C1 Esterase Inhibitors (Cinryze, Berinert, Haegarda, Ruconest)

Policy Number: 5.02.511
Origination: 7/2013
Last Review: 6/2021
Next Review: 6/2022

Policy
Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for C1 Esterase Inhibitors (Cinryze, Berinert, Haegarda, and Ruconest) when it is determined to be medically necessary because the following criteria are met.

When Policy Topic is covered
The use of Cinryze, Berinert, Haegarda or Ruconest may be considered medically necessary for the following:

1. Hereditary Angioedema (HAE) Prophylaxis

   Approve Cinryze, Haegarda or Berinert if the patient meets the following criteria (a and b):
   a) The patient has HAE as confirmed by the following diagnostic criteria (i and ii):
      i) Patient has low levels of functional C1-INH protein (< 50% of normal) as defined by the laboratory reference values; OR
      ii) Patient has lower than normal serum C4 levels, as defined by the laboratory reference values; AND
   b) The medication is prescribed by or in consultation with an allergist/immunologist or a physician that specializes in the treatment of HAE or related disorders.

   Cinryze is indicated in adults, adolescents and pediatric patients greater than 6 years of age.

   Haegarda is indicated in adults and adolescents. The safety and efficacy for pediatric use were evaluated in patients from 12 to 17 years of age.

   Cinryze and Haegarda are FDA-approved for this condition. Although Berinert is not indicated for this condition, guidelines recommend C1 inhibitor therapy for prophylaxis of HAE attacks. The guidelines do not differentiate between the C1 inhibitor products. Ruconest has no efficacy or dosing data for HAE prophylaxis, so it is not approved for this indication.

   The WAO guidelines and an international consensus algorithm note that HAE diagnosis can be confirmed by measuring functional C1-INH protein levels (usually < 50% of normal in patients with HAE), C4 levels, and C1-INH antigenic levels. Patients with HAE type 1 have low C4 and C1-INH antigenic protein levels, along with low levels of functional C1-INH protein. Patients with HAE type II have low C4 and functional C1-INH protein level, with a normal or elevated C1INH antigenic protein level. C1-INH replacement therapies are appropriate for both HAE type I and type II. Patients with the third type of HAE, previously referred to as HAE type III, have normal C4 and C1-INH antigenic protein levels.

2. Hereditary Angioedema (HAE) Treatment of Acute Attacks
Approve Berinert, Cinryze, or Ruconest if the patient meets the following criteria (a and b):

a) The patient has HAE as confirmed by following criteria (i and ii):
   i) Patient has low levels of functional C1-INH protein (< 50% of normal) as defined by the laboratory reference values; OR
   ii) Patient has lower than normal serum C4 levels, as defined by the laboratory reference values; AND

b) The medication is prescribed by or in consultation with an allergist/immunologist or a physician that specializes in the treatment of HAE or related disorders.

Berinert and Ruconest are FDA-approved for this condition. Although not indicated for acute HAE attacks, Cinryze has been used in this manner. Additional data indicate C1-INH therapy (specific formulation not reported) is effective for the acute treatment of HAE.

Drug must be sourced from an approved specialty infusion provider.

When Policy Topic is not covered
The use of Cinryze, Berinert, Haegarda or Ruconest is considered investigational for all other indications.

Considerations
Cinryze, Berinert, Haegarda and Ruconest require prior authorization through the Clinical Pharmacy Department.

This Blue Cross and Blue Shield of Kansas City policy statement was developed using available resources such as, but not limited to: Food and Drug Administration (FDA) approvals, Facts and Comparisons, National specialty guidelines, Local medical policies of other health plans, Medicare (CMS), Local providers.

Description of Procedure or Service
Cinryze, Berinert, Haegarda, and Ruconest are C1 esterase inhibitor (C1-INH) replacement therapies. Cinryze, Berinert and Haegarda are human plasma-derived C1-INH; whereas, Ruconest is a recombinant C1-INH purified from milk of transgenic rabbits. Cinryze is indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients with hereditary angioedema (HAE). The recommended dose is 1,000 units given IV at a rate of 1 mL/min every 3 to 4 days. Haegarda is also indicated for routine prophylaxis against angioedema attacks in adolescent and adult patients. The recommended dose is 60 units/kg subcutaneously every 3 or 4 days. Berinert is indicated for the treatment of acute abdominal, laryngeal, or facial attacks of HAE in adult and adolescent patients. The recommended dose is 20 units/kg body weight given by slow IV injection at a rate of approximately 4 mL/min. Ruconest is indicated for the treatment of acute HAE attacks in adult and adolescent patients.

Rationale
HAE is a rare, autosomal dominant disease. Two main forms of HAE have been described: patients with HAE type I have low C4 levels, low C1-INH antigen levels, with low functional protein (85% of patients); patients with HAE type II have low C4 levels with normal or elevated C1-INH antigen level, but with low C1-INH functional protein (15% of patients). A third type of HAE, HAE with normal C1-INH, previously referred to as type III HAE or estrogen-dependent HAE, includes HAE associated with mutations in the coagulation factor XII gene and other defects that are yet to be identified. Estrogens could exacerbate disease severity in most, but not all patients with HAE with normal C1-INH. Guidelines recommend that abnormal test results should be confirmed, and normal test results may need to be checked during an acute HAE attack. The guidelines or other literature do not provide specific values for the various HAE diagnostic tests since they can vary from one laboratory to another. If C4 antigenic protein and C1-inhibitor functional assays are both normal, this rules out type I and type II HAE, but does not rule out HAE with normal C1-INH or medication-related angioedema.
HAE is characterized by recurrent episodes of nonpruritic, nonpitting, subcutaneous or submucosal edema associated with pain syndrome, nausea, vomiting, diarrhea, and/or life-threatening airway swellings. Airway obstruction due to swelling is life-threatening if left untreated. There is a wide variation in the frequency and severity of attacks. Clinical experience suggests that minor trauma and/or stress, among other triggers, may precipitate attacks. Untreated attacks typically last over 48 to 96 hours. Short-term prophylaxis with a C1 esterase inhibitor is recommended if more than minor manipulation (e.g., mild dental work) is needed, and prior to intubation or major procedures. The dose for short-term prophylaxis with C1-INH varies from 10 U/kg to 20 U/kg or 1,000 units, 1 to 6 hours before procedure. Long-term prophylaxis should be considered in all severely symptomatic patients, taking into consideration the severity of disease, frequency of attacks, patient’s quality of life, availability of resources, and failure to achieve adequate control by on-demand therapy. C1-INH replacement therapies or attenuated androgens can be used for long-term prophylaxis; however, treatment with androgens must be critically considered since there are severe long-term effects with chronic use of androgens (e.g., virilization in women, hepatotoxicity). C1-INH is dosed twice a week (normal dose is 1,000 units each) for long-term prophylaxis. On-demand therapy should be available for all patients on prophylaxis because breakthrough attacks occur in most patients.

Guidelines
The World Allergy Organization (WAO) published guidelines (2012) for the management of HAE in patients throughout the world. WAO recommends that all attacks that result in debilitation/dysfunction and/or involve the face, the neck, or the abdomen should be considered for on-demand treatment. Treatment is mandatory for upper airway attacks. The recommended treatment options are C1-INH, Kalbitor® (ecallantine injection for SC use), or Firazyr® (icatibant for subcutaneous injection). If these medications are not available, the second-line option is to treat with solvent detergent-treated plasma (SDP). Treatment with frozen plasma (where safe supply is available) is the third option. Oral antifibrinolytics are not to be used as on-demand treatment. The guidelines also recommend that all patients should have on-demand treatment for two attacks and that patients should carry their on-demand treatments at all times. Short-term prophylaxis should be considered before surgeries, especially dental/intraoral surgery, or where the upper airway or pharynx is manipulated (e.g., bronchoscopy). C1-INH concentrate is the recommended short-term prophylactic option, followed by SDP. Androgens (danzaol, stanozolol) may be used for short-term prophylaxis (5 days before and 2 to 5 days post-event) when the surgery-related risk is relatively low and when C1-INH concentrate is not available. Long-term prophylaxis should be considered in patients based on the severity of the disease, frequency of attacks, the patient’s quality of life, availability of resources, and the failure to achieve adequate control by appropriate on-demand therapy. C1-INH concentrate or androgens can be used for long-term prophylaxis, though the use of androgens for long-term should be considered critically. Androgens can cause hepatitis in a dose-dependent manner. It can be hepatotoxic and can affect serum lipid levels. Virilization is the primary complication occurring in women; menstrual disorders, amenorrhea, and psychological disorders such as depression and aggression can also occur. Patients using androgens long-term are required to have semi-annual blood and urine tests, along with an ultrasound of the liver at least once a year. The preferred on-demand therapy for HAE attacks in children and in pregnant or lactating women is plasma-derived C1-INH. This is also the preferred therapy for long-term prophylaxis in adolescents.

The International Working Group published a consensus report (2012) on the treatment of HAE. Recommendations were that all patients with HAE, even if asymptomatic, should have access to at least one of the C1-INHs, Firazyr, or Kalbitor whenever possible. As indicated, patients should have the on-demand medication to treat acute attacks at home and should be trained to self-administer. All attacks, irrespective of location, are eligible for treatment as soon as they are recognized by the patient. For long-term prophylaxis, it is appropriate for patients in whom on-demand therapy was inadequate to minimize the suffering related to the disease. There is no consensus on what “inadequate” response to therapy is. Purified C1-INH can be considered for all groups of patients and evidence suggests that 1,000 units twice a week reduces rate by only 50%, so higher doses may be necessary and can be individualized to the patient based on response.
Another consensus guidelines for the management of gynecologic and obstetric events in women with HAE was published in 2012. For contraception in women with HAE, estrogens should be avoided. The recommended options are barrier methods, intrauterine devices, and progestins. C1-INH therapy is preferred for both acute and prophylactic treatments. If C1-INH is unavailable, tranexamic acid or virally inactivated fresh frozen plasma can be used for long-term prophylaxis. There are no safety data available on the use of Firazyr, Kalbitor, or Ruconest in pregnancy.

References:


Billing Coding/Physician Documentation Information

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### Additional Policy Key Words

**Policy Number:** 5.02.511

### Policy Implementation/Update Information

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<tr>
<th>Date</th>
<th>Change Description</th>
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<tr>
<td>07/2013</td>
<td>New Policy titled C1 Esterase Inhibitors (Cinryze and Berinert)</td>
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<tr>
<td>07/2014</td>
<td>Reviewed – no changes made</td>
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<tr>
<td>07/2015</td>
<td>Reviewed – Added Ruconest to PA policy. Added laboratory diagnosis criteria for confirming HAE diagnosis.</td>
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<tr>
<td>07/2016</td>
<td>Reviewed—no changes to policy statement; updated Ruconest Jcode from unclassified to J0596</td>
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<tr>
<td>05/2017</td>
<td>Added specialty infusion provider requirement</td>
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<tr>
<td>07/2017</td>
<td>Annual review—no changes to policy statement</td>
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<tr>
<td>10/2017</td>
<td>Haegarda added to policy</td>
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<tr>
<td>12/2017</td>
<td>Updated C9015 and C9399</td>
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