

#### Policy Applicability by Product

<table>
<thead>
<tr>
<th>Medication</th>
<th>BMC Health Plan</th>
<th>Well Sense Health Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MassHealth</td>
<td>QHP</td>
</tr>
<tr>
<td>Berinert</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Cinryze</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Firazyr</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Kalbitor</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Ruconest</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

The Plan may authorize coverage of Berinert®, Cinryze™, Firazyr®, Kalbitor®, and Ruconest® for members meeting the following criteria:

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A prior authorization request will be required for all prescriptions for Berinert®, Cinryze™, Firazyr®, Kalbitor®, and Ruconest®. These requests will be approved when the following criteria are met:

<table>
<thead>
<tr>
<th>Medication</th>
<th>Prior Authorization Criteria</th>
</tr>
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</table>
| **Initial Therapy (Duration of Approval – Maximum of 3 months)** | All of the following must be documented for Berinert®, Cinryze™, Firazyr®, Kalbitor®, and Ruconest®:  
1. The prescriber must be a specialist in Allergy or Immunology; **AND**  
2. A confirmed diagnosis of HAE* supported by results of genetic testing or laboratory tests indicating normal C1q levels with C4 and C1 inhibitor levels below the limits of the laboratory’s reference range (antigenic or functional levels). Baseline frequency of HAE attacks must be documented.  |
| **In addition to the above, the specified criteria below must also be met for each drug:** |  
**Berinert®**  
3. Treatment is required for acute HAE attacks; **AND**  
4. Age is at least 12 years old; **AND**  
5. A history of acute facial, laryngeal, or gastrointestinal angioedema attacks due to HAE  
**Firazyr®**  
3. Treatment is required for acute HAE attacks; **AND**  
4. Age is at least 18 years old; **AND**  
5. A history of acute facial, laryngeal, or gastrointestinal angioedema attacks due to HAE  
**Kalbitor®**  
3. Treatment is required for acute HAE attacks; **AND**  
4. Age is at least 12 years old; **AND**  
5. A history of acute facial, laryngeal, or gastrointestinal angioedema attacks due to HAE; **AND**  
6. There is a plan for medication administration by a healthcare professional in a facility equipped to provide appropriate medical support to manage anaphylaxis and hereditary angioedema  
**Cinryze™**  
3. Prophylactic treatment for HAE is required; **AND**  
4. Age is at least 12 years old; **AND**  
5. An inadequate response or intolerance to a trial of an attenuated androgen or a documented medical contraindication to androgen therapy** (e.g. danazol, oxandrolone, methyltestosterone); **AND**  
6. **At least one** of the following criteria for long-term HAE prophylaxis are met:  
   a. More than one severe event per month  
   b. More than 24 days per year affected by HAE  

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**Medication**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Prior Authorization Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruconest®</td>
<td>Documentation of the following:</td>
</tr>
<tr>
<td></td>
<td>3. Treatment is required for acute HAE attacks (except laryngeal attacks); <strong>AND</strong></td>
</tr>
<tr>
<td></td>
<td>4. Age is at least 13 years old; <strong>AND</strong></td>
</tr>
<tr>
<td></td>
<td>5. A history of acute angioedema attacks due to HAE; <strong>AND</strong></td>
</tr>
<tr>
<td></td>
<td>6. No history of an allergy to rabbits or rabbit-derived products</td>
</tr>
</tbody>
</table>

**Continuation of Therapy (Duration of Approval – Maximum of 3 months)**

The prescriber must provide **all** of the following documentation for continuation of Berinert®, Cinryze™, Firazyr®, Kalbitor®, and Ruconest® therapy:

- **Cinryze™**
  1. Significant improvement in severity and duration of attacks have been achieved and sustained; **AND**
  2. Clinical documentation of functional improvement have been achieved and sustained.

- **Berinert®, Firazyr®, Kalbitor®, and Ruconest®**
  1. Significant improvement in severity and duration of attacks have been achieved and sustained; **AND**
  2. The member is receiving prophylactic therapy with attenuated androgens or C1 INH if the member has filled Berinert®, Firazyr®, Kalbitor®, or Ruconest® more than once per month for 3 of the last 6 months (as evidenced by pharmacy claims); **AND**
  3. Adherence to prophylactic therapy for HAE if applicable.

*The Plan will NOT approve coverage of Berinert®, Cinryze™, Kalbitor®, and Ruconest® for the treatment or prevention of angioedema due to causes other than HAE.*

**Adherence to prescribed androgen therapy must be confirmed by prescription claims. If the member is new to the Plan and does not have a prescription claims history, the prescriber must certify that the member has been adherent to the prescribed androgen therapy.**

**Quantity Limitations Apply – see Appendix A**

**Applicable Coding:**

<table>
<thead>
<tr>
<th>J-Code</th>
<th>Medication</th>
</tr>
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<tbody>
<tr>
<td>J0597</td>
<td>C1 esterase inhibitor (human), 10 units (Berinert®)</td>
</tr>
<tr>
<td>J0598</td>
<td>C1 esterase inhibitor (human) 10 units (Cinryze™)</td>
</tr>
<tr>
<td>J1290</td>
<td>Ecallantide 1mg (Kalbitor®)</td>
</tr>
<tr>
<td>J1744</td>
<td>Icantibant 1mg (Firazyr®)</td>
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</tbody>
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**Limitations**

The Plan will **not** approve coverage of Berinert®, Cinryze™, Firazyr®, Kalbitor®, and Ruconest® in the following instances:

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- When the above criteria are not met.
- Ruconest® for the treatment of acute laryngeal HAE attacks

Clinical Background Information and References


Appendix A: Quantity Limitations for Cinryze™

<table>
<thead>
<tr>
<th>Medication Name</th>
<th>Quantity Limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinryze™ 500 unit vials</td>
<td>16 vials per 30 days</td>
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</table>

<table>
<thead>
<tr>
<th>Original Approval Date</th>
<th>Original Effective Date</th>
<th>Policy Owner</th>
<th>Approved by</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/10/2009</td>
<td>09/10/2009</td>
<td>Pharmacy Services</td>
<td>Pharmacy &amp; Therapeutics (P&amp;T) Committee</td>
</tr>
</tbody>
</table>

Policy Revisions History

* Plan refers to Boston Medical Center Health Plan, Inc. and its affiliates and subsidiaries offering health coverage plans to enrolled members. The Plan operates in Massachusetts under the trade name Boston Medical Center HealthNet Plan and in other states under the trade name Well Sense Health Plan.

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<table>
<thead>
<tr>
<th>Review Date</th>
<th>Summary of Revisions</th>
<th>Revision Effective Date</th>
<th>Approved by</th>
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<tbody>
<tr>
<td>03/11/2010</td>
<td>P&amp;T Annual Review, criteria added for Berinert® and Kalbitor®</td>
<td>07/01/2010</td>
<td>P&amp;T Committee</td>
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<tr>
<td>03/10/2011</td>
<td>P&amp;T Annual Review, no changes required</td>
<td>07/01/2011</td>
<td>P&amp;T Committee</td>
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<tr>
<td>07/14/2011</td>
<td>Policy applied to Commercial</td>
<td>11/01/2011</td>
<td>P&amp;T Committee</td>
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<tr>
<td>03/08/2012</td>
<td>P&amp;T Annual Review, removed requirement of healthcare professional administration for Berinert®, Kalbitor® and Firazyr®, criteria added for Firazyr®</td>
<td>07/01/2012</td>
<td>P&amp;T Committee</td>
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<tr>
<td>08/22/2012</td>
<td>Policy applied to NH Medicaid</td>
<td>12/01/2013</td>
<td>P&amp;T Committee NH DHHS</td>
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<tr>
<td>03/14/2013</td>
<td>P&amp;T Annual Review, removed prophylaxis requirements for initial approval of Berinert®, Kalbitor® and Firazyr®, added requirement of prophylaxis to COT criteria for Berinert®, Kalbitor® and Firazyr®, updated criteria for long-term prophylaxis</td>
<td>07/01/2013</td>
<td>P&amp;T Committee NH DHHS</td>
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<tr>
<td>12/13/2013</td>
<td>Policy applied to ConnectorCare/Qualified Health Plan (QHP)</td>
<td>04/01/2014</td>
<td>P&amp;T Committee NH DHHS</td>
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<tr>
<td>03/13/2014</td>
<td>P&amp;T Annual Review, removed REMS requirement for Kalbitor®</td>
<td>07/01/2014</td>
<td>P&amp;T Committee NH DHHS</td>
</tr>
<tr>
<td>03/12/2015</td>
<td>P&amp;T Annual Review, added criteria for Ruconest®, decreased age indication from 16 y.o. to 12 y.o. for Kalbitor, expanded limitations section to include Ruconest® for the treatment of acute laryngeal HAE attacks</td>
<td>09/08/2015</td>
<td>P&amp;T Committee NH DHHS</td>
</tr>
<tr>
<td>03/10/2016</td>
<td>P&amp;T Annual Review, no changes required</td>
<td>07/06/2016</td>
<td>P&amp;T Committee</td>
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**Next Review Date**

03/09/2017

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Other Applicable Policies

9.002 Mandatory Generic Substitution Policy
9.015 Quantity Limitation Policy

Reference to Applicable Laws and Regulations, If Any

Disclaimer Information

Medical Policies are the Plan’s guidelines for determining the medical necessity of certain services or supplies for purposes of determining coverage. These Policies may also describe when a service or supply is considered experimental or investigational, or cosmetic. In making coverage decisions, the Plan uses these guidelines and other Plan Policies, as well as the Member’s benefit document, and when appropriate, coordinates with the Member’s health care Providers to consider the individual Member’s health care needs.

Plan Policies are developed in accordance with applicable state and federal laws and regulations, and accrediting organization standards (including NCQA). Medical Policies are also developed, as appropriate, with consideration of the medical necessity definitions in various Plan products, review of current literature, consultation with practicing Providers in the Plan’s service area who are medical experts in the particular field, and adherence to FDA and other government agency policies. Applicable state or federal mandates, as well as the Member’s benefit document, take precedence over these guidelines. Policies are reviewed and updated on an annual basis, or more frequently as needed. Treating providers are solely responsible for the medical advice and treatment of Members.

The use of this Policy is neither a guarantee of payment nor a final prediction of how a specific claim(s) will be adjudicated. Reimbursement is based on many factors, including member eligibility and benefits on the date of service; medical necessity; utilization management guidelines (when applicable); coordination of benefits; adherence with applicable Plan policies and procedures; clinical coding criteria; claim editing logic; and the applicable Plan – Provider agreement.