HEREDITARY ANGIOEDEMA (HAE), TREATMENT AND PROPHYLAXIS

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INSTRUCTIONS FOR USE
This Drug Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee’s document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD)) may differ greatly. In the event of a conflict, the enrollee’s specific benefit document supersedes this Drug Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the plan benefit coverage prior to use of this Drug Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Drug Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

COVERAGE RATIONALE

C1 Esterase Inhibitor (human) [Berinert® and Cinryze®] and ecallantide (Kalbitor®) are proven in the treatment of acute attacks of hereditary angioedema (HAE).

C1 Esterase Inhibitor (human) [Cinryze®] is proven for prophylaxis against attacks in patients with hereditary angioedema (HAE).

Additional information to support medical necessity review where applicable:
The above indications and criteria also apply to medical necessity review.

Centers for Medicare and Medicaid Services (CMS):
Medicare does not have a National Coverage Determination (NCD) for Berinert, Cinryze or
Hereditary Angioedema (HAE): Drug Policy (Effective 07/01/2013)

Kalbitor. In general, Medicare covers outpatient (Part B) drugs that are furnished "incident to" a physician's service provided that the drugs are not usually self-administered by the patients who take them. See the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, section 50 Drugs and Biologicals at http://www.cms.hhs.gov/manuals/Downloads/bp102c15.pdf

Local Coverage Determinations (LCDs) for Selective Treatment of HAE with Cinryze, Berinert and Ecallantide exist and compliance with these policies is required where applicable.

(Accessed April 4, 2013)

BENEFIT CONSIDERATIONS

Some Certificates of Coverage allow for coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. The enrollee-specific benefit document must be consulted to make coverage decisions for this service. Some states mandate benefit coverage for off-label use of medications for some diagnoses or drugs under some circumstances when certain conditions are met. Where such mandates apply, they supersede language in the benefit document or in the medical or drug policy.

Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. See the Policy and Procedure addressing the treatment of serious rare diseases

BACKGROUND

C1 Esterase Inhibitor [human]

Cinryze and Berinert are highly purified, pasteurized, nanofiltered, lyophilized C1 inhibitor products prepared from large pools of human plasma from US donors. C1 inhibitor is a normal constituent of human blood and is one of the serine proteinase inhibitors (serpins). The primary function of C1 inhibitor is to regulate the activation of the complement and intrinsic coagulation (contact system) pathway. C1 inhibitor also regulates the fibrinolytic system. HAE patients have low levels of endogenous or functional C1 inhibitor. Although the events that induce attacks of angioedema in HAE patients are not well defined, it is thought that increased vascular permeability and the clinical manifestation of HAE attacks are primarily mediated through contact system activation. Suppression of contact system activation by C1 inhibitor through the inactivation of plasma kallikrein and factor XIIa is thought to modulate this vascular permeability by preventing the generation of bradykinin, the main mediator of HAE attacks.

C1 esterase inhibitor [human] (Cinryze) increases antigenic and functional plasma levels of C1 inhibitor, thereby increasing the deficient C1 inhibitor.

C1 esterase inhibitor [human] (Berinert) is a human plasma C1 esterase inhibitor to be reconstituted for intravenous administration. Administration of Berinert to patients with C1 esterase inhibitor deficiency replaces the missing or malfunctioning protein in patients.

Human Plasma Kallikrein Inhibitor [human]

Ecallantide (Kalbitor) is a human plasma kallikrein inhibitor for injection for subcutaneous use to treat symptoms hereditary angioedema (HAE). (HAE) is a rare genetic disorder caused by mutations to C1-esterase-inhibitor (C1-INH) located on Chromosome 1q and inherited as an autosomal dominant trait. HAE is characterized by low levels of C1 - INH activity and low levels of C4. C 1 - INH functions to regulate the activation of the complement and intrinsic coagulation (contact system pathway) and is a major endogenous inhibitor of plasma kallikrein. The kallikrein-
kinin system is a complex proteolytic cascade involved in the initiation of both inflammatory and coagulation pathways. One critical aspect of this pathway is the conversion of High Molecular Weight (HMW) kininogen to bradykinin by the protease plasma kallikrein. In HAE, normal regulation of plasma kallikrein activity and the classical complement cascade is therefore not present. During attacks, unregulated activity of plasma kallikrein results in excessive bradykinin generation. Bradykinin is a vasodilator which is thought by some to be responsible for the characteristic HAE symptoms of localized swelling, inflammation, and pain. Kalbitor is a potent (Ki = 25 pM), selective, reversible inhibitor of plasma kallikrein. Kalbitor binds to plasma kallikrein and blocks its binding site, inhibiting the conversion of HMW kininogen to bradykinin.

By directly inhibiting plasma kallikrein, ecallantide (Kalbitor) reduces the conversion of HMW kininogen to bradykinin and thereby treats symptoms of the disease during acute episodic attacks of HAE.

### CLINICAL EVIDENCE

#### Proven

**HAE (acute)**

**C1 Esterase Inhibitor [human] (Berinert)**

Utilizing data obtained during IMPACT-2, researchers performed a retrospective subgroup analysis to evaluate if repeated treatment with C1 esterase inhibitor (C1-INH) concentrate [Berinert] dosed at 20 U/kg for successive attacks had any effect on the treatment response to C1-INH concentrate. Fifty-seven patients were studied in IMPACT-2, and of those 57 patients, 18 patients (32%) were treated with C1-INH concentrate for at least 15 attacks each over a mean duration of 34 months (range, 10-51 months). Of the 18 patients treated for ≥15 attacks, 7 patients (39%) had between 15 and 25 HAE attacks and 11 patients (61%) had 25 HAE attacks. The distribution of body locations and the intensity of HAE attacks were similar for each of the first 15 attacks and subsequent attacks. Repeated treatment had no systematic effect on the frequency of HAE attacks, the intensity of HAE attacks, the time to onset of symptom relief, or the time to complete resolution of HAE symptoms (the median of individual linear regression coefficients was not statistically significantly different from 0). Additionally, repeated treatment with C1-INH concentrate is not associated with development of inhibitory anti–C1-INH antibodies. The authors concluded that treatment with 20 U/kg of C1-INH concentrate provided consistent response in patients treated for multiple successive HAE attacks regardless of location.

In a prospective, open-label, uncontrolled, multicenter extension study of IMPACT-1, safety and efficacy of long-term treatment with C1 esterase inhibitor concentrate (C1-INH) [Berinert] 20 U/kg was evaluated in subsequent hereditary angioedema (HAE) attacks at any body location (IMPACT-2). Patients were eligible if they had any type of HAE attack and had previously participated in IMPACT-1 for which they had to be at least 6 years of age with HAE type I or II. The primary efficacy endpoint was the time from start of treatment to onset of symptom relief, analyzed on a per-patient and per-attack basis. The secondary endpoint was the patient-reported time to complete resolution of HAE symptoms. Adverse events, vital signs, viral safety and anti-C1-INH antibodies were measured to evaluate safety. During a median study duration of 24 months (range: 0-51 months), 1085 attacks were treated in 57 patients (10-53 years of age). In the per-patient analysis, the median time to onset of symptom relief on any body location was 0.46 h (shortest for abdominal attacks: 0.39 h compared to 0.44 h for laryngeal, 0.43 h for peripheral and 0.48 h for facial); the median time to complete resolution of symptoms was 15.5 h (shortest for laryngeal attacks: 5.8 h compared to 12.8 h for abdominal, 22.7 h for peripheral and 26.6 h for facial attacks). Demographic factors, type of HAE, intensity of attacks, time to treatment, use of androgens and presence of anti-C1-INH antibodies had no clinically relevant effect on the efficacy outcomes. There were no treatment-related safety concerns. No inhibitory anti-C1-INH antibodies were detected in any patient. Authors conclude that a single dose of 20
U/kg C1-INH concentrate is safe and provides reliable efficacy in the long-term treatment of successive HAE attacks at any body location.

In a randomized, double-blind, placebo-controlled trial, the efficacy of pasteurized C1 esterase inhibitor concentrate (C1-INH) [Berinert] was studied in 125 patients at least 6 years of age with type I or type II hereditary angioedema (HAE) experiencing an acute abdominal or facial attack presenting for treatment within 5 hours of the attack (IMPACT-1). Patients were randomized to receive a single intravenous infusion of C1-INH 10 U/kg (n=40), C1-INH 20 U/kg (n=43) or placebo (n=42). The primary endpoint was time from start of treatment to onset of symptom relief, as determined by patient responses to a standard question posed at appropriate time intervals for as long as 24 hours after the start of treatment. Secondary outcomes were time to complete resolution of all HAE symptoms, proportion of patients with worsened intensity of angioedema symptoms between 2 and 4 hours after treatment, and number of vomiting episodes within 4 hours. Median time to onset of relief was significantly shorter with C1-INH concentrate at a dose of 20 U/kg than with placebo (0.5 vs 1.5 hours; p=0.0025), whereas with C1-INH 10 U/kg, the time to onset of relief was only slightly shorter than with placebo (1.2 vs 1.5 hours; p=0.2731). The reduction in time to onset of relief was greatest for severe attacks (0.5 vs 13.5 hour) as compared to placebo. Median time to onset of symptom relief was relatively short for abdominal attacks (placebo, 1.3 hours; C1-INH 10 U/kg, 1.2 hours; C1-INH 20 U/kg, 0.5 hours) compared with facial attacks (placebo, 24.0 hours; C1-INH 10 U/kg, 1.3 hours; C1-INH 20 U/kg, 0.9 hours). Secondary outcomes consistently supported the efficacy of the 20 U/kg dose. No difference in treatment effect in terms of time to onset of symptom relief could be confirmed by stratified analysis when comparing the efficacy of C1-INH 20 U/kg in facial and abdominal attacks, and in moderate and severe attacks. C1 esterase inhibitor concentrate was safe and well tolerated. No seroconversions were observed for HIV, hepatitis virus, or human B19 virus. Researchers conclude that C1-INH 20 U/kg administered intravenously is a safe and effective treatment for rapidly alleviating symptoms of abdominal and facial HAE attacks.

C1 Esterase Inhibitor [human] (Cinryze)

In a Phase 3, open-label study, safety and efficacy of repeat use of nanofiltered C1 esterase inhibitor (human) [C1 INH-nf, Cinryze] for treatment of acute attacks of hereditary angioedema (HAE) was evaluated. Patients age 1 year or older were included if they had previously enrolled or participated in LEVP2005-1/A and/or LEVP2005-1B trials. Patients received 1,000 units of C1 INH-nf administered intravenously. If there was no response to treatment 60 minutes after the first dose, a second 1,000 U dose could be administered. Primary endpoints included number of HAE attacks treated with C1 INH-nf and percent of HAE attacks with substantial symptom relief within 4 hours of treatment. Secondary endpoints measured included time to beginning of substantial relief of acute attack symptom after initial and multiple treatments, and the effects of treatment on antigenic and functional levels of C1 inhibitor and on C4 levels. Safety was monitored through adverse event reporting, vital signs measurements, and laboratory testing. A total of 113 patients were enrolled in the study and received 885 doses of C1 INH-nf. A total of 609 HAE attacks were treated with C1 INH-nf, and the numbers of attacks achieving unequivocal relief of the defining symptom within 1 and 4 hours after the initial dose were 412 (68%) and 529 (87%), respectively. Of 101 patients treated for an attack during the study period, 80 achieved unequivocal relief of their first attack within 4 hours after initial C1 INH-nf dose (response rate, 79%); median time to the beginning of unequivocal relief was 0.75 hour. C1 INH-nf was safe and well tolerated. Researchers conclude that C1 INH-nf is safe and efficacious for short-term treatment of HAE attacks.

Efficacy of nanofiltered C1 inhibitor concentrate (Cinryze) in treatment of acute attacks of hereditary angioedema (HAE) was evaluated in a randomized, double-blind, placebo-controlled trial (n=68) [LEVP2005-1/A]. Patients aged 6 years and older with HAE 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 excluded. Eligible patients were randomized to receive C1 inhibitor concentrate 1000 units (n=35) or 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. The primary end point was the time from administration of the study drug to unequivocal relief of symptoms at the defining site (i.e., the first of three consecutive reports of improvement). Secondary end points included the percentage of subjects who had an onset of unequivocal relief within 4 hours after treatment, the time to complete resolution of the attack (i.e., all symptoms of swelling absent), and the effects of treatment on antigenic and functional levels of C1 inhibitor and on C4 levels. 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. Injection-site rash was reported in 1 patient in the C1 inhibitor concentrate arm. Following treatment with nanofiltered C1 inhibitor concentrate for an acute attack, the median time to response was 30 min in 82 patients with HAE (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 hr after C1 inhibitor concentrate treatment. Researchers conclude that treatment with nanofiltered C1 inhibitor concentrate shortens duration of acute attack compared with placebo in patients with HAE.

Human Plasma Kallikrein Inhibitor [human] (Kalbitor)

In order to assess the potential risk for attack rebound or relapse following ecallantide treatment, Bernstein et al. conducted a post-hoc analysis of the study population from two pivotal double-blind, placebo-controlled ecallantide studies, EDEMA3-DB and EDEMA4. Measurement of symptoms was assessed by treatment outcome score (TOS), mean symptom complex severity (MSCS) score, and global response. Patients with improvement at 4 hours post-dosing in all three measures followed by any sign of worsening at 24 hours were considered to show potential rebound if worsening was beyond baseline or were considered to show potential relapse if not beyond baseline. Likelihood of rebound or relapse was determined by the number of measures showing worsening and the magnitude of worsening. Patients receiving placebo who met the criteria for rebound/relapse were utilized for descriptive comparison only. At 4 hours, improvement in at least one of three efficacy measures was seen in 51 (72.9%) ecallantide-treated and 37 (52.1%) placebo-treated patients (p=0.01). Improvement in all three measures (TOS, MSCS score, and global response) was seen in 42 (60%) ecallantide-treated and 26 (37%) placebo-treated patients (p<0.01). Of the 42 ecallantide-treated patients showing measured improvement, a total of 9 (21.4%) showed signs of worsening at 24 hours and were thus considered potential rebound/relapse. Of the nine ecallantide-treated patients with signs of worsening at 24 hours, none were likely to rebound, one was assessed as possible rebound, one as likely relapse, and two as possible relapse. No patient with potential rebound/relapse experienced new symptoms after dosing. Medical intervention was required in one ecallantide-treated patient (likely relapse, patient received danazol for an abdominal attack). Recognizing that relapse was observed in a small proportion of patients and there was little evidence of rebound, the authors concluded that ecallantide was efficacious for treating acute HAE attacks.
Efficacy and safety of ecallantide in the treatment of acute hereditary angioedema (HAE) attacks was evaluated in a double-blind, placebo-controlled study (EDEMA-4). Patients with moderate to severe HAE attacks were randomized 1:1 to receive subcutaneous ecallantide 30mg (n=48) or placebo (n=48). Patients aged 10 years and older with documented evidence of type I or II HAE who presented within 8 hours of a moderate to severe HAE attack affecting any anatomical location were included. The primary efficacy end point was change from baseline in mean symptom complex severity score (MSCS) 4 hours after dosing. Secondary end points included treatment outcome score (TOS) 4 hours after dosing and maintenance of significant overall improvement through 24 hours. Mean (SD) change from baseline in MSCS score 4 hours after dosing was significantly greater with ecallantide use (-0.8 [SD=0.6]) compared with placebo use (-0.4 [SD=0.8]) (p=0.01 comparing distributions). Ecallantide therapy was also associated with a significantly larger mean (SD) TOS 4 hours after dosing vs placebo use (ecallantide: 53.4 [SD=49.7]; placebo: 8.1 [SD=63.2]; p=0.003 comparing distributions). The benefit of ecallantide was apparent within 2 hours after dosing and was maintained through 24 hours after dosing as demonstrated by MSCS score (p=0.04 comparing the distributions) and TOS (p=0.03 comparing the distributions). A significantly greater proportion of ecallantide-treated patients (44%) maintained significant overall improvement through 24 hours compared with placebo users (21%) [p=0.02]. The safety profile was similar between the treatment groups. Researchers conclude that ecallantide treatment results in a rapid and significant reduction in symptom severity of acute HAE attacks and that this effect is sustained for up to 24 hours.

Efficacy of ecallantide in patients (n=72) with hereditary angioedema presenting with an acute attack was evaluated in a double-blind, placebo-controlled trial (EDEMA-3). Patients at least 10 years of age with an acute attack were randomly assigned, in a 1:1 ratio, to receive subcutaneous ecallantide 30 mg (n=36) or placebo (n=36) and observed for at least 4 hours after administration. Symptoms were assessed every 15 minutes for the first 2 hours, every 30 minutes for the next 2 hours, and finally at 24 hours. Two measures of patient-reported outcomes were used to assess the response: treatment outcome scores, which range from +100 (designated in the protocol as significant improvement in symptoms) to -100 (significant worsening of symptoms), and the change from baseline in the mean symptom complex severity score, which range from +2 (representing a change from mild symptoms at baseline to severe symptoms after) to -3 (representing a change from severe symptoms at baseline to no symptoms after). The primary trial end point was the treatment outcome score 4 hours after study-drug administration and secondary end points included the change from baseline in the mean symptom complex severity score at 4 hours and the time to significant improvement. At 4 hours, the median treatment outcome score was 50.0 in the ecallantide group and 0.0 in the placebo group (interquartile range [IQR], 0.0 to 100.0 in both groups; p=0.004). The median change in the mean symptom complex severity score at 4 hours reported was -1.00 (IQR, -1.50 to 0.00) with ecallantide, versus -0.50 (IQR, -1.00 to 0.00) with placebo (p=0.01). Median time to significant improvement was 165 minutes with ecallantide versus more than 240 minutes with placebo (p=0.14). There were no deaths, treatment-related serious adverse events, or withdrawals owing to adverse events. Researchers conclude that at four hours after administration of ecallantide or placebo for acute attacks of angioedema in patients with HAE, patient-reported treatment outcome scores and mean symptom complex severity scores were significantly better with ecallantide than with placebo.

**HAE (prophylaxis)**

**C1 Esterase Inhibitor [human] (Cinryze)**

Zuraw et al. conducted an open-label, multicenter extension study to assess the safety and efficacy of prophylactic nanofiltered C1-inhibitor (C1INH-nf) [Cinryze] in a large cohort of patients with hereditary angioedema. A total of 146 patients (age range, 3-82 years) with hereditary angioedema received prophylactic C1INH-nf for up to 2.6 years in centers throughout the United States. The primary efficacy endpoint for each patient was the number of angioedema attacks. Safety was evaluated by the number and severity of adverse events, and changes in clinical...
laboratory values (viral serology performed every 3 months) and vital signs. Patients experienced a 93.7% reduction in attacks while taking prophylactic C1INH-nf (0.19 attacks per month; interquartile range, 0.00-0.64) compared with the historical rate of attacks. The majority of patients (87.7%) reported an attack frequency of 1 or less attack per month during prophylactic C1INH-nf and 51 patients (34.9%) had no attacks during the study. Twice weekly dosing C1INH-nf resulted in a favorable response rate that varied from 95.7% at 30 days to 70.7% at 120 days. Once-weekly dosing resulted in a favorable response rate that varied from 69.3% at 30 days to 45.7% at 120 days. Twice-weekly dosing had a more favorable response rate than once-weekly dosing at each interval examined. Researchers noted that despite twice-weekly C1INH-nf dosing, 7.5% of patients experienced relatively frequent attacks. No clinical characteristics predicted the response to prophylactic C1INH-nf, including historical attack frequency. C1INH-nf was well tolerated. The authors concluded that prophylactic C1INH-nf treatment is highly effective and safe, and provides durable prophylaxis in the majority of patients with hereditary angioedema. Dosing of C1INH-nf at 1000 units twice weekly is supported by this study. Additionally, the authors commented that individual patients may benefit from further dose adjustment on the basis of response to therapy and individual treatment goals.

In a 24-week, randomized, double-blind, placebo-controlled, cross-over trial (n=22), prophylaxis with nanofiltered C1 inhibitor concentrate (Cinryze) was evaluated in preventing attacks of hereditary angioedema (HAE) [LEVP2005-1/B]. Patients aged 6 yr and older with HAE due to C1 inhibitor deficiency who had been randomized to receive C1 inhibitor concentrate for the treatment of acute attacks in a double-blind, placebo-controlled trial and who had a history of 2 or more attacks per month were eligible for enrollment. Eligible patients received either C1 inhibitor concentrate 1000 units (n=11) or placebo ( n=11) every 3 to 4 days for 12 weeks and then switched to the other therapy for the next 12 weeks. The primary efficacy end point was the number of attacks of angioedema during each treatment period. Secondary end points included the average severity of attacks, average duration of attacks, number of open-label injections of C1 inhibitor, and total number of days of swelling. The average number of attacks in a 12-week period (primary endpoint) was 6.26 attacks during the C1 inhibitor concentrate prophylaxis period and 12.73 attacks during the placebo period (attack rate difference, 6.47 attacks; 95% CI, 4.21 to 8.73 attacks; p<0.001). For attacks which occurred during the C1 inhibitor concentrate prophylaxis period compared with the placebo period, the mean severity score (evaluated using a 3-point scale: mild=1; moderate=2; severe=3) was significantly lower (1.3 +/- 0.85 vs 1.9 +/- 0.36, respectively; p<0.001) and the attack duration was significantly shorter (2.1 +/- 1.13 vs 3.4 +/- 2.39 days, respectively; p=0.002). Additionally, fewer rescue C1 inhibitor concentrate injections were required (4.7 +/- 8.66 vs 15.4 +/- 8.41 injections; p<0.001) and fewer days of swelling were reported (10.1 +/- 10.73 vs 29.6 +/- 16.9 days; p<0.001) during the C1 inhibitor concentrate prophylaxis period compared with the placebo period. Adverse events possibly associated with C1 inhibitor concentrate use included 1 report each of pruritus and rash, lightheadedness, and fever. Researchers conclude that nanofiltered C1 inhibitor concentrate significantly reduced the number of attacks compared with placebo in patients with HAE.

Professional Societies


The goal of acute treatments is to resolve angioedema symptoms as quickly as possible.

Recommendations for treatment include:

- Any angioedema attack in HAE patients can become disabling and/or life-threatening; therefore, all patients with HAE owing to C1-INH deficiency, even if still asymptomatic, should have access to at least one of the specific medicines, plasma-derived and recombinant C1-INHs, icatibant, and ecallantide.
• All attacks, irrespective of location, are eligible for treatment as soon as they are clearly recognized by the patient, ideally before visible or disabling symptoms develop.

The goal of prophylactic treatment is either to reduce the likelihood of swelling in those patients undergoing a stressor or procedure likely to precipitate an attack (short-term prophylaxis) or to decrease the number and severity of angioedema attacks (long-term prophylaxis).

Recommendations are as follows:

• Long-term prophylactic treatment is appropriate for patients in whom on-demand acute treatment is not adequate to minimize the suffering related to the disease.
• Plasma-derived C1-INH can be considered for long-term prophylactic treatment without exclusion for all groups of patients.
• Regimens of prophylactic plasma-derived C1-INH should be individualized to optimize clinical response.

Canadian Hereditary Angioedema Network (CHAEM): 2010 International Consensus Algorithm for the Diagnosis, Therapy and Management of Hereditary Angioedema

The first-line therapy for treatment of a severe event is C1 inhibitor. If C1 inhibitor is not available, other therapies might include pain management, intravenous fluids, or supportive therapies. C1 inhibitor is indicated for short-term prophylaxis. If C1 inhibitor is not available, the use of danazol or tranexamic acid or fresh frozen plasma is recommended for prophylaxis. If the patient experiences more than one severe event per month and if a treatment for acute attacks is not sufficiently effective or is not available, then long-term prophylaxis with androgens, antifibrinolytic agents or C1 inhibitor on demand (home-care) should be considered.

Primary Immunodeficiency Association (2005)

Treatment of acute attack depends on the severity. Episodes of only peripheral swelling usually do not require treatment, but stanozolol (not available in the U.S.) or danazol given early during an attack may shorten its duration. C1 inhibitor should be given promptly if there is any suspicion of airway involvement. Administering of C1 inhibitor shortens the duration of attack. NSAIDs are useful for acute abdominal attacks, while C1 inhibitor should be used if abdominal attack is severe. For short term prophylaxis, C1 inhibitor should be infused up to 24 hours before the procedure. Alternatively, attenuated androgens or antifibrinolytics can be started 5 days before and continued for 2 days after procedure. Long-term prophylaxis regimen should be guided by the severity of the disease. For peripheral angioedema involving extremities or trunk, prophylaxis may not be required. However, antifibrinolytics and/or synthetic attenuated androgens reduce the frequency and severity of attacks. Other androgens (e.g., methyltestosterone, fluoxyesterone, and oxymetholone) can be used in adult males. Maintenance treatment should be considered in any patient who has had more than one episode of severe abdominal pain in one year or any head or neck swellings or a requirement for concentrate more than once a year.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Berinert is a plasma-derived C1 Esterase Inhibitor (Human) FDA-labeled for the treatment of acute abdominal, facial, or laryngeal attacks of hereditary angioedema (HAE) in adult and adolescent patients. The safety and efficacy of Berinert for prophylactic therapy have not been established.

Kalbitor is a plasma kallikrein inhibitor FDA-labeled for treatment of acute attacks of hereditary angioedema (HAE) in patients 16 years of age and older.

Cinryze is a C1 esterase inhibitor FDA-labeled for routine prophylaxis against angioedema attacks in adolescent and adult patients with Hereditary Angioedema (HAE).
**APPLICABLE CODES**

The [Current Procedural Terminology (CPT), HCPCS and/or ICD-9] codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document.

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<td>Injection, C1 esterase inhibitor (human), Cinryze, 10 units</td>
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**ICD-10 Codes (Preview Draft)**

In preparation for the transition from ICD-9 to ICD-10 medical coding on **October 1, 2014***, a sample listing of the ICD-10 CM and/or ICD-10 PCS codes associated with this policy has been provided below for your reference. This list of codes may not be all inclusive and will be updated to reflect any applicable revisions to the ICD-10 code set and/or clinical guidelines outlined in this policy. *The effective date for ICD-10 code set implementation is subject to change.

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<td>D84.1</td>
<td>Defects in the complement system</td>
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**REFERENCES**


### POLICY HISTORY/REVISION INFORMATION

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<td>Policy revised for annual review with updates to the following sections: Coverage Rationale, CMS, Benefits Considerations, Clinical Evidence and References. Approved by National Pharmacy &amp; Therapeutics Committee on 5/21/2013. Policy 2012D0044A archived.</td>
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<td>11/14/2012</td>
<td>New policy drafted and approved by the National Pharmacy and Therapeutics Committee 5/15/2012.</td>
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