Hereditary Angioedema (HAE)
Drug Class Monograph

Line of Business: Medi-Cal
Effective Date: May 17, 2017
Revision Date: May 17, 2017

This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutic Subcommittee.

Drugs: Berinert (human C1 esterase inhibitor), Cinryze (human C1 esterase inhibitor), Danocrine (danazol), Firazyr (icatibant), Kalbitor (ecallantide), Ruconest (recombinant C1 esterase inhibitor)

Policy/Criteria:

A. Berinert (human C1 esterase inhibitor), Firazyr (icatibant)

Eligibility criteria: Check CCS eligibility for age less than 21 years

Diagnosis:
  a. Hereditary Angioedema (HAE)

Specialist: Immunologist, Allergist, Hematologist

Criteria:
  a. C4 level below the lower limit of normal laboratory range
  AND
  b. One of the following:
     i. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal laboratory range
     ii. C1-INH functional level below the lower limit of normal laboratory range
     iii. Documented C1-INH mutation
Quantity Limits:

a. **Berinert** (C1 esterase inhibitor): 8 vials
b. **Firazyr** (icatibant): 3 syringes

**Duration of Authorization:** May approve one time up to maximum quantity limits.

**Reauthorization Criteria:**

a. Documentation of ongoing HAE attacks and response to medication
b. May approve up to 3 months

---

**B. Kalbitor** (ecallantide), **Ruconest** (recombinant C1 esterase inhibitor)

**Eligibility Criteria:** Check CCS eligibility for age less than 21 years

**Diagnosis:**

a. Hereditary Angioedema (HAE)
   i. Ruconest is not indicated for laryngeal attacks

**Specialist:** Immunologist, Allergist, Hematologist

**Criteria:**

a. C4 level below the lower limit of normal laboratory range **AND**
b. **One of the following:**
   i. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal laboratory range
   ii. C1-INH functional level below the lower limit of normal laboratory range
   iii. Documented C1-INH mutation
c. Failure or clinically significant adverse effects to Berinert and Firazyr (Members aged 12-17 years old only require treatment failure to Berinert):
   i. Treatment intolerance may include but not limited to hypersensitivity reactions and/or thrombotic events (please refer to DrugDex adverse reaction section).
   ii. Treatment failure may include inadequate clinical response in resolving swelling attack.

**Quantity Limits:**

a. **Kalbitor** (ecallantide) - 6 vials
b. **Ruconest** (recombinant C1 esterase inhibitor) - 4 vials

**Duration of Authorization:** May approve one time up to maximum quantity limits.

**Reauthorization Criteria:**

a. Documentation of ongoing HAE attacks and response to medication
b. May approve up to 3 months
C. **Cinryze** (C1 Esterase Inhibitor, Human)

**Eligibility criteria:** Check CCS eligibility for age less than 21 years

**Diagnosis:**
- a. Hereditary Angioedema (HAE)

**Specialist:** Immunologist, Allergist, Hematologist

**Criteria:**

- a. C4 level below the lower limit of normal laboratory range
  
  **AND**
  
  b. One of the following:
     - i. C1 inhibitor (C1-INH) antigenic level below the lower limit of normal laboratory range
     - ii. C1-INH functional level below the lower limit of normal laboratory range
     - iii. Documented C1-INH mutation

**Long Term Prophylaxis of HAE attacks:**

- a. Documented history of more than one severe HAE attacks per month
  
  **OR**
  
  - b. Documented history of a laryngeal HAE attack or airway compromise
    
    **AND**
    
    - c. Inadequate response or clinically significant adverse effects to danazol

**Short Term Prophylaxis:**

- a. Documentation of anticipating invasive medical, surgical procedure, or extensive dental work

**Quantity Limits:**

- a. Short Term Prophylaxis prior to invasive medical, surgical procedure, or extensive dental work:
  
  - i. **Cinryze** (C1 Esterase Inhibitor, Human) 4 vials per procedure
  
  - b. Long Term Prophylaxis of HAE attacks:
    
    - i. **Cinryze** (C1 Esterase Inhibitor, Human) 20 vials per month

**Duration of Authorization:**

- a. Short Term Prophylaxis: May approve one time up to maximum quantity limits.
  
  - b. Long Term Prophylaxis: 6 months

**Reauthorization Criteria:**

- a. Documentation of clinical response to medication
  
  - b. Long Term Prophylaxis: may approve up to 6 months
Clinical Justification:

2013 Joint Task Force on Practice Parameters, AAAAI, ACAAI, and Joint Council of Allergy, Asthma and Immunology. A Focused Parameter Update: Hereditary Angioedema, Acquired C1 Inhibitor Deficiency, and ACEI-associated Angioedema:

Diagnosis of HAE

- Diagnosis of type I or type II HAE requires evidence of low C1-INH antigenic or functional levels, as well as decreased C4 levels and generally normal C1q levels. (A)

Treatment of HAE Attacks

- All patients with HAE should have access to an effective, on-demand HAE-specific agent.
- Evidence from double-blind, placebo-controlled randomized clinical trials demonstrates the efficacy and safety of treatment of HAE attacks with C1INH concentrates (Cinryze, Berinert and Ruconist), a plasma kallikrein inhibitor (ecallantide), or a bradykinin B2 receptor antagonist (icatibant) (A).
- Ecallantide required administration by a health care professional in a medically supervised setting due to the risk of anaphylactoid-type reactions.
- Treatment with HAE-specific agents is preferred for all acute laryngeal/oropharyngeal attacks and for moderate-to-severe attacks at other anatomic locations.

Prophylactic Treatment of HAE

- Short-term prophylaxis can be achieved by using fresh frozen plasma, C1INH replacement or short-term, high-dose anabolic androgen therapy. (B) It is critical that patients be educated concerning when to seek short-term prophylaxis. Because plasma-derived C1INH has now been approved in the United States for prophylactic use, administration of 1000 to 2000 U of plasma-derived C1INH might be a better short-term prophylactic therapy than fresh frozen plasma based on the more standardized dose of C1INH protein and the more rigorous viral inactivation steps used to produce C1INH concentrates.
- The need for long-term HAE prophylaxis must be individualized based on the patient’s situation. (D) Not all patients with HAE require long-term prophylaxis, and the decision regarding who should receive it must be individualized. Factors, such as attack frequency, attack severity, location of attacks, access to acute care, comorbid condition and patient preference can all influence the decision of whom to treat.
- Treatment with low-to-moderate doses of anabolic androgens (e.g. danazol) provides effective and relatively safe long-term HAE prophylaxis for many patients. (B) Parenterally administered androgens that are not 17α-alkylated are not effective for the treatment of HAE.
• Treatment with antifibrinolytic agents (e.g. tranexamic acid) provides somewhat effective and relatively safe long-term HAE prophylaxis but is generally less effective than androgens. (B)
• Treatment with replacement plasma-derived C1INH provides effective and safe long-term HAE prophylaxis (A).
• The dose and effectiveness of long-term prophylaxis should be based on clinical criteria and not laboratory parameters. (C)

**HAE with Normal C1INH Levels**

• Drugs developed for patients with HAE with reduced C1INH function (C1INH concentrates, ecallantide and icatibant) have been reported to be effective in some patients with HAE with normal C1INH levels. (C)
• Some patients with HAE with normal C1INH levels have been reported to show improvement with long-term prophylactic therapy with danazol, progesterone or tranexamic acid.

**Acquired C1INH Deficiency**

• The treatment of acquired C1INH deficiency is similar to that for HAE, although with some significant differences, such as increased efficacy of antifibrinolytic agents, decreased efficacy of C1INH replacement, and the need to treat an underlying condition associated with acquired C1INH deficiency. (C)
• The efficacy of ecallantide and icatibant for the treatment of acquired C1INH deficiency has been reported. Androgens and antifibrinolytic drugs have been successfully used for long-term prophylaxis in patients with acquired C1INH deficiency.

**ACE-I-Associated Angioedema**

• The management of ACE-I (or ARB)–associated angioedema is discontinuation of the ACEI (or ARB). (A)
Adapted from 2013 Joint Task Force on Practice Parameters, AAAAI, ACAAI, and Joint Council of Allergy, Asthma and Immunology
FIG E2. HAE treatment algorithm. AE, Angioedema.

Adapted from 2013 Joint Task Force on Practice Parameters, AAAAI, ACAAI, and Joint Council of Allergy, Asthma and Immunology
<table>
<thead>
<tr>
<th>Generic name (trade name, manufacturer)</th>
<th>FDA indications</th>
<th>Dosage</th>
<th>Mechanism</th>
<th>Anticipated potential side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma-derived nanofiltered C1INH (Cinryze, ViroPharma)</td>
<td>Long-term prophylaxis</td>
<td>1000 U administered intravenously every 3-4 d</td>
<td>Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin</td>
<td>Rare: risk of anaphylaxis. Theoretical: transmission of infectious agent</td>
</tr>
<tr>
<td>Plasma-derived nanofiltered C1INH (Berinert-P, CSL Behring)</td>
<td>Acute attacks</td>
<td>20 U/kg administered intravenously</td>
<td>Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin</td>
<td>Rare: risk of anaphylaxis. Theoretical: transmission of infectious agent</td>
</tr>
<tr>
<td>Ecallantide (Kalbitor, Dyax)</td>
<td>Acute attacks</td>
<td>30 mg administered subcutaneously (administered as 3 injections of 1 mL each)</td>
<td>Inhibits plasma kallikrein</td>
<td>Uncommon: anti-drug antibodies, risk of anaphylaxis</td>
</tr>
<tr>
<td>Icatibant (Firazyr, Shire)</td>
<td>Acute attacks</td>
<td>30 mg administered subcutaneously</td>
<td>Bradykinin B2 receptor antagonist</td>
<td>Common: injection-site reactions</td>
</tr>
<tr>
<td>Recombinant human C1INH (Rhucin, Pharming)</td>
<td>Acute attacks (pending)</td>
<td>50-100 U/kg administered intravenously</td>
<td>Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin</td>
<td>Uncommon: risk of anaphylaxis in rabbit-sensitized subjects</td>
</tr>
</tbody>
</table>

Adapted from 2013 Joint Task Force on Practice Parameters, AAAAI, ACAAI, and Joint Council of Allergy, Asthma and Immunology.
<table>
<thead>
<tr>
<th>Class</th>
<th>Drug name (generic, trade)</th>
<th>Adult dosage (usual, range)</th>
<th>Pediatric dosage* (usual, range)</th>
<th>FDA approved/HAE indication</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>17α-Alkylated androgens</td>
<td>Danazol (Danocrine)</td>
<td>200 mg/d (100 mg every 3 d-600 mg/d)</td>
<td>50 mg/d (50 mg/wk-200 mg/d)</td>
<td>Yes/Yes</td>
<td>Common: weight gain, virilization, acne, altered libido, muscle pains and cramps, headaches, depression, fatigue, nausea, constipation, menstrual abnormalities and increase in liver enzymes, hypertension, alterations in lipid profile; Unusual: Decreased growth rate in children, masculinization of the female fetus, cholestatic jaundice, peliosis hepatitis and hepatocellular adenoma</td>
</tr>
<tr>
<td></td>
<td>Stanazolol (Winsrol)</td>
<td>2 mg/d (1 mg every 3 d-6 mg/d)</td>
<td>0.5 mg/d (0.5 mg/wk-2 mg/d)</td>
<td>Yes/yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxandrolone (Anadrol)</td>
<td>10 mg/d (2.5 mg every 3 d-20 mg/d)</td>
<td>0.1 mg/kg/d (2.5 mg/wk-7.5 mg/d)</td>
<td>Yes/no</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methyltestosterone (Androli)</td>
<td>Men only: 10 mg/d (5 mg every 3 d-30 mg/d)</td>
<td>Not recommended for children</td>
<td>Yes/no</td>
<td></td>
</tr>
<tr>
<td>Antiandrogens</td>
<td>e Aminocaproic acid (Amicar)</td>
<td>2 g TID (1 g BID-4 g TID)</td>
<td>0.05 g/kg/BID (0.025 gm/kg BID-0.1 g/kg BID)</td>
<td>Yes/no</td>
<td>Potential side effects: nausea, vertigo, diarrhea, postural hypotension, fatigue, muscle cramps with increased muscle enzymes; Unusual: enhanced thrombosis</td>
</tr>
<tr>
<td></td>
<td>Tranexamic acid (available in US for oral and intravenous administration [Lysteda, Cyclocyprin])</td>
<td>1 g BID (0.25 g BID-1.5 g BID)</td>
<td>20 mg/kg BID (10 mg/kg BID-35 mg/kg TID)</td>
<td>Yes/no</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from 2013 Joint Task Force on Practice Parameters, AAAAI, ACAAI, and Joint Council of Allergy, Asthma and Immunology
<table>
<thead>
<tr>
<th><strong>Cinryze</strong> <em>(human C1 esterase inhibitor)</em></th>
<th><strong>Berinert</strong> <em>(human C1 esterase inhibitor)</em></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MOA</strong></td>
<td>Inhibits plasma kallikrein, coagulation factors XIIa and XIa, C1s, C1r, MASP-1, MASP-2, and plasmin</td>
</tr>
<tr>
<td><strong>Usual Dosing</strong></td>
<td>1,000 units every 3 to 4 days</td>
</tr>
<tr>
<td><strong>Administration</strong></td>
<td>IV</td>
</tr>
<tr>
<td><strong>Dosage adjustment in renal impairment</strong></td>
<td>No</td>
</tr>
</tbody>
</table>
| **PK/PD** | • Absorption: Rapid  
• Distribution: 3 L  
• Metabolism: Not extensively metabolized  
• Bioavailability: 39.7%  
• Half-life elimination: 56 hours  
• Time to peak, plasma: 4 hours  
• Excretion: Not renal or fecal |
| **Drug-drug interaction** | No |
| **Common Side effects** | Headache, nausea, rash and vomiting  
Nausea, headache, abdominal pain, dysgeusia, vomiting, pain, muscle spasms, diarrhea, back pain, facial pain |
| **Serious allergic and hypersensitivity** | Yes; anaphylaxis, hives, hypersensitivity  
Yes; hives, anaphylaxis, hypersensitivity |
| **Hepatic failure** | No |
| **Risk of heart failure** | No |
| **Pregnancy** | No human or animal data. Use only if clearly needed  
Use only if clearly needed |
| **Lactation** | Unknown; caution should be exercised in nursing women  
Unknown; caution should be exercised in nursing women |
| **Storage and stability** | Store at 2°C–25°C (36°F–77°F) |
| **How supplied** | Single-use glass vial that contains 500 units of lyophilized powder to be reconstituted with 5 mL Sterile Water for Injection  
Single-use 500 IU vial for reconstitution with 10 mL Sterile Water for Injection |
<table>
<thead>
<tr>
<th>MOA</th>
<th>Competitive antagonist of the bradykinin B2 receptor</th>
<th>Reversible and selective plasma kallikrein inhibitor and inhibits conversion of HMW kininogen to bradykinin</th>
<th>Increases C1INH activity and irreversibly binds proteases of the contact and complement systems resulting in decrease in bradykinin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual Dosing</td>
<td>30 mg</td>
<td>30 mg</td>
<td>50 units/kg as a single dose for &lt;84 kg; 4,200 units as a single dose for ≥84 kg</td>
</tr>
<tr>
<td>Administration</td>
<td>SQ</td>
<td>SQ</td>
<td>IV</td>
</tr>
<tr>
<td>Dosage adjustment in renal impairment</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
| PK/PD | - Absorption: Rapid  
- Distribution: 29 L  
- Protein binding: 44%  
- Metabolism: Metabolized extensively hepatically  
- Bioavailability: 97%  
- Half-life elimination: 1.5 hours  
- Time to peak, plasma: 0.75 hours  
- Excretion: Renal excretion to inactive metabolites; less than 10% unchanged | - Absorption: Rapid  
- Distribution: 26 L  
- Bioavailability: 90%  
- Half-life elimination: 2 hours  
- Time to peak, plasma: 2-3 hours  
- Excretion: urine | - Absorption: Rapid  
- Distribution: 3 L  
- Half-life elimination: 2.5 hours  
- Time to peak, plasma: 0.3 hours |
| Drug-drug interaction | ACE inhibitors | No | No |
| Common Side effects | Injection site reactions, pyrexia, transaminase increase, dizziness, rash | Headache, nausea, diarrhea, pyrexia, injection site reactions, and nasopharyngitis | Headache, nausea, diarrhea |
| Serious allergic and hypersensitivity | Yes; hives, anaphylaxis, hypersensitivity | Yes; hives, anaphylaxis, hypersensitivity | |
| Hepatic failure | No | No | No |
| Risk of heart failure | No | No | No |
| Pregnancy | Category C; use only if the benefits outweigh the risks to the fetus. | Category C; use only if clearly needed. | Limited animal data and no human data. Use only if clearly needed. |
| Lactation | Excreted into milk of rats; caution should be exercised in nursing women | Unknown; caution should be exercised in nursing women | Unknown; caution should be exercised in nursing women |
| How supplied | Single-use, 3 mL prefilled syringe with 30 mg of icatibant | Three 10 mg/mL single-use vials. Each vial contains 10 mg of ecallantide. | One 14 mL single-use vial to be reconstituted |
References:


### Change Control

<table>
<thead>
<tr>
<th>Date</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/17/2017</td>
<td>• Berinert and Firazyr are the non-formulary preferred HAE agents for acute attacks</td>
</tr>
<tr>
<td></td>
<td>• Changed Ruconest quantity limit to 4 vials per authorization</td>
</tr>
<tr>
<td></td>
<td>• Revised criteria for Ruconest and Kalbitor:</td>
</tr>
<tr>
<td></td>
<td>o Failure or clinically significant adverse effects to Berinert and Firazyr (Members aged 12-17 years old only require treatment failure to Berinert)</td>
</tr>
</tbody>
</table>