IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

*Benefit determinations should be based in all cases on the applicable contract language.* To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

**Description**

Ecallantide (Kalbitor) is a subcutaneously administered plasma kallikrein inhibitor for the treatment of acute attacks of hereditary angioedema (HAE). Due to the risk of anaphylaxis ecallantide (Kalbitor) should only be administered by a healthcare professional.
Policy/Criteria

I. Most contracts require prior authorization approval of ecallantide (Kalbitor) prior to coverage. Ecallantide (Kalbitor) may be considered medically necessary for the acute treatment of hereditary angioedema (HAE) or acquired angioedema (AAE) attacks when criteria A or B below are met.

A. A diagnosis of Type I, Type II, or Type III (HAE with normal C1-INH) HAE has been established by, or in consultation with a provider specializing in allergy, immunology, or hematology, and criteria 1 and 2 below are met.

1. Clinical documentation of serum C4 and C1-INH (antigenic or functional level) that are below the limits of the laboratory’s normal reference range (for Type I and Type II only).

   AND

2. Clinical documentation of at least one of the following:
   
   i. Family history of HAE.
   
   OR
   
   ii. Normal level of serum C1q antigenic protein based on the laboratory’s normal reference range.

   OR

B. A diagnosis of AAE established by or in consultation with a provider specializing in allergy, immunology, or hematology, and criteria 1 through 3 below are met.

1. Clinical documentation of serum C4 and C1-INH (antigenic or functional level) that are below the limits of the laboratory’s normal reference range.

   AND

2. The patient has been evaluated for an underlying B cell lymphoproliferative disorder.

   AND

3. C1q levels are below the limits of the laboratory’s normal reference range.

II. Administration, Quantity Limitations, and Authorization Period

A. OmedaRx does not consider ecallantide (Kalbitor) to be a self-administered medication.

B. When criteria IA or IB above are met and prior authorization is approved, ecallantide (Kalbitor) may be authorized in quantities of nine 10 mg/1 mL vials per month (three treatments).

C. Ecallantide (Kalbitor) in quantities of ten to eighteen 10 mg/1 mL vials per month (up to six treatments) may be considered medically necessary for acute treatment of HAE and AAE attacks when IA or IB above are met AND both criteria 1 and 2 below are met.

1. The patient has been evaluated for potentially treatable triggers of HAE and AAE attacks and is maximally managed with respect to avoiding triggers.
AND

2. Prophylaxis with an oral attenuated androgen medication (e.g. danazol, stanozolol) or antifibrinolytic (e.g. aminocaproic acid or tranexamic acid) medication has been ineffective, is contraindicated, or not tolerated due to serious adverse effects.

D. Quantities exceeding 18 vials per month are considered not medically necessary.

E. Authorization shall be reviewed at least every three months to confirm that current medical necessity criteria are met and that the medication is effective.

III. Ecallantide (Kalbitor) is considered investigational when used for the treatment of all other conditions, including but not limited to:

A. Treatment of angioedema due to causes other than HAE or AAE, including but not limited to drug-induced angioedema, allergic angioedema, and idiopathic angioedema.

B. Prevention of HAE or AAE attacks.

Position Statement

Summary

- HAE is a rare and potentially life-threatening disorder characterized by recurrent, self-limited episodes of swelling. HAE is characterized by inadequate or non-functional C1-INH proteins in the blood. C1-INH protein is a normal component of blood that helps regulate the inflammatory and clotting systems. Ecallantide (Kalbitor) works by inhibiting plasma kallikrein, an enzyme involved in the bradykinin cascade, which leads to a reduction in the formation of bradykinin thereby to reducing swelling, pain, and inflammation.[1]

- Early detection of HAE symptoms and timely treatment of HAE attacks can prevent further progression of angioedema.

- Treatment strategies for HAE include long-term prevention, short-term prevention, and on-demand treatment [e.g. ecallantide (Kalbitor)] for acute HAE attacks. Medications used in HAE management (other than oral medications) are associated with high healthcare costs. Strategies in managing HAE should be focused on avoiding or treating triggers, and utilizing oral attenuated androgen as first line therapy where indicated. The evidence for ecallantide (Kalbitor) is of low quality, which is consistent with the evidence quality for other medications in the acute treatment of HAE attacks. However, data does suggest that ecallantide (Kalbitor) is effective in treating acute HAE attacks.[1]

- AAE is a rare disorder similar to HAE, as characterized by recurrent episodes of swelling and a deficiency of C1-INH, although AAE develops in older patients and is often associated with lymphoproliferative disorders.[2,3]
Hereditary and Acquired Angioedema

- HAE is diagnosed with clinical presentation, family history, and low serum levels of C4 and C1-INH antigenic proteins (for Type I and Type II only). HAE with normal C1-INH (also called Type III) is a subset of HAE that may be caused by a mutation in coagulation factor XII. If acquired angioedema (AAE) is suspected due to lack of family history or late onset of symptoms (age over 40 years), C1q antigenic protein testing is used to rule out AAE. Serum C1q level is low in patients with AAE but normal in patients with HAE. The symptoms of HAE attacks vary in location and severity, and are highly unpredictable even within the same individual. Symptoms can range from swelling in the extremities or gastrointestinal tract, to cases involving the face and throat which are less frequent but could be life threatening.

- Ecallantide (Kalbitor) is a subcutaneously administered medication for the treatment of acute attacks of HAE. Ecallantide (Kalbitor) is available as a 10 mg/mL single use vials and is given subcutaneously in the abdomen, thigh, or upper arm during an acute HAE attack. The recommended dose for an acute attack is 30 mg (3 mL) administered as three 10 mg (1 mL) injections. If an attack persists an additional 30 mg dose may be given in within a 24 hour period.

- There are three other medications [Berinert (plasma-derived C1-INH), Ruconest (recombinant human C1-INH), and icatibant (Firazyr)] currently available to treat acute HAE attacks. All are approved for self-administration in patients who are adequately trained. Berinert (plasma-derived C1-INH (Berinert) is given intravenously and carries a risk of blood-borne disease. Ruconest (recombinant human C1-INH) is also given intravenously, but is not FDA approved for the treatment of laryngeal attacks. Icatibant (Firazyr) is given subcutaneously and like ecallantide (Kalbitor) acts on the bradykinin cascade.

- If HAE attacks become frequent, are not controlled with on-demand therapies, and prophylactic oral medications (e.g. attenuated androgen, tranexamic acid), prophylaxis with plasma derived C1-INH (Cinryze) is likely to be more cost effective.

- Treatment options for the management of AAE are limited. There are no FDA-approved therapies for AAE and treatment is extrapolated from that of HAE. While no controlled studies have been performed in patients with AAE, observational data from case studies has demonstrated that ecallantide (Kalbitor), icatibant (Firazyr), Berinert, and Ruconest were successfully used to treat AAE attacks. Expert consensus recommendations include these agents for the treatment of AAE. Additionally, management of the underlying lymphoproliferative disorder may control angioedema symptoms.

Clinical Efficacy

- Ecallantide (Kalbitor) has not been proven in high quality clinical studies to be more effective than placebo. Ecallantide (Kalbitor) has not been compared in head-to-head studies against other HAE-specific medications used in the treatment of acute HAE attacks.
The efficacy and safety of ecallantide (Kalbitor) in Type I and Type II HAE were studied in two randomized, controlled clinical trials. These studies were appraised as low confidence due to high attrition and protocol violations and modifications that may have affected study results. While the quality of individual studies was considered low, the two studies indicate that ecallantide (Kalbitor) improves HAE symptoms more than placebo at 4 hours after study-drug administration.

Based on expert consensus, it is recommended that treatment be initiated as early as possible for HAE attacks involving the face, neck, abdomen, and larynx. Recommended therapies include C1-INH (Berinert), ecallantide (Kalbitor), and icatibant (Firazyr). There were no preferences given to these acute treatment options; although, C1-INH (Berinert) does have the longest track record. [1,12,13]

The treatment effect of both preventative and on-demand therapies in Type III HAE is uncertain; however, due to the possible influence of bradykinin in some of these patients, ecallantide (Kalbitor) for acute attacks is among the possible treatment options. [2]

**Safety**

- Ecallantide (Kalbitor) is given subcutaneously and carries a boxed warning for anaphylactic reactions (3.9%). Due to the risk of anaphylaxis ecallantide (Kalbitor) should only be administered by a healthcare professional with appropriate medical support to manage anaphylaxis and hereditary angioedema. [9]

- The most common adverse reactions with ecallantide (Kalbitor) are headache, nausea, diarrhea, pyrexia, injection site reactions, and nasopharyngitis. [9]

### Appendix 1: FDA approved treatments for acute attacks of HAE [7-9,14]

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Dose and Route</th>
<th>FDA Approved Age Range</th>
<th>FDA Approved for the Treatment of Laryngeal Attacks</th>
<th>Approved for Self-Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalbitor (ecallantide)</td>
<td>30 mg injected subcutaneously in three 10 mg injections</td>
<td>Age 12 and older</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Firazyr (icatibant)</td>
<td>30 mg injected subcutaneously to the abdominal area</td>
<td>Age 18 and older</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Berinert (pdC1-INH)</td>
<td>20 IU per kg injected intravenously</td>
<td>Age 13 and older</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Ruconest (rhC1-INH)</td>
<td>50 IU per kg injected intravenously; Max dose 4200 IU</td>
<td>Age 13 and older</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- IU = international units
Cross References

<table>
<thead>
<tr>
<th>Cross References</th>
<th>Document Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cinryze®, C1 inhibitor, OmedaRx Medication Policy Manual, Policy No. 172</td>
<td></td>
</tr>
<tr>
<td>Ruconest®, recombinant human C1 inhibitor, OmedaRx Medication Policy Manual, Policy No. 373</td>
<td></td>
</tr>
<tr>
<td>Berinert®, plasma-derived C1 inhibitor, OmedaRx Medication Policy Manual, Policy No. 374</td>
<td></td>
</tr>
<tr>
<td>Firazyr®, icatibant, OmedaRx Medication Policy Manual, Policy No. 256</td>
<td></td>
</tr>
</tbody>
</table>

Codes

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCPCS</td>
<td>J1290</td>
<td>Injection, ecallantide, 1 mg</td>
</tr>
<tr>
<td>ICD-10</td>
<td>D84.1</td>
<td>Defects in the complement system</td>
</tr>
</tbody>
</table>

References


Revision History

<table>
<thead>
<tr>
<th>Revision Date</th>
<th>Revision Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>12/15/2015</td>
<td>Coverage criteria added for AAE; requirement for FXII mutation testing for Type III HAE removed; addition of ICD-10 code</td>
</tr>
</tbody>
</table>