I. Aetna considers Cinryze, a human C1 esterase inhibitor, medically necessary for prophylaxis against angioedema attacks in adolescents and adults with hereditary angioedema (HAE) when the following criteria are met:

- Member has a history of at least 1 HAE attack per month; and
- Diagnosis* of HAE is documented based on evidence of a low C4 level (C4 less than 14 mg/dL; normal range 14 to 40 mg/dL, or C4 below the lower limit of normal as defined by the laboratory performing the test) plus:
  - (a) A low C1 inhibitor (C1INH) antigenic level (C1INH less than 19 mg/dL; normal range 19 to 37 mg/dL, or C1INH antigenic level below the lower limit of normal as defined by the laboratory performing the test); or
  - (b) A normal C1INH antigenic level (C1INH greater than or equal to 19 mg/dL) and a low C1INH functional level (functional C1INH less than 50 % or C1INH functional level below the lower limit of normal as defined by the laboratory performing the test); or
  - (c) A known HAE-causing C1INH mutation; and
- Medications known to cause angioedema (i.e. ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate; and
- Member has tried and failed or is intolerant to or has a contraindication to 17 alpha-alkylated androgens (e.g., danazol and stanozolol) or anti-fibrinolytic agents (e.g.,aminocaproic acid (Amikar), tranexamic acid (Cyklokapron)) for HAE prophylaxis.

Aetna considers Cinryze experimental and investigational for the treatment of acute angioedema attacks, cerebral ischemic injury, cytokine-induced vascular leak syndrome, myocardial infarction, sepsis, and all other indications because its effectiveness for these indications has not been established.

II. Aetna considers Berinert (human C1 esterase inhibitor) medically necessary for treatment of adolescents (13 years of age or older) and adults with acute abdominal, facial, or laryngeal attacks associated with HAE when the following criteria are met:
Member must have a diagnosis of HAE, where diagnosis is based on evidence of a low C4 level (C4 less than 14 mg/dL; normal range 14 to 40 mg/dL, or C4 below the lower limit of normal as defined by the laboratory performing the test) plus:

(a) A low C1 inhibitor (C1INH) antigenic level (C1INH less than 19 mg/dL; normal range 19 to 37 mg/dL, or C1INH antigenic level below the lower limit of normal as defined by the laboratory performing the test); or

(b) A normal C1INH antigenic level (C1INH greater than or equal to 19 mg/dL) and a low C1INH functional level (functional C1INH less than 50 %, or

(c) Below the lower limit of normal as defined by the laboratory performing the test); and

Member should be educated to use when experiencing at least 1 symptom of the moderate or severe attack (e.g., airway swelling, severe abdominal pain, facial swelling, laryngeal swelling, nausea and vomiting, painful facial distortion); and Medications known to cause angioedema (i.e. ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate.

Aetna considers Berinert (human C1 esterase inhibitor) medically necessary for the treatment of adolescents (13 years of age or older) and adults with acute abdominal, facial, or laryngeal attacks associated with hereditary angioedema in persons with HAE with normal C1INH deficiency (formerly type III HAE) who meet all of the following diagnostic criteria for this condition:

A history of recurrent angioedema in the absence of concomitant hives or concomitant use of a medication known to cause angioedema; and

Documented normal or near normal C4, C1INH antigen, and C1INH function; and

One of the following:

- Demonstration of a F12 mutation that is associated with the disease; or
- A positive family history of angioedema and documented evidence of lack of efficacy of chronic high-dose antihistamine therapy (cetirizine at 40 mg/day or the equivalent, for at least 1 month and an interval expected to be associated with three or more attacks of angioedema); and

Member should be educated to use when experiencing at least 1 symptom of the moderate or severe attack (e.g., airway swelling, severe abdominal pain, facial swelling, laryngeal swelling, nausea and vomiting, painful facial distortion); and Medications known to cause angioedema (i.e. ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate.

Aetna considers Berinert experimental and investigational for prophylaxis against angioedema attacks, for use in combination with Kalbitor or Firazyr or Ruconest, and for other indications because its effectiveness for these indications has not been established.

III. Aetna considers Kalbitor (ecallantide) medically necessary for the treatment of acute attacks of HAE in persons 12 years of age and older when the following criteria are met:
Member must have a diagnosis* of HAE, where diagnosis is based on evidence of a low C4 level (C4 less than 14 mg/dL; normal range 14 to 40 mg/dL, or C4 below the lower limit of normal as defined by the laboratory performing the test) plus:
(a) A low C1 inhibitor (C1INH) antigenic level (C1INH less than 19 mg/dL; normal range 19 to 37 mg/dL, or C1INH antigenic level below the lower limit of normal as defined by the laboratory performing the test); or
(b) A normal C1INH antigenic level (C1INH greater than or equal to 19 mg/dL) and a low C1INH functional level (functional C1INH less than 50 %, or
(c) Below the lower limit of normal as defined by the laboratory performing the test); and

Member should be educated to use when experiencing at least 1 symptom of the moderate or severe attack (e.g., airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion); and Medications known to cause angioedema (i.e. ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate.

IV. Aetna considers Kalbitor (ecallantide) medically necessary for the treatment of persons 12 years of age and older with acute attacks of hereditary angioedema in persons with HAE with normal C1INH deficiency (formerly type III HAE) who meet all of the following diagnostic criteria for this condition:

A history of recurrent angioedema in the absence of concomitant hives or concomitant use of a medication known to cause angioedema; and
Documented normal or near normal C4, C1INH antigen, and C1INH function; and
One of the following:

Demonstration of a F12 mutation that is associated with the disease; or
A positive family history of angioedema and documented evidence of lack of efficacy of chronic high-dose antihistamine therapy (cetirizine at 40 mg/day or the equivalent, for at least 1 month and an interval expected to be associated with three or more attacks of angioedema); and

Member should be educated to use when experiencing at least 1 symptom of the moderate or severe attack (e.g., airway swelling, severe abdominal pain, facial swelling, laryngeal swelling, nausea and vomiting, painful facial distortion); and Medications known to cause angioedema (i.e. ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate.

V. Aetna considers Kalbitor experimental and investigational for all other indications (e.g., reduction of blood loss during surgery), use in combination with Berinert or Firazyr or Ruconest) because its effectiveness for these indications has not been established.

VI. Aetna considers Ruconest (recombinant C1 esterase inhibitor) medically necessary for the treatment of acute attacks of HAE in persons 12 years of age and older
when the following criteria are met:

Member must have a diagnosis* of HAE, where diagnosis is based on evidence of a low C4 level (C4 less than 14 mg/dL; normal range 14 to 40 mg/dL, or C4 below the lower limit of normal as defined by the laboratory performing the test) plus:

(a) A low C1 inhibitor (C1INH) antigenic level (C1INH less than 19 mg/dL; normal range 19 to 37 mg/dL, or C1INH antigenic level below the lower limit of normal as defined by the laboratory performing the test); or

(b) A normal C1INH antigenic level (C1INH greater than or equal to 19 mg/dL) and a low C1INH functional level (functional C1INH less than 50 %, or

(c) Below the lower limit of normal as defined by the laboratory performing the test); and

Member must be experiencing at least 1 symptom of the moderate or severe attack (e.g., airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion); and

Medications known to cause angioedema (i.e. ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate.

VII. Aetna considers Ruconest (recombinant C1 esterase inhibitor) medically necessary for the treatment of persons 12 years of age or older with attacks associated with hereditary angioedema in persons with HAE with normal C1INH deficiency (formerly type III HAE) who meet all of the following diagnostic criteria for this condition:

A history of recurrent angioedema in the absence of concomitant hives or concomitant use of a medication known to cause angioedema; and

Documented normal or near normal C4, C1INH antigen, and C1INH function; and

One of the following:

Demonstration of a F12 mutation that is associated with the disease; or

A positive family history of angioedema and documented evidence of lack of efficacy of chronic high-dose antihistamine therapy (cetirizine at 40 mg/day or the equivalent, for at least 1 month and an interval expected to be associated with three or more attacks of angioedema); and

Member must be experiencing at least 1 symptom of the moderate or severe attack (e.g., airway swelling, severe abdominal pain, facial swelling, laryngeal swelling, nausea and vomiting, painful facial distortion); and

Medications known to cause angioedema (i.e. ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate.

Aetna considers Ruconest experimental and investigational for use in combination with Berinert, Kalbitor or Firazyr and all other indications because its effectiveness for these indications has not been established.
VIII. Aetna considers Firazyr (icatibant) injection medically necessary for the treatment of acute attacks of angioedema induced from angiotensin-converting enzyme (ACE) inhibitors.

IX. Aetna considers Firazyr (icatibant) injection medically necessary for the treatment of acute attacks of HAE in people aged 18 years and older when the following criteria are met:

Member must have a diagnosis* of HAE, where diagnosis is based on evidence of a low C4 level (C4 less than 14 mg/dL; normal range 14 to 40 mg/dL, or C4 below the lower limit of normal as defined by the laboratory performing the test) plus:

(a) A low C1 inhibitor (C1NH) antigenic level (C1NH less than 19 mg/dL; normal range 19 to 37 mg/dL, or C1NH antigenic level below the lower limit of normal as defined by the laboratory performing the test); or
(b) A normal C1NH antigenic level (C1NH greater than or equal to 19 mg/dL) and a low C1NH functional level (functional C1NH less than 50 %, or
(c) Below the lower limit of normal as defined by the laboratory performing the test); and

Member must be experiencing at least 1 symptom of the moderate or severe attack (e.g., airway swelling, severe abdominal pain, facial swelling, nausea and vomiting, painful facial distortion); and

Medications known to cause angioedema (i.e. ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate.

X. Aetna considers Firazyr (icabitant) medically necessary for the treatment of persons 18 years of age or older with attacks associated with hereditary angioedema in persons with HAE with normal C1INH deficiency (formerly type III HAE) who meet all of the following diagnostic criteria for this condition:

A history of recurrent angioedema in the absence of concomitant hives or concomitant use of a medication known to cause angioedema; and

Documented normal or near normal C4, C1INH antigen, and C1INH function; and

One of the following:

Demonstration of a F12 mutation that is associated with the disease; or

A positive family history of angioedema and documented evidence of lack of efficacy of chronic high-dose antihistamine therapy (cetirizine at 40 mg/day or the equivalent, for at least 1 month and an interval expected to be associated with three or more attacks of angioedema); and

Member must be experiencing at least 1 symptom of the moderate or severe attack (e.g., airway swelling, severe abdominal pain, facial swelling, laryngeal swelling, nausea and vomiting, painful facial distortion); and

Medications known to cause angioedema (i.e. ACE-Inhibitors, estrogens, angiotensin II receptor blockers) have been evaluated and discontinued when appropriate.
Aetna considers Firazyr experimental and investigational for prophylaxis against angioedema attacks and other indications (e.g., acute pancreatitis, airways disease, thermal injury, use in combination with Berinert or Kalbitor or Ruconest, and refractory ascites in persons with liver cirrhosis) because its effectiveness for these indications has not been established.

*Note:* According to an International Consensus Statement on Hereditary Angioedema (Bowen, et al., 2010), testing must be performed more than once to confirm the diagnosis.

**Background**

Hereditary angioedema (HAE) is a rare, severely debilitating, potentially life-threatening disorder caused by a deficiency of C1 inhibitor (C1-INH). The prevalence of HAE is unclear but is estimated to be about 1 in 50,000, without known differences among ethnic groups. This condition is the result of autosomal dominant inheritance affecting the synthesis of C1-INH, which is a normal constituent of human blood and is one of the serine proteinase inhibitors (serpins). The primary function of C1-INH is to regulate the activation of the complement and intrinsic coagulation (contact system) pathway. In addition, C1-INH also regulates the fibrinolytic system. In patients with HAE, C1-INH is low or does not function properly. These individuals experience recurrent attacks of inflammation affecting the abdomen, extremities, face, as well as laryngeal and urogenital tracts; they experience about 20 to 100 days of incapacitation per year. These attacks, which affect an estimated 10,000 people in the United States, are often unpredictable and may be spontaneous or precipitated by trauma or psychological stress. Estrogen has also been reported to exacerbate attacks. In general, HAE attacks occur within a 24-hour period and then subside with 48 to 72 hours (Agostoni et al, 2004; Frank 2008; Zuraw, 2008).

There are 2 principal types of HAE: (i) type I, which accounts for 85 % of cases and is characterized by low levels and reduced functional tests of C1-INH, both of which usually range from 0 % to 30 % of normal. These abnormalities result from deficient amounts of normally-functioning inhibitor, and (ii) type II, which accounts for 15 % of cases and is characterized by reduced functional tests of C1-INH in the presence of normal or elevated C1-INH protein levels. This is explained by a dysfunctional inhibitor, which is present in normal or elevated amounts. Most patients have decreased plasma complement protein C4 levels. The 2 types of HAE are indistinguishable in clinical presentation but are caused by different mutations. Diagnosis is confirmed by decreased serum levels of C4 and absence or marked decrease of the level or function of C1-INH (Gompels et al, 2005; Atkinson et al, 2008).

Based on an European workshop in 2004, diagnostic criteria for C1-INH disorders were proposed. The diagnosis of HAE is established in patients with 1 clinical criterion and 1 laboratory criterion (Agostoni et al, 2004; Atkinson et al, 2008):

**Clinical criteria:**

- Recurrent laryngeal edema.
- Self-limiting, non-inflammatory subcutaneous angioedema without urticaria, recurrent, and lasting more than 12 hours.
- Self-remitting abdominal pain without clear organic etiology, recurrent, and lasting more than 6 hours.
A family history of recurrent angioedema and/or abdominal pain and/or laryngeal edema, if present, supports the diagnosis of HAE, although it is not required because the patient may have a new mutation or an acquired disorder.

Laboratory criteria:

C1-INH levels less than 50 % of the lower limit of normal at 2 separate determinations (at least 1 month apart) with the patient in their basal condition and after the first year of life.
C1-INH function of less than 50 % of normal at 2 separate determinations (at least 1 month apart) with the patient in their basal condition and after the first year of life.
Mutation in C1-INH gene altering protein synthesis and/or function. This is the only laboratory criterion that can be used to make the diagnosis in patients younger than 1 year of age.

The criteria stipulate that C1-INH antigenic/functional levels must be below 50 %. In most cases of type I HAE, the levels are below 30 %, although some patients have levels slightly higher (between 30 % and 50 %) and patients with acquired forms can have levels between 30 % and 50 % as well.

Gompels et al (2005) as well as Pedraz et al (2007) stated that diagnosis of HAE is confirmed by decreased serum levels of C4 and absence or marked decrease (less than 50 % of normal) of the level or function of C1-INH.

Management of patients with HAE entails treatment of acute attacks, short-term prophylaxis to prevent an attack, and long-term prophylaxis to minimize the frequency and severity of recurrent attacks. Commonly employed drugs for prophylaxis and treatment of these patients include 17 alpha-alkylated androgens (e.g., danazol and stanozolol), antifibrinolytic agents (e.g., epsilon aminocaproic acid tranexamic acid), and infusion of C1-INH concentrate. Moreover, fresh frozen plasma is also an option to be considered for short-term prophylaxis or treatment of acute attacks (Széplaki et al, 2005; Pedraz et al, 2007; Frank 2008; Zuraw, 2008; Epstein and Bernstein, 2008; Temiño and Peebles, 2008).

A consensus panel on hereditary angioedema with normal C1INH (HAE type III) (Zuraw, et al., 2012) found that there have been no randomized or controlled clinical trials of therapy for HAE with normal C1INH. Angioedema attacks in patients with HAE with normal C1INH do not respond to either corticosteroids or antihistamines, even at high doses. Prophylactic use of 17-alkylated androgens, the antifibrinolytic drug tranexamic acid, or progestins have shown promising results in some but not all patients. The consensus panel stated that there is relatively little experience regarding the efficacy of on-demand C1INH, icatibant, or ecallantide in HAE with normal C1INH; however, anecdotal reports suggest that each of these agents may be beneficial. The consensus panel concluded that, until data from randomized controlled studies become available, no firm recommendations regarding the treatment of HAE with normal C1INH can be made

Cinryze

Epstein and Bernstein (2008) stated that currently only Cinryze, a C1-esterase inhibitor product derived from human plasma, has been approved for prophylactic use against HAE attacks in the United States. In clinical trials, Cinryze was effective in preventing or reducing the frequency of attacks in most but not all HAE patients. Moreover, the approval by the Food and Drug Administration (FDA) for other novel agents to treat HAE and for the use of Cinryze in the treatment of acute attacks is pending.
The FDA's approval of Cinryze was based on the results of a phase III clinical trial that examined the safety and effectiveness of Cinryze prophylaxis therapy to reduce the incidence, severity, and duration of HAE attacks. Patients were screened to confirm a diagnosis of HAE and a history of at least 2 HAE attacks per month. A total of 24 patients (mean age of 38.1 years with a range of 9 to 73) were randomized to one of two treatment groups: (i) Cinryze prophylaxis for 12 weeks followed by 12 weeks of placebo prophylaxis; or (ii) placebo prophylaxis for 12 weeks followed by 12 weeks of Cinryze prophylaxis. Two subjects dropped out (1 in each arm); 22 patients crossed-over into period 2 and were included in the effectiveness analysis. Patients were given blinded injections (Cinryze or placebo) every 3 to 4 days, approximately 2 times per week. Patients recorded all angioedema symptoms daily. An attack was defined as the subject-reported indication of swelling at any location following a report of no swelling on the previous day. Subjects in the Cinryze-treated group had a 52% reduction in the number of HAE attacks compared to the placebo-treated group (6.1 versus 12.7; p < 0.0001). In addition, subjects in the Cinryze-treated group had a 66% reduction in days of swelling (10.1 versus 29.6 days; p < 0.0001), a 32% decrease in the average severity of attacks (1.3 versus 1.9 based on a scoring of 1 to 3; p = 0.0006), and a 38% reduction in the average duration of attacks (2.1 versus 3.4 days; p = 0.0023).

Currently, there are no submitted data on the safety profile of an intensified dose schedule of Cinryze for routine prophylaxis. The FDA has requested that post-marketing studies be performed to address the following issues: (i) the optimal dose for prophylaxis in males and females, (ii) immunogenicity, and (iii) long-term safety.

Caliezi et al (2000) noted that there is accumulating evidence, obtained from studies in animals as well as observations in patients, that administration of C1-INH may have a beneficial effect in clinical conditions such as sepsis, cytokine-induced vascular leak syndrome, myocardial infarction, or other diseases. In this regard, Wouters et al (2008) considered C1-INH an experimental therapy in diseases such as sepsis and myocardial infarction. Longhurst (2008) reported that a recombinant human C1-INH is also being investigated for the potential treatment of cerebral ischemic injury. The clinical value of C1-INH for these indications needs to be validated by well-designed studies. Zuraw (2008) also noted that more studies are needed to ascertain the value of prophylactic treatment as compared with on-demand treatment for acute HAE attacks as well as to evaluate the risks and benefits of allowing patients to use these new drugs at home to treat attacks at an early point in their course.

Craig and colleagues (2009) determined when newer agents, such as C1-INH, should be considered as prophylaxis to decrease HAE attacks as an alternative to androgens, which have significant adverse events. A literature review (PubMed, Google, and Ovid), guideline review, expert panel meeting, and group discussion were performed to decide when prophylaxis is indicated. The retrieved studies demonstrate that C1-INH is effective and that the half-life makes it attractive for prophylactic use. The short half-lives of ecallantide, icatibant, and recombinant human C1-INH limit their use as prophylactic agents. Patients with severe anxiety, more than 1 attack per month, rapid progression of attacks, limited access to health care, more than 10 days lost from work or school per year, previous laryngeal swelling, more than 3 emergency department visits per year, more than 1 hospitalization per year, previous intubation, previous intensive care unit care, significant compromise in quality of life, or narcotic dependency should be considered for androgen or C1-INH prophylaxis therapy. The authors concluded that patients with HAE with frequent attacks, severe attacks, past laryngeal attacks, excessive loss of work or school, significant anxiety, and poor quality of life should be considered for C1-INH prophylaxis, especially those who fail, are intolerant of, have adverse reactions to, or are not candidates for androgen therapy.
Bygum and associates (2009) assessed the impact of self-administered home therapy with intravenous C1-INH concentrate on quality of life (QOL) in patients with HAE. A total of 9 patients experiencing frequent or severe debilitating HAE attacks were offered self-administration of C1-INH concentrate. Quality of life was evaluated before and after home therapy using the Dermatology Life Quality Index (DLQI) and 36-item Short Form Survey (SF-36) questionnaires. Seven patients were recruited into the study. Quality of life was assessed at baseline and after 3 to 48 months of home therapy. The mean DLQI score fell from 12.6 +/- 4.65 to 2.7 +/- 1.38 (p < 0.001). Mean SF-36 scores for the individual and combined components also improved significantly. No serious complications were documented during a follow-up period of 27 to 72 months. The authors concluded that self-administration of C1-INH improved QOL on both physical and psychological parameters. Patients were able to resume a normal life without restrictions caused by the condition.

The adverse event profile of Cinryze is similar to that of placebo. The most common side effects observed have been headache, rash, sinusitis, and upper respiratory infection. No drug-related serious adverse events, no immunogenicity and no decrease in efficacy have been observed in clinical trials. Severe hypersensitivity reactions may occur. Thrombotic events have occurred in patients receiving high dose off-label C1-INH therapy well above the approved treatment dosage regimen. With any blood or plasma derived product, there may be a risk of transmission of infectious agents (e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent). The risk has been reduced by screening patients for prior exposure to certain virus infections and by manufacturing steps to reduce the risk of viral transmission including pasteurization and nanofiltration.

Cinryze is for intravenous use only. Cinryze is administered at an injection rate of 1 ml/min for 10 mins.

According to the FDA-approved labeling for Cinryze, the recommended dose for HAE prophylaxis is 1,000 units (two 8-ml vials) every 3 or 4 days. Thus, a maximum of 10,000 units are considered medically necessary per 30 days for HAE prophylaxis.

Berinert

On October 9, 2009, the FDA approved Berinert (a human C1 esterase inhibitor) for the treatment of adults and adolescents with acute attacks associated with HAE. The agent has been approved in Europe for about 20 years for prophylaxis as well as for treatment of acute attacks.

Berinert for the treatment of acute abdominal or facial attacks in patients with HAE was examined in a prospective, multi-national, randomized, double-blind, placebo-controlled, parallel-group, dose-finding, 3-arm, clinical study -- referred to as the randomized clinical trial (RCT). The RCT evaluated the safety and effectiveness of Berinert in 124 adult and pediatric subjects with C1 esterase inhibitor deficiency who were experiencing an acute moderate-to-severe attack of abdominal or facial HAE. Patients ranged in age from 6 to 72 years of age; 67.7 % were female and 32.3 % were male; and approximately 90 % were Caucasian. The aims of the study were to assess if Berinert shortens the time to onset of relief of symptoms of an abdominal or facial attack compared to placebo and to compare the effectiveness of 2 different doses of Berinert. The time to onset of relief of symptoms was determined by the patient’s response to a standard question posed at appropriate time intervals for as long as 24 hrs after start of treatment taking into account all single HAE symptoms. In addition, the severity of the single HAE symptoms were assessed over time. Subjects were randomized to receive a single 10 unit/kg body weight dose of Berinert (n = 39), a single 20 unit/kg dose of Berinert (n = 43), or a single dose of
placebo (n = 42) by slow intravenous infusion (recommended to be given at a rate of approximately 4 ml/min) within 5 hrs of an attack. At least 70 % of the patients in each treatment group were required to be experiencing an abdominal attack. If a patient experienced no relief or insufficient relief of symptoms by 4 hrs after infusion, investigators had the option to administer a second infusion of Berinert (20 units/kg for the placebo group, 10 units/kg for the 10 units/kg group), or placebo (for the 20 units/kg group). This masked (blinded) “rescue study medication” was administered to subjects and they were then followed until complete resolution of symptoms was achieved. Adverse events were collected for up to 7 to 9 days following the initial administration of Berinert or placebo. In the rare case that a subject developed life-threatening laryngeal edema after inclusion into the study, immediate start of open-label treatment with a 20 unit/kg body weight dose of Berinert was allowed.

All patients who received confounding medication (rescue medication) before symptom relief were regarded as “non-responders”. Thus, time to onset of symptom relief was set at 24 hrs if a subject received any rescue medication (i.e., rescue study medication, narcotic analgesics, non-narcotic analgesics, anti-emetics, open-label C1esterase inhibitor, or fresh frozen plasma) between 5 hrs before administration of blinded study medication until time to onset of relief.

Patients treated with 20 units/kg body weight of Berinert experienced a significant reduction (p = 0.0016) in time to onset of relief from symptoms of an HAE attack as compared to placebo (median of 50 mins for Berinert 20 units/kg body weight, as compared to greater than 4 hrs for placebo). The time to onset of relief from symptoms of an HAE attack for subjects in the 10 unit/kg dose of Berinert was not statistically significantly different from that of subjects in the placebo group.

According to the FDA-approved labeling, the recommended dose of Berinert is 20 units per kg body weight by intravenous injection.

Berinert is contraindicated in individuals who have had life-threatening hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations. The most serious adverse reaction reported in clinical studies was an increase in the severity of pain associated with HAE. The most common adverse reactions include subsequent HAE attack, headache, abdominal pain, nausea, muscle spasms, pain, diarrhea and vomiting. Berinert is administered by intravenous infusion.

In December 2011, the FDA has expanded the label of Berinert (C1 esterase inhibitor [human]) to permit self-treatment of HAE during acute attacks. With appropriate training from a physician, patients can now self-administer Berinert by intravenous infusion at the first sign of an HAE attack, potentially averting more severe symptoms. Already indicated for acute abdominal and facial attacks of this rare but serious genetic disorder, Berinert, as part of the label expansion, has now also been approved for use in laryngeal attacks.

Kalbitor

Schneider et al (2007) stated that ecallantide, a kallikrein inhibitor, is a promising new therapy for HAE attacks. In a double-blind, placebo-controlled, ascending-dose study, these investigators examined the efficacy and tolerability of ecallantide (5, 10, 20, or 40 mg/m(2) intravenously) in individuals experiencing acute HAE attacks (n = 49). Twelve patients were assigned to each dose level: 10 to ecallantide and 2 to placebo, per cohort. Ecallantide treatment improved the symptoms of HAE attacks: 72.5 % (29/40) of patients treated with ecallantide versus 25.0 % (2/8) of placebo patients reported significant improvement in symptoms within 4 hours (p = 0.0169). Ecallantide was well-tolerated at all doses. The authors concluded that ecallantide significantly improved HAE symptoms.
over placebo. The trial provides strong support for the role of the kallikrein-kinin cascade and its end product, bradykinin, in the pathophysiology of HAE. Lehmann (2008) noted that ecallantide is a recombinantly produced and engineered small protein based on the first Kunitz domain of human tissue factor pathway inhibitor. The author stated that the drug is being studied for 2 major indications: (i) treatment of HAE, and (ii) reduction of blood loss during on-pump cardiothoracic surgery.

On December 1, 2009, the FDA approved Kalbitor (ecallantide), a plasma kallikrein inhibitor, for the treatment of acute attacks of HAE in patients 16 years of age and older. The safety and effectiveness of Kalbitor was assessed in 2 randomized, double-blind, placebo-controlled trials -- EDEMA 4 and EDEMA3 that included 168 patients. Patients having an attack of HAE, at any anatomic location and at least 1 moderate or severe symptom, were treated with a 30-mg subcutaneous dose of Kalbitor or placebo. Because patients could participate in both trials, a total of 143 unique patients participated. There were 24 with laryngeal attacks, 55 with peripheral attacks, and 64 patients with abdominal attacks.

In both clinical trials, the effects of Kalbitor were evaluated using the Mean Symptom Complex Severity (MSCS) score as well as the Treatment Outcome Score (TOS). These indices measured the severity of attacks at all anatomical locations (MSCS score) and response to therapy (TOS). The MSCS score is a point-in-time measure of symptom severity. At baseline, 4 hrs, and 24 hrs, patients rated the severity on a categorical scale (0 = normal to 3 = severe) for symptoms at each affected anatomical site. Ratings were averaged to obtain the MSCS score. A decrease in the MSCS score indicated an improvement in symptoms. The TOS is a measure of symptom response to treatment. At 4 hrs and 24 hrs, patient assessment of response characterized by their change from baseline in symptom severity and collected by anatomical site of attack involvement, was recorded on a categorical scale (significant improvement = 100, improvement = 50, same = 0, worsening = -50, significant worsening = -100). The response at each anatomical site was weighted by baseline severity and then the weighted scores across all involved sites were averaged to calculate the TOS. A TOS value of greater than "0" indicated an improvement in symptoms from baseline.

A total of 96 patients were included in the EDEMA4 trial and they were randomized in a 1:1 manner to receive 30-mg Kalbitor subcutaneous injection or placebo for acute attacks of HAE. The primary endpoint was the TOS at 4 hrs, and the key secondary efficacy endpoint was the change from baseline in MSCS at 4 hrs. Patients treated with Kalbitor reported a greater decrease from baseline in the MSCS than placebo and a greater TOS than patients with placebo and the results were statistically significant. At 24 hrs, patients treated with Kalbitor also demonstrated a greater decrease from baseline in the MSCS than placebo (-1.5 versus -1.1; p = 0.04) and a greater TOS (89 versus 55, p = 0.03). More patients in the placebo group (24/48, 50 %) needed medical intervention to treat unresolved symptoms within 24 hrs compared to the Kalbitor-treated group (16/48, 33 %). Some patients reported improvement following a second 30-mg subcutaneous dose of Kalbitor, given within 24 hrs following the initial dose for symptom persistence or relapse, however, effectiveness was not systematically assessed for the second dose.

A total of 72 patients were enrolled in the EDEMA3 trial, and they were randomized 1:1 to receive Kalbitor or placebo for acute attacks of HAE. The design of EDEMA3 was similar to EDEMA4 with the exception of the order of the pre-specified effectiveness endpoints. In EDEMA3, the primary endpoint was the TOS at 4 hrs, and the key secondary efficacy endpoint was the change from baseline in MSCS at 4 hrs. As in EDEMA4, patients treated with Kalbitor reported a greater decrease from baseline in the MSCS than placebo and a greater TOS than patients treated with placebo and the results were statistically significant. In addition, more patients in the placebo group (13/36, 36 %) needed medical
intervention to treat unresolved symptoms within 24 hrs compared to the Kalbitor-treated group (5/36, 14%).

Kalbitor is administered subcutaneously in three 10-mg (1 ml) injections (a total of 30 mgs in 3 mls). If an attack persists, an additional 30-mg dose may be administered in a 24-hr period. The most serious side effect of Kalbitor is anaphylaxis. Other adverse events include diarrhea, fever, headache, nausea, skin irritations, as ell as swelling in the nose and throat.

**Firazyr**

Icatibant (Firazyr, HOE 140, JE049), a potent and specific peptidomimetic bradykinin 2 receptor antagonist, inhibits the effects of bradykinin, which is thought to cause HAE. It was studied in 2 phase III clinical trials: FAST-1 (For Angioedema Subcutaneous Treatment) did not achieve statistical significance for the primary end point; but did so for secondary end points, whereas FAST-2 achieved statistical significance for primary and secondary end points. Icatibant was approved by the European Medicines Agency (EMEA) for the treatment of HAE (Bernstein, 2008; Gras, 2009).

In an uncontrolled pilot study, Bork et al (2007) examined if icatibant is effective in acute edema attacks of hereditary angioedema. A total of 15 patients with 20 attacks were treated with icatibant. The attacks were analyzed by using a standardized and validated visual analog scale (VAS) measurement and compared with historical data of untreated attacks. Plasma bradykinin concentration was measured before and 4 hrs after intravenous icatibant treatment. Symptom intensity decreased within 4 hrs after administration of icatibant; the median time to onset of symptom relief was 1.50, 1.42, and 1.13 hrs in the intravenous groups and 0.58 and 0.45 hrs in the subcutaneous groups, respectively. The median difference in the 10-cm VAS 4 hrs after start of treatment was 4.11 cm (95 % confidence interval [CI]: 1.72 to 6.07). Compared with untreated attacks, icatibant treatment reduced the mean (SD) time to onset of symptom relief by 97 % from 42 +/- 14 to 1.16 +/- 0.95 hrs (all groups combined). Median bradykinin concentration was 7-fold above the norm during acute attacks at 48.5 pmol/L and decreased to 18.0 pmol/L 4 hours after Icatibant infusion or injection. The authors concluded that icatibant was effective in treating acute attacks of HAE.

In 2 double-blind, randomized, multi-center trials, Cicardi et al (2010) evaluated the effect of icatibant in patients with HAE presenting with cutaneous or abdominal attacks. In the FAST-1 trial, patients received either icatibant or placebo; in the FAST-2 trial, patients received either icatibant or oral tranexamic acid, at a dose of 3 g daily for 2 days. Icatibant was administered once, subcutaneously, at a dose of 30 mg. The primary end point was the median time to clinically significant relief of symptoms. A total of 56 and 74 patients underwent randomization in the FAST-1 and FAST-2 trials, respectively. The primary end point was reached in 2.5 hrs with icatibant versus 4.6 hrs with placebo in the FAST-1 trial (p = 0.14) and in 2.0 hrs with icatibant versus 12.0 hrs with tranexamic acid in the FAST-2 trial (p < 0.001). In the FAST-1 study, 3 recipients of icatibant and 13 recipients of placebo needed treatment with rescue medication. The median time to first improvement of symptoms, as assessed by patients and by investigators, was significantly shorter with icatibant in both trials. No icatibant-related serious adverse events were reported. The authors concluded that in patients with HAE having acute attacks, a significant benefit of icatibant as compared with tranexamic acid in one trial and a non-significant benefit of icatibant as compared with placebo in the other trial with regard to the primary end point were reported. The early use of rescue medication may have obscured the benefit of icatibant in the placebo trial.
FAST-3 was a placebo-controlled study of 98 adult patients with a median age of 36 years. The primary end point was assessed using a 3-item composite VAS, comprised of averaged assessments of skin swelling, skin pain, and abdominal pain. The median time to 50% reduction in symptoms for patients with cutaneous or abdominal attacks treated with icatibant (n = 43) compared to placebo (n = 45) was 2.0 hrs [95% CI: 1.5 to 3.0] versus 19.8 hrs [95% CI: 6.1 to 26.3], respectively (p < 0.001). The median times to almost complete symptom relief were 8.0 versus 36.0 hrs for icatibant and placebo, respectively. Additional rescue medications were used by 3 patients (7%) treated with icatibant and 18 patients (40%) treated with placebo.

On August 25, 2011, the FDA approved icatibant (Firazyr) injection for the treatment of acute attacks of HAE in people ages 18 years and older. According to the FDA, Firazyr provides a new option to treat acute attacks of HAE; and because it can be self-administered via an injection in the abdominal area, patients can treat themselves upon recognition of an HAE attack. The safety and effectiveness of Firazyr was shown in 3 controlled clinical trials, with open-label extension periods, in which 225 patients received 1,076 doses of 30 mg Firazyr. The median time for patients treated with Firazyr to report onset of symptom relief was 2 hrs compared with almost 20 hrs with placebo. Firazyr is the third drug approved in the United States to treat HAE attacks. In October 2009 the FDA approved Berinert to treat facial and abdominal attacks of HAE, and Kalbitor was approved in December 2009 to treat acute attacks of HAE in patients aged 16 years and older. The most common adverse reactions reported by those using Firazyr were injection site reactions, fever, increased liver enzymes, dizziness, and rash. Patients are trained on how to self-administer the Firazyr injection. The majority of patients respond to 1 dose. Sometimes, up to 2 additional doses may be administered within a 24-hr period. If this is necessary, each additional dose must be done at least 6 hrs apart.

Cruden and Newby (2008) noted that a therapeutic role for icatibant has also been proposed in several other human conditions including acute pancreatitis, airways disease, thermal injury, drug-induced angioedema (e.g., angiotensin-converting enzyme inhibitor-induced angioedema), and refractory ascites in patients with liver cirrhosis, although this work remains largely experimental.

Angioedema induced by treatment with angiotensin-converting-enzyme (ACE) inhibitors accounts for one third of angioedema cases in the emergency room; it is usually manifested in the upper airway and the head and neck region. There is no FDA approved treatment for this potentially life-threatening condition. The current standard therapy for treating ACEI-induced angioedema includes glucocorticoids and antihistamines, even though this type of angioedema is not histamine-mediated. As a result, the therapeutic response is limited.

A clinical trial by Bas, et al. (2015) found that, among patients with ACE-inhibitor-induced angioedema, the time to complete resolution of edema was significantly shorter with icatibant than with combination therapy with a glucocorticoid and an antihistamine. In this multicenter, double-blind, double-dummy, randomized phase 2 study, investigators assigned patients who had ACE-inhibitor-induced angioedema of the upper aerodigestive tract to treatment with 30 mg of subcutaneous icatibant or to the current off-label standard therapy consisting of intravenous prednisolone (500 mg) plus clemastine (2 mg). The primary efficacy end point was the median time to complete resolution of edema. All 27 patients in the per-protocol population had complete resolution of edema. The median time to complete resolution was 8.0 hours (interquartile range, 3.0 to 16.0) with icatibant as compared with 27.1 hours (interquartile range, 20.3 to 48.0) with standard therapy (P=0.002). Three patients receiving standard therapy required rescue intervention with icatibant and prednisolone; 1 patient required tracheotomy. Significantly more patients in
the icatibant group than in the standard-therapy group had complete resolution of edema within 4 hours after treatment (5 of 13 vs. 0 of 14, P=0.02). The median time to the onset of symptom relief (according to a composite investigator-assessed symptom score) was significantly shorter with icatibant than with standard therapy (2.0 hours vs. 11.7 hours, P=0.03). The results were similar when patient-assessed symptom scores were used. This study was too small to robustly evaluate safety; however, none of the patients discontinued the study because of adverse events. The most common adverse events were local redness, pain, and swelling at the injection site.

**Ruconest**

The U.S. Food and Drug Administration approved Ruconest, a recombinant C1-Esterase Inhibitor, for the treatment of acute attacks in adult and adolescent patients with hereditary angioedema (HAE). Ruconest is a human recombinant C1-esterase inhibitor purified from the milk of genetically modified (transgenic) rabbits. Ruconest is intended to restore the level of functional C1-esterase inhibitor in a patient’s plasma, thereby treating the acute attack of swelling.

The safety and efficacy of Ruconest was evaluated in a multicenter controlled clinical trial. Forty-four adult and adolescent patients with acute attacks were treated with Ruconest. The most common adverse reactions reported in patients treated with Ruconest were headache, nausea and diarrhea. Ruconest received orphan-drug designation for acute attacks by the FDA because it is intended for treatment of a rare disease or condition.

Ruconest is manufactured by Pharming Group NV, Leiden, the Netherlands, and will be distributed in the United States by Santarus Inc., a wholly owned subsidiary of Salix Pharmaceuticals Inc., Raleigh, NC.

Patients who have not previously received Ruconest should first be tested for the presence of IgE antibodies against rabbit epithelium (dander). Only patients shown to have negative results for such a test should be treated with Ruconest. IgE antibody testing should be repeated once a year or after 10 treatments, whichever occurs first.

The recommend dose of Ruconest is one intravenous injection of 50 U/kg for adults with a body weight ≤84 kg and one intravenous injection of 4200 U (two vials) for adults with a body weight ≥84 kg. In the majority of cases, a single dose of Ruconest is sufficient to treat an acute angioedema attack. No more than two doses should be administered within 24 hours.

**CPT Codes / HCPCS Codes / ICD-9 Codes**

**Cinryze:**

**Other CPT codes related to the CPB:**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>96365 - 96368</td>
<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug)</td>
</tr>
<tr>
<td>96374 - 96376</td>
<td>Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push</td>
</tr>
<tr>
<td>96379</td>
<td>Unlisted therapeutic, prophylactic, or diagnostic intravenous or intra-arterial injection or infusion</td>
</tr>
</tbody>
</table>
HCPCS codes covered if selection criteria are met:
J0598 Injection, C1 esterase inhibitor (human) cinryze, 10 units

ICD-9 codes covered if selection criteria are met:
277.6 Other deficiencies of circulating enzymes [acute attacks of hereditary angioedema (HAE) in adolescents and adults]

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):
410.00 - 410.92 Acute myocardial infarction
430 - 438.9 Cerebrovascular disease
995.90 - 995.94 Systemic inflammatory response syndrome (SIRS)

Berinert:

Other CPT codes related to the CPB:
96365 - 96368 Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug)
96372 Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular
96374 intravenous push, single or initial substance/drug
96379 Unlisted therapeutic, prophylactic, or diagnostic intravenous or intrarterial injection or infusion

HCPCS codes covered if selection criteria are met:
J0597 Injection, C-1 esterase inhibitor (human), berinert, 10 units

ICD-9 codes covered if selection criteria are met:
277.6 Other deficiencies of circulating enzymes [adolescents 13 yrs or older and adults with abdominal attacks or facial swelling associated with HAE - not for prophylaxis]

Other ICD-9 codes related to the CPB (symptoms of moderate to severe attack):
478.6 Edema of larynx
784.0 Headache [painful facial distortion]
786.09 Other dyspnea and respiratory abnormalities [airway swelling]
787.01 Nausea with vomiting
789.00 - 789.09 Abdominal pain [adolescents and adults with abdominal attacks associated with HAE]
784.2 Swelling, mass, or lump in head and neck [facial swelling associated with HAE]

Kalbitor (ecallantide)
Other CPT codes related to the CPB:

96372 Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular

HCPCS codes covered if selection criteria are met:

J1290 Injection, ecallsantide, 1 mg

ICD-9 codes covered if selection criteria are met:

277.6 Other deficiencies of circulating enzymes [acute attacks of hereditary angioedema (HAE) in persons 12 years or older]

Other ICD-9 codes related to the CPB (symptoms of moderate to severe attack):

478.6 Edema of larynx
784.0 Headache [painful facial distortion]
784.2 Swelling, mass, or lump in head and neck [facial swelling associated with HAE]
786.09 Other dyspnea and respiratory abnormalities [airway swelling]
787.01 Nausea with vomiting
789.00 -789.09 Abdominal pain [adolescents and adults with abdominal attacks associated with HAE]

_Ruconest (recombinant C1 esterase inhibitor):_

No specific code

Other CPT codes related to the CPB:

96374 - 96376 Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push
96379 Unlisted therapeutic, prophylactic, or diagnostic intravenous or intra-arterial injection or infusion

ICD-9 codes covered if selection criteria are met:

277.6 Other deficiencies of circulating enzymes [acute attacks of HAE in persons 12 years of age and older]

Other ICD-9 codes related to the CPB (symptoms of moderate to severe attack):

478.6 Edema of larynx
784.0 Headache [painful facial distortion]
784.2 Swelling, mass, or lump in head and neck [facial swelling associated with HAE]
786.09 Other dyspnea and respiratory abnormalities [airway swelling]
787.01 Nausea with vomiting
789.00 - 789.09 Abdominal pain [adolescents and adults with abdominal attacks associated with HAE]

Icatibant (Firazyr):

Other CPT codes related to the CPB:

96372 Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); subcutaneous or intramuscular

HCPCS codes covered if selection criteria are met:

J1744 Injection, icatibant, 1 mg

Other HCPCS codes related to the CPB:

J1380 Injection, estradiol valerate, up to 10 mg
J1410 Injection, estrogen conjugated, per 25 mg
J1435 Injection, estrone, per 1 mg

ICD-9 codes covered if selection criteria are met:

277.6 Other deficiencies of circulating enzymes [attacks of hereditary angioedema (HAE) in adolescents and adults - see criteria]

Other ICD-9 codes related to the CPB (symptoms of moderate to severe attack):

478.6 Edema of larynx
784.0 Headache [painful facial distortion]
786.09 Other dyspnea and respiratory abnormalities [airway swelling]
787.01 Nausea with vomiting
789.00 - 789.09 Abdominal pain [adolescents and adults with abdominal attacks associated with HAE]
784.2 Swelling, mass, or lump in head and neck [facial swelling associated with HAE]

The above policy is based on the following references:


