

## Medical Policy



**Title: Hereditary Angioedema  
(Berinert, Cinryze, Firazyf, Kalbitor)**

**Prior Authorization Form:**

[http://www.bcbsks.com/CustomService/Forms/pdf/PriorAuth\\_Hereditary-Angioedema.pdf](http://www.bcbsks.com/CustomService/Forms/pdf/PriorAuth_Hereditary-Angioedema.pdf)

Prime Therapeutics will review Prior Authorization requests.

**For information concerning Prior Authorization Prescription Drugs:**

[http://www.bcbsks.com/CustomService/PrescriptionDrugs/prior\\_authorization.htm](http://www.bcbsks.com/CustomService/PrescriptionDrugs/prior_authorization.htm)

**Link to Drug List (Formulary):**

[http://www.bcbsks.com/CustomService/PrescriptionDrugs/drug\\_list.htm](http://www.bcbsks.com/CustomService/PrescriptionDrugs/drug_list.htm)

**Professional**

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**DESCRIPTION**

The intent of the Hereditary Angioedema (HAE) medical drug criteria is to ensure appropriate selection of patients for treatment according to product labeling and/or clinical studies and/or guidelines and according to dosing recommended in product labeling. The policy will consider these agents appropriate for patients with FDA labeled indication(s) or indications supported in clinical studies and/or clinical guidelines. Dosing will be limited to the FDA labeled or clinically supported dosage for the specific indication.

**Target Drugs**

**Berinert** (C1 Esterase Inhibitor [human])  
**Cinryze** (C1 Esterase Inhibitor [human])  
**Firazyr** (icatibant)  
**Kalbitor** (ecallantide)

**FDA Approved Indications and Dosage**

<b>Agents</b>	<b>FDA Labeled Indications<sup>1-4</sup></b>	<b>Dosing</b>
<b>Berinert</b> (C1 Esterase Inhibitor [human])	Treatment of acute abdominal, facial, or laryngeal attacks of hereditary angioedema (HAE) in adult and adolescent patients.  Safety and efficacy for prophylactic therapy have not been established.	20 International Units (IU) per kg body weight at 4 mL/minute by intravenous injection.  Patient may self-administer
<b>Cinryze</b> (C1 Esterase Inhibitor [human])	For routine prophylaxis against angioedema attacks in adolescent and adult patients with hereditary angioedema (HAE).	1,000 units of Cinryze can be administered every 3 or 4 days by intravenous injection for routine prophylaxis.  Patient may self-administer
<b>Firazyr</b> (icatibant)	Treatment of acute attacks of hereditary angioedema (HAE) in adults 18 years of age and older.	30 mg by subcutaneous injection in abdominal area. Additional doses may be given at least 6 hours apart up to a maximum of 3 doses in a 24 hour period.  Patient may self-administer
<b>Kalbitor</b> (ecallantide)	Treatment of acute attacks of angioedema (HAE) in patients 16 years of age and older	30 mg (3 mL) administered subcutaneously in three 10 mg (1 mL) injections. If the attack persists, an additional dose of 30 mg may be administered within a 24 hour period.  Must be administered by a health care provider.

**POLICY****Berinert, Firazyr, Kalbitor****Initial Criteria**

Berinert, Firazyr, or Kalbitor will be approved when the following are met:

1. The patient does not have any FDA labeled contraindications to therapy  
**AND**
2. ALL of the following:
  - a. The patient has a diagnosis of hereditary angioedema (HAE) which has been diagnosed with measurement of C1-INH antigenic level, C1-INH functional level, and C4 level  
**AND**
  - b. The requested agent will be used to treat HAE acute attacks  
**AND**
3. The dose is within the FDA labeled dose

**Length of Approval:** 12 months

**Renewal Criteria**

1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process  
**AND**
2. The patient has received benefit from use of the requested agent to treat HAE acute attacks  
**AND**
3. The patient does not have any FDA labeled contraindications to therapy  
**AND**
4. The dose is within the FDA labeled dose

**Length of Approval:** 12 months

**Cinryze****Initial Criteria**

Cinryze will be approved when the following are met:

1. The patient does not have any FDA labeled contraindications to therapy  
**AND**
2. ALL of the following:
  - a. The patient has a diagnosis of hereditary angioedema (HAE) which has been diagnosed with measurement of C1-INH antigenic level, C1-INH functional level, and C4 level  
**AND**
  - b. ONE of the following:
    - i. The requested agent will be used to treat HAE acute attacks  
**OR**
    - ii. The requested agent will be used for prophylaxis against HAE attacks  
**AND** the patient has tried danazol or has a documented intolerance, FDA labeled contraindication, or hypersensitivity to danazol  
**AND**
3. The patient has a history of at least 2 acute HAE attacks per month  
**AND**
4. The dose is within the FDA labeled or clinically supported dose

**Length of Approval:** 12 months

**Renewal Criteria**

1. The patient has been previously approved for therapy through Prime Therapeutics Medical Drug Review process  
**AND**
2. The patient has received benefit from use of the requested agent to prevent or treat HAE acute attacks  
**AND**
3. The patient has does not have any FDA labeled contraindications to therapy  
**AND**
4. The dose is within the FDA labeled dose

**Length of Approval:** 12 months

**Contraindications**

<b>Agent</b>	<b>Contraindications</b>
<b>Berinert</b> (C1 Esterase Inhibitor [human])	Patients with history of life-threatening hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations
<b>Cinryze</b> (C1 Esterase Inhibitor [human])	Patients with history of life-threatening hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations
<b>Firazyr</b> (icatibant)	None
<b>Kalbitor</b> (ecallantide)	Patients with known hypersensitivity to ecallantide

**Program Quantity Limits**

<b>Brand (generic)</b>	<b>Quantity Per Day Limit (or as noted)</b>
<b>Berinert</b> <sup>®</sup> (C1 Esterase Inhibitor [Human]) 500 units/ 10 mL	10,000 unit (20 vials)/30 days*
<b>Cinryze</b> <sup>®</sup> (C1 Esterase Inhibitor [Human]) 500 units/ 10 mL	10,000 unit (20 vials)/30 days*
<b>Firazyr</b> <sup>®</sup> (icatibant) 30 mg/3 mL syringe	12 syringes/30 days
<b>Kalbitor</b> <sup>®</sup> (ecallantide) 3 - 10 mg/mL single use vials	8 kits/30 days

**RATIONALE**

C1 esterase inhibitor (C1-INH) is a normal constituent of human plasma and belongs to the group of serine protease inhibitors. It has an important inhibiting potential on several of the major cascade systems of the human body, including the complement system, the intrinsic coagulation system, the fibrinolytic system, and the coagulation cascade. Regulation of these systems is performed through the formation of complexes between the proteinase and the inhibitor, resulting in inactivation of both and consumption of the C1-INH. C1-INH is the only known inhibitor for the subcomponent of the complement component 1 (C1r), C1s, coagulation factor XIIa, and kallikrein. Hereditary angioedema (HAE) patients have low levels of endogenous or functional C1-INH.

C1 esterase inhibitors [human] (Berinert, Cinryze) replace the missing or malfunctioning protein; they are thought to modulate vascular permeability by preventing the generation of bradykinin through the inactivation of plasma kallikrein and factor XIIa.<sup>1,2</sup>

Ecaltantide (Kalbitor) is a selective, reversible inhibitor of plasma kallikrein. It binds to plasma kallikrein and blocks its binding site, inhibiting the conversion of high molecular weight (HMW)

kininogen to bradykinin. By directly inhibiting plasma kallikrein, ecallantide reduces conversion of HMW kininogen to bradykinin and thereby treats symptoms during acute episodic attacks of HAE.<sup>4</sup>

Icatibant (Firazyr) is a competitive antagonist selective for the bradykinin B2 receptor, with an affinity similar to bradykinin. It inhibits bradykinin from binding the B2 receptor and thereby treats the clinical symptoms of an acute, episodic attack of HAE.<sup>3</sup>

### Safety

C1 esterase inhibitor [human] products (Berinert and Cinryze) are contraindicated in patients who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1-INH preparations. Serious hypersensitivity reactions, including anaphylaxis may occur. Epinephrine should be immediately available for treatment of acute hypersensitivity reactions. Thrombotic events have been reported following administration of C1-INH products when used off-label at higher than labeled doses.<sup>1,2</sup>

Anaphylaxis has been reported after administration of ecallantide (Kalbitor). The prescribing information contains a boxed warning for this, and it requires administration by a healthcare professional with appropriate medical support. Anaphylaxis occurred in 3.9% of treated patients in clinical trials.<sup>4</sup>

The most common adverse event(s) experienced with these agents are:

- C1 esterase inhibitor [human] (Berinert) - dysgeusia.<sup>1</sup>
- C1 esterase inhibitor [human] (Cinryze) - headache, nausea, rash, and vomiting.<sup>2</sup>
- Ecallantide (Kalbitor) - headache, nausea, pyrexia, injection site reactions, and nasopharyngitis.<sup>4</sup>
- Icatibant (Firazyr) - local injection site reactions (97%) and worsening of HAE symptoms.<sup>3</sup>

Given the potential for airway obstruction during acute laryngeal HAE attacks, patients should be advised to seek medical attention in an appropriate healthcare facility immediately in addition to treatment with Berinert, Firazyr, or Kalbitor.<sup>1,3,4</sup>

### Hereditary Angioedema (HAE)

Hereditary Angioedema (HAE) is an autosomal dominant disease caused by a deficiency of C1-INH. Deficiencies in the C1-INH allow unchecked activation of the classic complement pathway and other biochemical systems. HAE is characterized by recurrent episodes of nonpruritic, nonpitting, subcutaneous or submucosal edema that may involve the extremities, bowels, genitalia, trunk, face, tongue, or larynx.<sup>5,6</sup>

Symptoms begin in the first or second decade of life, worsen during puberty, and persist throughout life. Attacks may occur every 7-14 days on average in untreated individuals. Triggers for attacks may vary but can include minor trauma or stress, but episodes often occur without a defined precipitating factor. HAE attacks result in progressive swelling without erythema over the first 24 hours and then gradually subside during the following 48 to 72 hours. Death due to an acute attack of HAE is often the result of abdominal or laryngeal involvement. HAE occurs in approximately 1 in 50,000 persons, without known differences between ethnic groups.<sup>5,6</sup>

There are 3 types of HAE, caused by different genetic mutations:

- Type I is defined by low plasma levels of a normal C1-INH protein (85% of patients).

- Type II HAE is characterized by the presence of normal or elevated levels of a dysfunctional C1-INH (15% of patients).
- Type III HAE has been recently identified as an estrogen-dependent inherited form of angioedema occurring mainly in women with normal functional and quantitative levels of C1-INH. (C1-INH products are ineffective as treatment.)<sup>5,6</sup>

Diagnosis of Type I or Type II HAE requires evidence of a low C1-INH antigenic or functional level, as well as decreased C4 levels and generally normal C1q levels.<sup>9</sup> The World Allergy Organization (WAO) and an international consensus (2012) recommend that assessments of blood levels of C4, C1-INH protein, and C1-INH function should be done to make the diagnosis of HAE. Testing in children may not be reliable before the age of 12 months; screening of children should be deferred until the age of 12 months.<sup>8,10</sup>

Prior to C1-INHs, icatibant, and ecallantide, treatment of acute attacks involved fresh frozen plasma and fluid/ventilation support. Danazol and other 17 alpha-alkylated androgens have been used for long term prophylaxis with success, and are still recommended for use.<sup>5</sup> Androgens have undesirable side effects including liver toxicity and limited use in pregnancy. Outside of the United States epsilon aminocaproic acid (EACA) and tranexamic acid (TA) are approved as chronic long-term therapy in HAE, but these are not thought to be effective in acute attacks.<sup>5,6</sup>

### Guidelines

Consensus guidelines from HAE International Working Group<sup>7</sup> recommend:

- HAE attacks: with a high level of evidence that all patients have access to at least one of the plasma-derived and recombinant C1-INHs, icatibant, and ecallantide. They also recommend that patients should have on-demand medicine to treat acute attacks at home and should be trained to self-administer when possible and supported by product labeling.
- HAE Prophylaxis: long-term prophylactic treatment is appropriate for patients in whom acute treatment is inadequate, but no consensus was reached on a definition of inadequate acute treatment. A suggestion from a substantial minority was to use an objective measure of more than 12 severe attacks per year or more than 24 days per year with symptoms. Clinical studies for the only FDA approved agent used for prophylaxis required patients to have at least 2 acute HAE attacks per month.<sup>2</sup> This group also confirmed efficacy of 17-alpha-alkylated androgens and C1-INH for prophylaxis.

A focused parameter update<sup>9</sup> developed by a joint task force representing the American Academy of Allergy, Asthma & Immunology (AAAAI), the American College of Allergy, Asthma & Immunology (ACAAI), and the Joint Council of Allergy, Asthma and Immunology supports:

- HAE attacks: symptomatic treatment, efficacy of fresh frozen plasma often, and safety and efficacy of C1-INHs, plasma kallikrein inhibitor, or bradykinin B2 receptor antagonist.
- HAE Prophylaxis: anabolic androgens as effective and relatively safe; antifibrinolytic agents as somewhat effective and relatively safe but generically less effective than androgens; and C1-INH as safe and effective.

World Allergy Organization (WAO) guidelines<sup>8</sup> recommend:

- HAE attacks: treat attacks as early as possible; treat attacks with C1-INH, ecallantide, or icatibant, or solvent detergent-treated plasma if these drugs are not available. It is also recommended that patients have available on-demand treatment for 2 attacks.

- HAE long-term prophylaxis: should be considered in all severely symptomatic HAE I or HAE II 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 appropriate on-demand therapy; C1-INH or androgens can be used and the decision to use one or the other depends on contraindications, adverse events/risk of adverse events, tolerance, response, dose required.

An international consensus from AAAAI, ACAAI, WAO, and the European Association of Allergy and Clinical Immunology recommend the following:<sup>10</sup>

- HAE attacks: C1-INH, ecallantide, and icatibant are all efficacious and safe; fresh frozen plasma should be used when no other treatments are available.
- HAE prophylaxis: patients not treated successfully with on-demand therapy should be considered for long-term prophylaxis. C1-INH is effective; 17 alpha-alkylated androgens may decrease frequency and severity of HAE attacks but have potential adverse effects if used long term; antifibrinolytic agents have been used but are less effective.

### **Pediatrics**

Recommendations for treatment of pediatric patients are found in the WAO guidelines:<sup>8</sup>

- HAE attacks: C1-INH is the preferred on-demand therapy for HAE I/HAE II attacks in children. Solvent detergent-treated plasma is preferred over fresh frozen plasma but either can be used as second-line therapy if C1-INH is not available. Ecallantide and icatibant are not licensed for use in children and experience with these drugs in this patient population is very limited.
- HAE prophylaxis: The majority of children do not require long-term prophylaxis and on-demand therapy of attacks is preferable.

Consensus guidelines from the European<sup>15</sup> recommend either a "wait and see" strategy, depending on location and intensity of attacks, or the use of C1-INH for treatment or prophylaxis of attacks. They note that only Cinryze is actually approved for prophylaxis and ecallantide and icatibant (as well as recombinant C1-INH concentrate which is not available in the United States) are not approved for children and adolescents in Europe; studies in these age groups are required.<sup>15</sup>

Lumry et al.<sup>12</sup> conducted a post-hoc analysis of the pediatric participants (those <18 years of age) in the studies of Zuraw<sup>11</sup> and open-label extensions following these studies.<sup>13,14</sup> There were 46 children and adolescents ranging in age from 2 to 17 years included, with a total of 2237 C1-INH infusions, including 49 infusions in 3 patients aged 2-5 years, 1056 infusions in 17 patients aged 6-11 years, and 1132 infusions in 26 patients aged 12-17 years. Results from the placebo-controlled, acute-attack treatment study show that 71% of children who received C1-INH for treatment of an acute attack achieve unequivocal relief within 4 hours, which was consistent with the rate observed in the study population as a whole (60%). Similar results were observed in the placebo-controlled prophylaxis study; the average number of attacks during the 12-week treatment period for children (7.0 for C1-INH and 13.0 for placebo) was consistent with those for the study population as a whole (6.26 for C1-INH and 12.73 for placebo). C1-INH function and antigen levels after treatment of children were consistent with those observed for the overall study populations that included adults. Neither weight nor age appeared to affect clinical response. C1-INH was well tolerated; many adverse events reported in children were associated



with common childhood infections, including pharyngitis, sinusitis, and other upper respiratory tract infections.<sup>12</sup>

Pivotal clinical trial data for each of the products can be accessed in the prescribing information.<sup>1-4</sup>

For the purposes of the criteria, indications deemed appropriate are those that are supported by at least two compendia where one of the compendia is DrugDex with a level of evidence of 2B and strength of recommendation of B or supported in guidelines with a high level of evidence recommendation.

### **Cinryze (C1 esterase inhibitor [human]) for HAE acute attack**

In a randomized, double-blind, placebo-controlled trial (n=68), treatment with nanofiltered C1 inhibitor concentrate (Cinryze) led to significantly faster relief from attack compared with placebo in patients with hereditary angioedema. Patients aged 6 years and older with hereditary angioedema due to C1 inhibitor deficiency (low C4 level, normal C1q level, and a low antigenic or functional C1 inhibitor level or a mutation in the C1 inhibitor gene which causes hereditary angioedema) who presented to the study site within 4 hours of a moderate or severe acute attack involving the abdomen, face, or external genitalia were eligible for study enrollment. Patients presenting with laryngeal angioedema were not enrolled in the study and were treated with open-label C1 inhibitor concentrate. Eligible patients were randomized to receive C1 inhibitor concentrate 1000 units in 10 mL of sterile water (n=35) or 10 mL of saline (placebo; n=33) given as an IV push over 10 minutes (min). A second dose of study medication (permitted if symptoms were not absent or better after 60 min) was given in 23 patients in the C1 inhibitor concentrate arm and 28 patients in the placebo arm and all patients in the placebo arm who did not have significant symptom improvement after 4 hours received open-label C1 inhibitor concentrate. At baseline, 16 patients (45.7%) in the C1 inhibitor concentrate arm and 11 patients (33.3%) in the placebo arm were receiving androgen therapy. The estimated median time to onset of unequivocal relief (primary endpoint) was 2 hours in the C1 inhibitor concentrate arm and longer than 4 hours in the placebo arm (estimated success rate ratio, 2.41; 95% CI, 1.17 to 4.95; p=0.02); additionally, the onset of unequivocal relief was achieved within 4 hours in 21 (60%) and 14 (42%) patients in each study arm, respectively (p=0.06). The median time to complete symptom resolution was 12.3 hours in the C1 inhibitor concentrate arm and 25 hours in the placebo arm (p =0.004). Antigenic and function C1 inhibitor levels significantly increased in the C1 inhibitor concentrate arm compared with the placebo arm (p <0.001); however, C4 levels were not significantly different between the 2 study arms during the first 4 hours.<sup>11</sup>

Following treatment with nanofiltered C1 inhibitor concentrate (Cinryze) for an acute attack, the median time to response was 30 min in 82 patients with hereditary angioedema (median number of attacks per patient, 3; range, 1 to 57 attacks) in an open-label extension trial (median follow-up of 11 months). Additionally, 93% of attacks responded within 4 hours after C1 inhibitor concentrate treatment.<sup>11</sup>

**CODING**

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

**HCPCS**

J0597	Injection, C-1 esterase inhibitor (human), Berinert, 10 units (Berinert 500 units/vial)
J0598	Injection, C-1 esterase inhibitor (human), Cinryze, 10 units (Cinryze 500 units/vial)
J1290	Injection, ecallantide, 1 mg (Kalbitor 10 mcg/ 1 mL vial (3 vials/carton))
J1744	Injection, icatibant, 1 mg (Firazyr 30 mg/3 mL syringe, Firazyr 30 mg/3 mL syringe [pack of 3 syringes])

**REVISIONS**

04-01-2014	Policy added to the bcbsks.com web site on 02-28-2014 for an effective date of 04-01-2014.
04-24-2014	Link to Prior Authorization form added.

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