Medication Policy Manual

Policy No: dru172

Topic: Cinryze®, C1 Inhibitor (human)

Date of Origin: March 13, 2009

Committee Approval Date: November 11, 2016

Next Review Date: November 2017

Effective Date: December 1, 2016

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

Cinryze [plasma derived C1-esterase inhibitor (pdC1-INH)], is an intravenous form of C1 Inhibitor (C1-INH) that may be helpful in reducing the frequency of angioedema attacks in patients with hereditary angioedema (HAE). It is made from pooled blood proteins from donors in the United States.
Policy/Criteria

I. Most contracts require prior authorization approval of Cinryze (pdC1-INH) prior to coverage. Cinryze (pdC1-INH) may be considered medically necessary for the prevention of hereditary angioedema (HAE) attacks when all criteria A through D below are met.

A. The diagnosis of hereditary angioedema has been established by 1, 2 and 3 below:
   1. A diagnosis of Type I or Type II HAE has been established by, or in consultation with a provider specializing in allergy, immunology, or hematology.
   AND
   2. 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
   3. Clinical documentation of at least one of the following:
      a. Family history of HAE.
      OR
      b. Normal level of serum C1q antigenic protein based on the laboratory’s normal reference range.
   AND

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

AND

C. A history of attacks that are considered severe with swelling of the face, throat, or gastrointestinal tract. Severe is defined as events that significantly interrupt usual daily activity despite short term symptomatic treatment.

AND

D. Prior treatment with at least one preventative therapy has been ineffective or not tolerated due to serious adverse effects unless all are contraindicated for either of the following indications:
   1. **Long-term prevention.** Long-term preventative treatment with attenuated androgens (e.g. danazol, stanozolol), tranexamic acid (Lysteda), and aminocaproic acid (Amicar) for frequent and severe HAE attacks. (See Appendix 1 for common oral medication dosing information).

OR
2. **Short-term prevention.** Short-term preventative treatment with attenuated androgens (e.g. danazol, stanozolol) for severe HAE attacks in triggering situations, including but not limited to substantial dental work, invasive medical procedures, and surgical procedures. (See Appendix 1 for common oral medication dosing information).

II. **Administration, Quantity Limitations, and Authorization Period**
   
   A. OmedaRx considers Cinryze (pdC1-INH) to be either a self-administered medication or a medication administered by a healthcare provider.
   
   B. When prior authorization is approved, Cinryze (pdC1-INH) may be authorized in quantities as follows:
      
      1. **Long-term prevention:** 1,000 dosage units every three or four days for a total of 10,000 dosage units (20 of the 500-unit vials) every 30 days.
      
      OR
      
      2. **Short-term prevention:** 1,000 dosage units (2 of the 500-unit vials) per procedure.
      
   C. Authorization shall be reviewed at least **every three months** to confirm that current medical necessity criteria are met and that the medication is effective as defined by at least a 50% decrease in frequency of HAE attacks subsequent to start of therapy, significant improvement/stability in severity and duration of attacks, and clinical documentation of functional improvement/stability.

III. Cinryze (pdC1-INH) is considered not medically necessary when used in doses exceeding 1,000 dosage units every three or four days (10,000 dosage units every 30 days).

IV. Cinryze (pdC1-INH) is considered investigational when used for all other conditions, including, but not limited to:
   
   A. Angioedema due to causes other than HAE, including but not limited to drug-induced angioedema, acquired angioedema, allergic angioedema, and idiopathic angioedema.
   
   B. Myocardial infarction.
   
   C. Sepsis.
   
   D. Treatment of graft rejection.
   
   E. Prevention of transplant rejection.
   
   F. Stroke.
Position Statement

- HAE is a rare and potentially life-threatening genetic blood disease 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.

- HAE is diagnosed with clinical presentation, family history and low serum levels of C4 and C1-INH antigenic proteins. 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.

- Patients with frequent attacks, attacks involving swelling of the face or throat, or incapacitating gastrointestinal attacks may benefit from long-term preventive therapy.

- Patients who are not on long-term preventive therapy that are undergoing surgical or dental procedures may benefit from short-term preventive therapy.

- Attenuated androgens have a long-standing track record as an established treatment to prevent HAE attacks. Regular monitoring for safety and dosage adjustments are recommended in patients receiving attenuated androgens.

- There is low quality evidence that C1-INH replacement is effective in preventing or treating acute HAE attacks. However, C1-INH replacement has been used in Europe for over 30 years with a long track record of safety and efficacy, and is recognized by international guidelines as the standard of therapy for both prevention and acute treatment of HAE attacks.

Other medications used for the management of HAE

- The standard of treatment for prevention of HAE is attenuated androgens. Attenuated androgens increase the production of C1-INH protein in the liver. [5] Danazol and stanozolol are well recognized for the prevention of HAE attacks. Stanozolol is no longer available commercially at this time, but can be compounded by local pharmacies.

- Low-dose danazol has been shown to be safe and effective in for both long-term and short-term prevention in pediatric patients. [11]

- Oxandrolone is FDA approved for weight gain in pediatric patients and may be considered as an alternative androgen for the prevention of HAE attacks in children based on case reports. [11,12]

- Attenuated androgen is contraindicated in pregnant woman. Doses above 200 mg/day should be avoided in prepubescent adolescents due to side effects on growth and development.
- Aminocaproic acid (Amicar) and tranexamic acid (Lysteda) have been reported for use in prevention of HAE attacks based on low quality evidence and expert consensus. Serious side effects have been associated with the use of these antifibrinolytic agents; however, these are rare.

- There are four FDA approved medications, Berinert (pdC1-INH), Ruconest (recombinant human C1-INH), ecallantide (Kalbitor), and icatibant (Firazyr), indicated for the treatment of acute attacks of HAE. Ecallantide (Kalbitor) is the only medication not approved for self-administration and Ruconest (recombinant human C1-INH) is the only medication not labeled for the treatment of laryngeal attacks.

Clinical Efficacy \(^{[6,20]}\)

- The evidence that prophylaxis with Cinryze (pdC1-INH) reduces the frequency, duration and severity of HAE attacks is of low quality.

- There is one U.S. clinical trial to date that examines Cinryze (pdC1-INH) in HAE attack prevention. The study is a prospective, randomized, double-blinded, placebo-controlled multi-center crossover study with 22 HAE patients aged ≥ 6 years of age (range 9 to 73 years) for a 24-week period (12-week placebo and 12-week C1-INH).

* Patients received twice weekly injections of either placebo or 1,000 units of C1-INH.

* Patients included in the study had a history of at least two HAE attacks per month. Inclusion was not dependent on the severity of attack.

* Patients were permitted to continue current medications, but dose changes to androgen or aminocaproic acid were not allowed during the study or 30-days prior to the study.

* Cinryze (pdC1-INH) reduced the number of HAE attacks by 52% (primary endpoint), the severity of HAE attacks by 32% and duration of swelling by 66% (secondary endpoints). All values were statistically significant.

* Only half of study patients responded with a 50% or greater reduction in frequency of HAE attacks.

* The study evidence was appraised as low confidence due to flaws including:
  - More than 5% of patients dropped out from the study and were not included in the final analysis of HAE attack frequency.
  - C1-INH was allowed during the entire duration of the study to treat acute HAE attacks. This can lead to uncertainty regarding the effectiveness of C1-INH for prevention.

- There are no studies to date evaluating the efficacy of Cinryze (pdC1-INH) compared to other standard treatments for prevention of HAE attacks.

- There is no evidence that Cinryze (pdC1-INH) is more effective than danazol or stanozolol in prevention of HAE attacks as no comparative studies have been performed.
- The Cinryze brand of plasma-derived C1-INH has not been proven to be effective for acute treatment of HAE attacks due to flaws in the conduct and design of the trial that was submitted to the FDA for approval of this indication. However, two other brands of C1-INH (Berinert and Ruconest) have been FDA approved for acute treatment of HAE attacks.

- C1-INH (Cinryze) is currently being studied in a variety of other conditions including angioedema due to causes other than HAE, myocardial infarction, and sepsis; however, due to lack of published data, it is considered investigational in these conditions.

**Safety** [6,20]

- The prescribing information includes the following warnings:
  * Thrombotic events have been reported in association with C1-INH products when used off-label at high, repeated, doses.
  * C1-INH is made from human plasma and therapy may potentially transmit infectious agents.

- The most common adverse events reported with plasma-derived C1-INH (Cinryze) include headache, nausea, rash and vomiting.

- Plasma-derived C1-INH replacement therapy has been used in Europe for over 30 years without evidence of drug interactions or immunogenicity. No cases of pathogen transmission have been reported. [15]

- The main difference between European and U.S. plasma-derived C1-INH products is the requirement that U.S. C1-INH be manufactured with only U.S. donors. There is also an added step in the manufacturing process, called nanofiltration, to increase safety of the product. U.S. plasma-derived C1-INH, manufactured in Holland, does not contain added hepatitis B immunoglobulin.
# Appendix 1: Oral Prophylactic Medications for Hereditary Angioedema [1,2,9]

## Long-Term Prophylaxis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual Adult Dose</th>
<th>Dosage Range</th>
<th>FDA Approved for HAE</th>
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</thead>
<tbody>
<tr>
<td>danazol (Danocrine®)</td>
<td>200 mg/day</td>
<td>100 mg every 3 days – 600 mg/day</td>
<td>Yes</td>
</tr>
<tr>
<td>stanozolol (Winstrol®)</td>
<td>2 mg/day</td>
<td>1 mg every 3 days – 6 mg/day</td>
<td>Yes</td>
</tr>
<tr>
<td>oxandrolone (Oxandrin®)</td>
<td>10 mg/day</td>
<td>2.5 mg every 3 days – 20 mg/day</td>
<td>No</td>
</tr>
<tr>
<td>epsilonaminocaproic acid (Amicar®)</td>
<td>2 g three times/day</td>
<td>1 g twice/day – 4 g three times/day</td>
<td>No</td>
</tr>
<tr>
<td>tranexamic acid (Lysteda®)</td>
<td>20-50 mg/kg/day</td>
<td>3-6 g/day maximum</td>
<td>No</td>
</tr>
</tbody>
</table>

## Short-Term Prophylaxis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
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</thead>
<tbody>
<tr>
<td>danazol (Danocrine®)</td>
<td>2.5 to 10 mg/kg/day, with a maximum of 600 mg/day</td>
</tr>
<tr>
<td>stanozolol (Winstrol®)</td>
<td>2-6 mg/day</td>
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</tbody>
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## Cross References

- Compounded Medications, Medication Policy Manual, Policy No. 135
- Firazyr®, icatibant, Medication Policy Manual, Policy No. 256
- RuconestTM, recombinant human C1 inhibitor, Medication Policy Manual, Policy No. 373
- Berinert®, plasma-derived C1 inhibitor, Medication Policy Manual, Policy No. 374
- Kalbitor®, ecallantide, Medication Policy Manual, Policy No. 375

## Codes

<table>
<thead>
<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
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<tbody>
<tr>
<td>HCPCS</td>
<td>J0598</td>
<td>Injection, C1 esterase inhibitor (human), 10 units</td>
</tr>
<tr>
<td>ICD-10</td>
<td>D84.1</td>
<td>Defects in the complement system</td>
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References

### Revision History

<table>
<thead>
<tr>
<th>Revision Date</th>
<th>Revision Summary</th>
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<tbody>
<tr>
<td>11/11/2016</td>
<td>Increased quantity limit to 10,000 dosage units (20 vials) every 30 days</td>
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<tr>
<td>12/11/2015</td>
<td>Addition of ICD-10 code</td>
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