C1 Esterase Inhibitor (Berinert®)
New Molecular Entity Drug Monograph
August 2010

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VHA PBM-MAP-VPE drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

Indication: The C1 esterase inhibitor (human) Berinert® was approved by the FDA for treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adult and adolescent patients.

Efficacy: In a randomized, double-blind, placebo-controlled trial of 125 patients presenting with acute abdominal or facial symptoms of HAE, treatment with C1 inhibitor (Berinert) at a dose of 20 units/kg reduced the median time from treatment to onset of symptom relief compared to placebo (0.5 hours vs. 1.5 hours, respectively; p=0.0025). C1inhibitor (Berinert) 10 units/kg did not reduce time to symptom relief compared to placebo. Treatment with the 20 units/kg dose improved the secondary endpoints of time to complete resolution of all HAE symptoms (81.84 hours vs. 125.08 hours with placebo), the percent of patients that experienced worsening of their HAE symptoms within 2 to 4 hours after treatment initiation (4.7% vs. 31.0% with placebo), and the number of vomiting episodes within 4 hours of the start of treatment (0.1 vs. 0.8 with placebo). Data from randomized controlled clinical trials are not available on the use of C1 inhibitor (Berinert) for prophylaxis of HAE attacks.

Safety: The most frequently occurring adverse events (reported in $\geq$ 4%) in patients receiving C1 inhibitor (Berinert) included HAE attack recurrence, headache, abdominal pain, nausea, muscle spasms, pain, diarrhea, and vomiting. Serious treatment-emergent adverse events reported in 5 patients in the clinical trial described above, included laryngeal edema, facial attack with laryngeal edema, swelling of the shoulder and chest, HAE exacerbation, and laryngospasm. Adverse reactions including hypersensitivity or anaphylactic reactions, possible viral transmission (including acute hepatitis C), injection site pain and redness, chills, and fever have been reported in Europe in patients who received C1 inhibitor (Berinert). Since C1 inhibitor (Berinert) is derived from human blood, it has the potential for transmitting infectious diseases including viruses and Creutzfeldt-Jakob disease. If it is felt that an infection could possibly be the result of C1 inhibitor (Berinert) administration, this should be reported by the provider to the manufacturer. The risk vs. benefit of treatment with C1 inhibitor (Berinert) should also be discussed with the patient prior to therapy.

Dose: C1 inhibitor (Berinert) should be administered as a dose of 20 units per kg of body weight (each vial contains 500 units of drug) by slow intravenous injection at an approximate rate of 4 ml/minute. Once reconstituted, the dose should be administered as soon as possible within 8 hours.

Conclusions: C1 inhibitor (Berinert) appears to be effective in reducing the time to relief of symptoms of acute HAE attacks. Treatment with C1 inhibitor (Berinert) is reported to be well-tolerated, with the percent of patients experiencing an adverse event less than with placebo. C1 inhibitor (Berinert) carries the same risk as with other blood derived products; therefore, the risk vs. benefit of treatment should be carefully considered and discussed with the patient. Treatment with another form of C1 inhibitor (Cinryze) also reduced the time to onset of relief of acute HAE attacks compared to placebo; however, it is not approved for this indication and a direct comparison cannot be made between the two formulations of C1 inhibitor. The C1 inhibitor (Cinryze) is indicated for routine prophylaxis against angioedema attacks in patients with HAE; the safety and efficacy of the C1 inhibitor (Berinert) for the prophylaxis of HAE attacks has not been established. In patients with HAE, treatment with C1 inhibitor (Berinert) has not been compared to other treatments used for the acute treatment of angioedema attacks (e.g., fresh frozen plasma, ecallantide) or evaluated against treatment for prophylaxis of HAE attacks.

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Introduction[1-13]

C1 esterase inhibitor (human) (Berinert®, CSL Behring) was approved by the FDA October 9, 2009 for the treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adolescent and adult patients. The safety and efficacy of Berinert has not been adequately studied in children ≤ 12 years of age.[1]

Hereditary angioedema is an autosomal dominant disorder caused by a deficiency in functional C1 inhibitor that has been estimated to affect approximately 1 in 50,000 persons (there are estimated to be approximately 6,000 patients in the United States with HAE). Patients may first present with symptoms in early childhood, with continued attacks for the duration of their lives. The frequency of attacks is variable, occurring on average every 1 to 2 weeks. Some patients will rarely experience an attack while others have them on a more frequent basis.[2]

The most common location for an acute attack is the skin or abdomen, with attacks of the skin most commonly involving the extremities, then face, genitals, and chest/neck. Symptoms may include swelling (most common in the hands, feet, arms, legs, and abdomen; less frequently involving the oropharynx) and a nonpruritic rash; often associated with tingling prior to the appearance of symptoms. Swelling may worsen over the first 24 hours then diminish over the next 2 to 3 days. Symptoms associated with the abdomen also include pain, nausea, vomiting, and hypotension due to a shift in fluid. Death has occurred with laryngeal angioedema. Triggers may include stress or trauma, including surgical or dental procedures; although, attacks may occur without a precipitating factor.[2] Diagnosis can be made in a patient with a history of recurrent angioedema, and abdominal pain without urticaria. Measurement of C4 levels can be used to rule-out HAE, since nearly all patients with HAE will have decreased levels. Further testing may be conducted to evaluate the antigenic or functional C1 inhibitor level to determine the HAE type.[2,3] Patients with HAE have a mutation in the C1 inhibitor gene and may be classified into type I (85% of patients) or type II (15%), the two main types of HAE that result in reduced levels of antigenic (type I) and functional (type I and II) levels of C1 inhibitor. Another type of familial angioedema has been described, primarily involving women during pregnancy or who received estrogen therapy (although, this form has also been found in men), that present with normal levels of antigenic and functional C1 inhibitor.[2]

Management of HAE includes recognition and avoidance of potential triggers, treatment of acute symptoms, and short and long-term prophylaxis.[2-5] For the management of significant acute HAE attacks, use of C1 inhibitor has been recommended.[2-5] Ecallantide, a kallikrein inhibitor has recently been approved by the FDA for treatment of acute HAE attacks.[4] Fresh frozen plasma that contains C1 inhibitor has also been used for acute attacks although it is controversial as to whether treatment with fresh frozen plasma can exacerbate symptoms in some patients due to the potential for bradykinin production.[2,3,6] Symptom control includes narcotic analgesics for abdominal pain, antiemetics, and hydration. Intubation may be necessary in patients with oropharyngeal involvement if closure of the airway occurs.[2] Although not adequately studied, treatment with C1 inhibitor has been recommended for short-term prophylaxis prior to a procedure or event that may trigger an attack.[3,5] Administration of 17-alpha alkylated androgens (e.g., danazol), antifibrinolytics, or fresh frozen plasma has also been used for short-term prophylaxis.[2,3,5] It has been recommended that long-term prophylaxis be considered for patients with frequent or severe attacks, HAE with laryngeal symptoms, or if there is considerable disease burden that affects the patient's quality of life.[2,3,5,7] Treatment with androgens (e.g., danazol) or antifibrinolytic agents (e.g., aminocaproic acid, tranexamic acid) reduces the frequency of attacks compared to placebo; although, side effects may limit their use in some patients.[2,7-10] On-demand treatment or prophylaxis with C1 inhibitor (Cinryze™) has been shown to be effective in reducing the number of attacks and decreasing their severity and duration, and has been recommended as a treatment option.[3,5,7,11,12]

Patients with a history of angiotensin-converting enzyme inhibitor (ACEI) associated angioedema would not be expected to respond to treatment with C1 inhibitor as these patients have normal levels of C4 and functional C1

inhibitor.[2] There is insufficient evidence to recommend treatment with C1 inhibitor for ACEI induced angioedema at this time.[13]

Pharmacology/Pharmacokinetics[1,2]

C1 inhibitor is found in human blood and is a serine protease inhibitor that is involved in the regulation of the complement and intrinsic coagulation or contact system pathway, as well as the fibrinolytic system. C1 inhibitor forms a complex with the protease causing inactivation. When there are low levels of functional C1 inhibitor, activation of the above pathways is not regulated. Treatment with C1 inhibitor results in an increase in plasma levels of C1 inhibitor to help regulate activation of the contact system, by inactivation of coagulation factor XIIa and kallikrein, preventing the release of bradykinin, which is thought to be responsible for the symptoms associated with HAE and increased vascular permeability.[2]

C1 Inhibitor (Berinert)*	AUC (hr X IU/ml)	CL (ml/hr/kg)	V (ml/kg)	Half-life (hrs)	MRT (hrs)
Unadjusted for baseline	27.5±8.5	0.60±0.17	18.6±4.9	21.9±1.7	31.5±2.4
Adjusted for baseline	12.8±6.7	1.44±0.67	35.4±10.5	18.4±3.5	26.4±5.0

* Single dose (500 to 1500 units)
AUC=Area Under the Curve; CL=Clearance; V=Volume at steady state; MRT=Mean Residence Time

FDA Approved Indication(s)[1]

C1 inhibitor (Berinert) is FDA-approved for the treatment of acute abdominal or facial attacks of HAE in adolescent and adult patients.[1]

Potential Off-Label Uses[1,14-19]

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Potential for off-label uses of C1 inhibitor (Berinert) include treatment of acute laryngeal attacks, long-term prophylaxis, on-demand therapy, and short-term prophylaxis; based on reports with a Berinert product approved outside the U.S.,[14-17] or due to data with other formulations of C1 inhibitor.[18,19] According to a case series (N=42), treatment with C1 inhibitor (Berinert HS, Germany) 500 to 1000 units in 193 laryngeal episodes of acute HAE was effective in disrupting the progression of symptoms, and reducing the mean duration of symptoms compared to patients who did not receive treatment with C1 inhibitor.[14] Use of C1 inhibitor (Berinert) for prophylaxis of HAE attacks has not been adequately studied.[1] Long-term prophylaxis with other formulations of C1 inhibitor have been found to be effective in reducing the number of attacks per patient when administered on a chronic basis (e.g., once or twice weekly) compared to placebo or historical controls.[18,19] In a comparison of 22 patients with severe HAE and inadequate efficacy or intolerance to danazol, treatment with C1 inhibitor (Berinert P, Germany) at an individualized dose (usual dose 500 to 1000 units twice weekly, with patients instructed to administer treatment at early signs of an acute attack) reduced the number of attacks per year compared to historical controls.[15] Another retrospective case control study evaluated 75 patients with abdominal HAE attacks treated with C1 inhibitor (Berinert P, Germany), 25 of which utilized on-demand therapy. Overall, the mean duration of abdominal attacks decreased with treatment compared to untreated episodes.[16] Case reports are available on the effectiveness of C1 inhibitor (Berinert P, Germany) in short-term prophylaxis (e.g., 500 to 1000 units) prior to or during surgical procedures.[17] There are a few case reports available outside the U.S. describing the effect of C1 inhibitor in treating patients with ACEI-induced angioedema. One patient presenting with ACE-induced angioedema and normal C1 inhibitor levels responded to treatment with 1500 units C1 inhibitor (Berinert).[13]

Current VA National Formulary Alternatives[2,3,5,7,11]

Danazol, a synthetic androgen, is approved for use in HAE and prevents attacks involving edema of the face, abdomen, extremities, and airway. Danazol increases C1 esterase inhibitor levels as well as levels of C4. Danazol is also used for short-term prophylaxis prior to an event or procedure.

Antifibrinolytic agents such as aminocaproic acid have been used for long-term prophylaxis in patients with HAE, but have not been FDA-approved for this indication. It has been suggested that treatment with antifibrinolytic agents may not be as effective as androgen therapy; although, direct comparison trials have not been conducted.

Cinryze™, another C1 inhibitor, is available nonformulary in the VA, and is approved for prophylaxis of HAE; it has also been studied in the treatment of acute HAE attacks and as on-demand therapy for the management of HAE.

Dosage and Administration[1,2]

General Recommendations: C1 inhibitor (Berinert) is available as a kit that includes a single-use vial of Berinert 500 units, a 10 ml vial of sterile water (diluent), one Mix2Vial™ transfer set, and an alcohol swab. The Berinert freeze-dried powder should be protected from light prior to reconstitution and stored at 36°F to 77°F (2°C to 25°C) and the powder and sterile water for injection should be brought to room temperature prior to reconstitution. The procedure for reconstitution using the contents of the kit is available in the product information and summarized as follows. After using the alcohol swab on both vial stoppers, snap the blue end of the Mix2Vial™ transfer set onto the vial stopper of the diluent, then snap the opposite end of the Mix2Vial™ onto the Berinert vial stopper; gently swirl the Berinert vial until the powder is dissolved (do not shake contents). Unscrew the set so that it is in two sections. After drawing air into an empty sterile syringe, screw the syringe to the Mix2Vial™ and inject the air into the vial containing the Berinert. Invert the vial and slowly draw the contents into the syringe. Unscrew the syringe from the Mix2Vial™ transfer set; attach the syringe to an appropriate IV administration set. The reconstituted solution should be colorless and clear; do not use if any particulate material is visible or if the solution appears cloudy or is discolored. If more than one vial is required for a single dose, the required contents can be added to one administration device (note: a new Mix2Vial™ transfer set should be used to reconstitute each Berinert vial) to administer the dose at a rate of approximately 4 ml per minute. Once reconstituted, the dose should not be refrigerated and administration should begin within 8 hours.

Recommended Dose of C1 Inhibitor (Berinert) for Treatment of Acute HAE Attacks

Availability	Dose	Infusion Rate
500 units single dose vial (reconstituted with 10 ml diluent)	20 units/kg IV	4 ml/min

Product Access

C1 inhibitor (Berinert®) is available through specialty pharmacies and distributors via the Berinert Expert Network (B.E.N.); additional information available by calling 1-877-236-4423.

Efficacy

A literature search was performed on PubMed/Medline using the search terms C1 inhibitor and hereditary angioedema through 16 Apr 2010. The search was limited to clinical trials in humans that were published in the English language. Reference lists of review articles were searched for relevant clinical trials. All controlled trials published in peer-reviewed journals evaluating treatment with C1 inhibitor (Berinert) in patients with hereditary angioedema in other than healthy subjects were included. One clinical trial that evaluated C1 inhibitor (Berinert) in the treatment of patients presenting with an acute attack of HAE met these criteria and is discussed below (details provided in the Appendix); data from randomized controlled clinical trials are not available on the use of C1 inhibitor (Berinert) for prophylaxis of HAE attacks. The manufacturer's AMCP dossier was not available at the time this review was prepared.

Efficacy Measures (Pivotal Clinical Trial)[20]

Primary Endpoint
- Time from initiation of treatment to onset of symptom relief

Secondary and Other Endpoints
- Time to complete HAE symptom resolution
- Percent of patients with worsened HAE symptoms between 2 and 4 hours after treatment initiation vs. baseline for at least 1 baseline HAE symptom
- Number of vomiting episodes within 4 hours of treatment initiation

Clinical Trial Data[20]

The efficacy and safety of C1 inhibitor (Berinert) was evaluated in a phase II/III multicenter, randomized, parallel-group, double-blind, placebo-controlled trial of 125 patients with type I or II HAE who presented with acute abdominal (79.0%) or facial (20.2%; not lanryngeal) symptoms of HAE that were of moderate to severe intensity and within 5 hours of the attack progressing to moderate intensity.[20] Patients were randomized to treatment with C1 inhibitor (Berinert) at a dose of 10 units/kg (n=40), 20 units/kg (n=43), or placebo (n=42). If the patient reported inadequate or no symptom relief at 4 hours, they could receive an additional dose as follows: Berinert 10 units/kg, if previously given 10 units/kg; Berinert 20 units/kg, if previously given placebo; or placebo, if previously administered 20 units/kg. It was reported that 11.3% of patients were taking danazol during the study. The primary endpoint of time from initiation of treatment to onset of symptom relief was evaluated by response to a standard question asked of patients at specified time intervals for up to 24 hours after treatment was started. Patients who received rescue medication or analgesics, antiemetics, open-label C1 inhibitor, or fresh frozen plasma after 4 hours had their time to onset of symptom relief set at 24 hours (14.0% of patients treated with 20 units/kg; 28.2% who received 10 units/kg; 40.5% in the placebo group). Treatment with C1 inhibitor (Berinert) 20 units/kg reduced the median time from initiation of treatment to onset of symptom relief compared to placebo (0.5 hours vs. 1.5 hours, respectively; p=0.0025). C1inhibitor (Berinert) 10 units/kg did not reduce time to onset of symptom relief compared to placebo (1.2 hours vs. 1.5 hours, respectively). The median time to onset of symptom relief was shorter for abdominal attacks (0.5 hours with C1 inhibitor 20 units/kg vs. 1.3 hours with placebo) compared to facial attacks (0.9 hours C1 inhibitor 20 units/kg vs. 24.0 hours with placebo). Although not statistically significant, there was a greater difference in the time to response with C1 inhibitor 20 units/kg compared to placebo in patients with severe symptoms compared to patients experiencing moderate symptoms (p=0.463). Treatment with the 20 units/kg dose improved the secondary endpoints of time to complete resolution of all HAE symptoms (median 4.92 hours vs. 7.79 hours with placebo; p=0.0237), the percent of patients that experienced worsening of their HAE symptoms within 2 to 4 hours after treatment initiation (4.7% vs. 31.0% with placebo; p=0.0014), and the mean number of vomiting episodes within 4 hours after the start of treatment (0.1 vs. 0.8 with placebo; median episodes p=0.0329). The reduction in the median time to onset of symptom relief was more pronounced with patients reported to have severe attacks who were treated with C1 inhibitor 20 units/kg (0.50 hours; range 0.17-24.0 vs. placebo 13.50 hours; range 0.20-24.0) compared to patients with moderate HAE attacks treated with C1 inhibitor 20 units/kg (0.78 hours; range 0.17-24.0 vs. placebo 1.33 hours; range 0.25-24.0). Rescue medication was administered to 18.6% of patients initiated on 20 units/kg compared to 33.3% who received 10 units/kg, and 57.1% of patients in the placebo group.[20]

Among the 126 patients included in the safety analysis, 19.6% of patients treated with C1 inhibitor (Berinert) 20 units/kg reported an adverse event within 4 hours of treatment compared to 43.9% of patients receiving placebo. For adverse events that were thought possibly related to treatment, this occurred in 10.9% of patients receiving C1 inhibitor 20 units/kg vs. 19.5% of patients on placebo. The most frequently reported adverse events with any dose C1 inhibitor included gastrointestinal complaints, muscle spasms, and pain. No serious adverse events were reported within 4 hours of administration; after this time, 4 patients reported 9 serious adverse events (exacerbation HAE). It was reported that there were no seroconversions for HIV, hepatitis virus, or human B19 virus up to 12 weeks following treatment.[20]

Adverse Events (Safety Data)[1]

Deaths and Other Serious Adverse Events[1]

In the product information referring to the pivotal clinical trial, it was reported that serious treatment-emergent adverse events in 5 patients (reported as in 4 patients in the clinical trial publication described above) included laryngeal edema, facial attack with laryngeal edema, swelling of the shoulder and chest, HAE exacerbation, and laryngospasm.

Common Adverse Events[1]

The most frequently occurring adverse events (reported in ≥ 4%) in patients receiving C1 inhibitor (Berinert) included HAE attack recurrence, headache, abdominal pain, nausea, muscle spasms, pain, diarrhea, and vomiting.

Adverse Event	C1 Inhibitor (Berinert) (n=43) Number of Patients (%)	Placebo (n=42) Number of Patients (%)
Nausea	3 (7)	5 (11.9)
Dysgeusia	2 (4.7)	0
Abdominal pain	2 (4.7)	3 (7.1)
Vomiting	1 (2.3)	3 (7.1)
Diarrhea	0	4 (9.5)
Headache	0	2 (4.8)

For further details on the safety results as reported in the pivotal clinical trial, refer to the Appendix.

Postmarketing Safety Experience[1,21]

Adverse reactions including hypersensitivity or anaphylactic reactions, and shock; possible viral transmission (including acute hepatitis C); and injection site pain and redness, chills, and fever have been reported in Europe in patients who received C1 inhibitor (Berinert). There have also been case reports of increased frequency of HAE attacks in patients receiving frequent treatments for acute HAE over a long period of time (e.g., over 18 to 27 years) with C1 inhibitor (Berinert P, Germany).[21]

Sentinel Events

No data.

Contraindications[1]

C1 inhibitor (Berinert) is contraindicated in patients who have experienced a life-threatening acute hypersensitivity reaction or anaphylaxis to the medication or other C1 inhibitor formulations.

Warnings and Precautions[1]

Hypersensitivity: The use of C1 inhibitor (Berinert) has been associated with severe hypersensitivity reactions including anaphylaxis, hives, urticaria, chest tightness, wheezing, and hypotension. Treatment options should take into consideration that symptoms associated with hypersensitivity to the medication may be similar to the symptoms associated with HAE. In patients with hypersensitivity, the C1 inhibitor infusion should be discontinued and appropriate treatment administered; epinephrine should be available for acute severe hypersensitivity reactions.

Thrombotic Events: The off-label use of C1 inhibitor (Berinert) at high doses has been associated with thrombotic events.

Transmission of Infectious Agents: Since C1 inhibitor (Berinert) is derived from human blood it has the potential risk for transmitting infectious diseases including viruses and Creutzfeldt-Jakob disease. Screening and testing

measures as well as manufacturing processes have been implemented to reduce this risk. If it is felt that an infection could possibly be the result of C1 inhibitor administration, this should be reported by the provider to the manufacturer (CSL Behring Pharmacovigilance Department 1-866-915-6958). The risk vs. benefit of treatment with C1 inhibitor should also be discussed with the patient.

Specific Populations[1]

Pregnancy: C1 inhibitor (Berinert) is Pregnancy Category C. It is not known if the use of C1 inhibitor in pregnant females may cause harm to the fetus or if there are untoward effects on reproduction; therefore, the risk vs. benefit should be considered before administering C1 inhibitor to a pregnant woman. In a retrospective case control study, use of repeated doses of Berinert (up to 3,500 units per attack) in 20 pregnant females did not result in delivery complications or have an adverse effect on the newborn infant. Berinert has not been evaluated in animal reproduction studies.

Labor and Delivery: The effects of C1 inhibitor (Berinert) have not been studied in this setting; the risk vs. benefit to the mother and child should be considered before administering C1 inhibitor.

Nursing Mothers: It is unknown if C1 inhibitor (Berinert) is excreted in human milk; use only if necessary in a nursing mother.

Demographics (Age): According to the manufacturer, data are inadequate to determine whether the safety and efficacy differs depending on the patient's age as there were only five children, eight adolescent patients, and four patients over the age of 65 included in the trials evaluating C1 inhibitor (Berinert).

Look-alike/Sound-alike (LA/SA) Error Risk Potential

As part of a Joint Commission standard, LA/SA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	First DataBank	USP	ISMP	Clinical Judgment
C1 Inhibitor powder inj (Human)	None	None	None	None	Carnitor, C1 Inhibitor (Cinryze™)
Berinert®	None	None	None	None	None

Drug Interactions[1]

The manufacturer reports that there are no drug interaction studies that have been conducted with C1 inhibitor (Berinert).

Acquisition Cost

Availability	Acute Treatment Dose	Price[a]/Vial	Price/Treatment Dose[b]
C1 Inhibitor (Berinert) 500 unit vial kit	20 units/kg (e.g., 1440 units/72kg patient)	$991.79	$2,975.37 (e.g., 3 vials)

[a] Price per Low2000 as of 08062010; check VA pricing sources for updated information
[b] Dose estimate for 72 kg patient

Price Comparison

Availability	Acute Treatment Dose	Price[b]/Vial	Price/Treatment Dose
C1 Inhibitor (Cinryze) 500 unit vial	1000 units[a]	$1,489.45	$2,978.90 (2 vials)
Ecallantide[c] 10mg/ml vial (3 vials/pkg)	30 mg	$2,650.00	$7,950.00 (3 vials)

[a] Off-label use
[b] Price per Low2000 as of 08062010; check VA pricing sources for updated information
[c] Ecallantide is a kallikrein inhibitor, recently approved for the treatment of acute HAE attacks

Cost-Effectiveness Analysis

There are currently no published economic evaluations with C1 inhibitor (Berinert).

Conclusions

According to one published randomized controlled trial of 125 patients with acute abdominal or facial (not laryngeal) symptoms of HAE, treatment with C1 inhibitor (Berinert) at a dose of 20 units/kg significantly reduced the primary endpoint of time from treatment to onset of symptom relief compared to placebo (median 0.5 hours vs. 1.5 hours, respectively). Treatment with the 20 units/kg dose also improved the time to complete resolution of all HAE symptoms (mean 81.84 hours vs. 125.08 hours with placebo; median 4.92 vs. 7.79 hours with placebo). It appears the reduction in median time to onset of symptom relief was more pronounced with C1 inhibitor treatment in patients reported to have severe attacks compared to patients who reported their HAE attack to be of moderate intensity.

Treatment with another form of C1 inhibitor (Cinryze), also reduced the time to onset of relief of acute HAE attacks compared to placebo; however, it is not approved for this indication and a direct comparison cannot be made between the two formulations of C1 inhibitor due to difference in study design and inclusion criteria. The C1 inhibitor (Cinryze) is indicated for routine prophylaxis against angioedema attacks in patients with HAE and has been studied for the off-label use as on-demand therapy. The safety and efficacy of the C1 inhibitor (Berinert) for prophylaxis (routine or on-demand) of HAE attacks has not been established.

In patients with HAE, treatment with C1 inhibitor (Berinert) has not been compared to other treatments used for the management of acute HAE attacks (e.g., fresh frozen plasma, ecallantide) or evaluated against treatment for prophylaxis of HAE attacks (e.g., attenuated androgens, antifibrinolytics).

Neither formulation of C1 inhibitor (Berinert or Cinryze) has been studied for short-term prophylaxis; although, it has been recommended outside the U.S. as an option (attenuated androgens, antifibrinolytics, fresh frozen plasma have also been recommended) for short-term prophylaxis in patients undergoing a major procedure or requiring intubation. As with the C1 inhibitor Cinryze, there is insufficient evidence to recommend treatment with the C1 inhibitor Berinert for ACEI induced angioedema at this time.

Treatment with C1 inhibitor (Berinert) is reported to be well-tolerated with the percent of patients experiencing an adverse event to be less than placebo. The most frequently occurring adverse events in patients receiving C1 inhibitor (Berinert) included HAE attack recurrence, headache, abdominal pain, nausea, muscle spasms, pain, diarrhea, and vomiting. C1 inhibitor (Berinert) carries the same risk as with other blood derived products; therefore, the risk vs. benefit of treatment should be carefully considered and discussed with the patient.

References

1. Berinert® [C1 Esterase inhibitor (human)] prescribing information. Kankakee, IL:CSL Behring LLC.; 2009 Oct.
2. Zuraw BL. Hereditary angioedema. N Engl J Med 2008;359:1027-36.
3. Bowen T, Cicardi M, Bork K, et al. Hereditary angioedema: a current state-of-the-art review. VII. Canadian Hungarian 2007 International Consensus Algorithm for the Diagnosis, Therapy, and Management of Hereditary Angioedema. Ann Allergy Asthma Immunol 2008;100:Suppl 2:S30-40.
4. Levy JH, Freiberger DJ, Roback J. Hereditary angioedema: current and emerging treatment options. Anesth Analg 2010;110:1271-80.
5. Gompels MM, Lock RJ, Abinum M, et al. C1 inhibitor deficiency: consensus document. Clin and Exp Immunol 2005;139:379-94.
6. Prematta M, Gibbs JG, Pratt EL, Stoughton TR, Craig TJ. Fresh frozen plasma for the treatment of hereditary angioedema. Ann Allergy Asthma Immunol 2007;98:383-8.
7. Craig T, Riedl M, Dykewicz MS, et al. When is prophylaxis for hereditary angioedema necessary? Ann Allergy Asthma Immunol 2009;102:366-72.
8. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. Arch Intern Med 2001;161:2417-29.
9. Frank MM, Sergent JS, Kane MA, Alling DW. Epsiolon aminocaproic acid therapy of hereditary angioneurotic edema: a double-blind study. N Engl J Med 1972;286:808-812.
10. Gelfand JA, Sherins RJ, Alling DW, Frank MM. Treatment of hereditary angioedema with danazol: reversal of clinical and biochemical abnormalities. N Engl J Med 1976;295:1444-8.
11. Levi M, Choi G, Picavet C, Hack CE. Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency. J Allergy Clin Immunol 2006;117:904-8.
12. Longhurst HJ, Carr S, Khair K. C1-inhibitor concentrate home therapy for hereditary angioedema: a viable, effective treatment option. Clin Exp Immunol 2007;147:11-7.
13. Nielsen EW, Gramstad S. Angioedema from angiotensin-converting enzyme (ACE) inhibitor treated with complement 1 (C1) inhibitor concentrate. Acta Anaesthesiol Scand 2006;50:120-2.
14. Bork K, Barnstedt SE. Treatment of 193 episodes of laryngeal edema with C1 inhibitor concentrate in patients with hereditary angioedema. Arch Intern Med 2001;161:714-8.
15. Kreuz W, Martinez-Saguer I, Aygören-Pürsün E, et al. C1-inhibitor concentrate for individual replacement therapy in patients with severe hereditary angioedema refractory to danazol prophylaxis. Transfusion 2009;49:1987-95.
16. Bork K, Meng G, Staubach, Hardt J. Treatment with C1 inhibitor concentrate in abdominal pain attacks of patients with hereditary angioedema. Transfusion 2005;45:1774-84.
17. De Serres J, Gröner A, Lindner J. Safety and efficacy of pasteurized C1 inhibitor concentrate (Berinert® P) in hereditary angioedema: a review. Transfus Apher Sci 2003;29:247-54.
18. Cinryze™ (C1 inhibitor [human]) prescribing information. New York, NY:Lev Pharmaceuticals, Inc.; 2008 Oct.
19. Levi M, Choi G, Picavet C, Hack CE. Self-administration of C1-inhibitor concentrate in patients with hereditary or acquired angioedema caused by C1-inhibitor deficiency. J Allergy Clin Immunol 2006;117:904-8.
20. Craig TJ, Levy RJ, Wasserman RL, et al. Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. J Allergy Clin Immunol 2009;124:801-8.
21. Bork K, Hardt J. Hereditary angioedema: increased number of attacks after frequent treatments with C1 inhibitor concentrate. Am J Med 2009;122:780-3.

Prepared (May 2010)/Contact Person: Elaine M. Furmaga, Pharm.D, Clinical Pharmacy Specialist, VA National PBM Services

Appendix: Published Clinical Trials

<table>
<tr><th>Citation</th><th>Eligibility Criteria</th><th>Interventions</th><th>Efficacy Results/Author's Conclusions</th><th>Safety Results/Study Limitations</th></tr>
<tr>
<td>Craig TJ et al, 2009[19]

MC, R, DB, PC

Argentina, Australia, Canada, Eastern Europe, Israel, Macedonia, Spain, Sweden, U.K., U.S.

n=125

Sponsored by CSL Behring</td>
<td><u>Inclusion Criteria</u>
At least 6 years of age; laboratory confirmed C1 INH deficiency (type I or II HAE); acute moderate to severe attack with abdominal or facial sx (not laryngeal) presenting within 5 hrs of becoming moderate in intensity

<u>Exclusion Criteria</u>
Hypersensitivity to C1 INH, acquired or other types of angioedema or abdominal pain not associated with C1 INH deficiency, use of pain medication during current attack, habitual narcotic use, tx with other form of C1 INH or other tx for acute HAE, or use of FFP within 7d of study tx</td>
<td>Single IV infusion of:
C1 INH (Berinert) 10U/kg,
C1 INH (Berinert) 20U/kg,
or Placebo

If patients reported inadequate or no symptom relief at 4 hrs, patients could receive an additional dose as follows:
C1 INH (Berinert) 10U/kg (if previously given 10U/kg);
C1 INH (Berinert) 20U/kg (if previously given placebo);
or Placebo
(if previously given 20U/kg)

Time to relief of sx set at 24hrs if pt received rescue medication, analgesics, antiemetics, open-label C1 INH, or FFP after 4 hrs</td>
<td><u>Endpoints</u>
Primary: time from tx initiation to onset of sx relief
Secondary: time to complete HAE sx resolution; % patients with worsened HAE sx 2 to 4 hrs after tx initiation vs. baseline for ≥ 1 baseline HAE sx; number vomiting episodes within 4 hr tx initiation

<u>Baseline</u>
HAE: 87% Type I; 12% Type II
Mean age (yrs): 33.1±13.76; Gender: 32.3% male
Race: 89.5% White; 3.2% Black; 4.0% Hispanic; 2.4% Asian
Attack intensity: 68.5% moderate; 31.5% severe

<u>Results</u>
<table>
<tr><th></th><th>C1 INH 20U/kg (n=43)</th><th>Placebo (n=42)</th><th>p value</th></tr>
<tr><td colspan="4">Time to onset sx relief (hrs)*</td></tr>
<tr><td>Mean (SD)</td><td>3.89 (8.2)</td><td>10.27 (11.48)</td><td></td></tr>
<tr><td>Median (range)</td><td>0.5 (0.17-24.0)</td><td>1.5 (0.2-24.0)</td><td>0.0025</td></tr>
<tr><td colspan="4">Time to HAE sx resolution (hrs)</td></tr>
<tr><td>Mean (SD)</td><td>81.84 (314.4)</td><td>125.08 (382.8)</td><td></td></tr>
<tr><td>Median (range)</td><td>4.92 (0.5-1486.2)</td><td>7.79 (0.3-1486.2)</td><td>0.0237</td></tr>
<tr><td colspan="4">% with increased HAE attack intensity within 2 to 4 hrs tx</td></tr>
<tr><td>n (%)</td><td>2 (4.7)</td><td>13 (31.0)</td><td>0.0014</td></tr>
<tr><td colspan="4">Number episodes vomiting within 4 hrs tx</td></tr>
<tr><td>Mean (SD)</td><td>0.1 (0.41)</td><td>0.8 (2.59)</td><td></td></tr>
<tr><td>Median (range)</td><td>0 (0-2)</td><td>0 (0-16)</td><td>0.0329</td></tr>
</table>
* Primary endpoint; time to onset sx relief set at 24hrs as follows:
C1 INH 20U/kg (14.0%); C1 INH 10 U/kg (28.2%); Placebo (40.5%)

Median time (hrs) to onset of sx relief by intensity of attack:
Moderate: C1 INH 20 U/kg (0.78; range 0.17-24.0) vs. placebo (1.33; range 0.25-24.0)
Severe: C1 INH 20 U/kg (0.50; range 0.17-24.0) vs. placebo (13.50; range 0.20-24.0)

Rescue medication (% pts):
C1 INH 20U/kg (18.6%); C1 INH 10 U/kg (33.3%); Placebo (57.1%)

<u>Study Conclusions</u>
Treatment with C1 INH (Berinert) 20U/kg was safe and effective in reducing the time to onset of symptom relief in patients with acute abdominal and facial HAE attacks</td>
<td><u>Adverse Events</u>
9 SAEs (HAE exacerbation) reported in 4 pts
<table>
<tr><th>AE</th><th>C1 INH 20U/kg</th><th>Placebo</th></tr>
<tr><td>Any AE</td><td>9(19.6%)</td><td>18 (44%)</td></tr>
<tr><td>Tx related AE</td><td>5 (10.9%)</td><td>8 (19.5%)</td></tr>
<tr><td>HA</td><td>0</td><td>2 (4.9%)</td></tr>
<tr><td>Abdominal pain</td><td>2 (4.3%)</td><td>3 (7.3%)</td></tr>
<tr><td>Nausea</td><td>3 (6.5%)</td><td>5 (12.2%)</td></tr>
<tr><td>Muscle spasms</td><td>1 (2.2%)</td><td>2 (4.9%)</td></tr>
<tr><td>Pain</td><td>1 (2.2%)</td><td>1 (2.4%)</td></tr>
<tr><td>Diarrhea</td><td>0</td><td>4 (9.8%)</td></tr>
<tr><td>Vomiting</td><td>1 (2.2%)</td><td>3 (7.3%)</td></tr>
<tr><td>Back pain</td><td>0</td><td>1 (2.4%)</td></tr>
<tr><td>Dysgeusia</td><td>2 (4.3%)</td><td>0</td></tr>
<tr><td>Peripheral edema</td><td>1 (2.2%)</td><td>0</td></tr>
<tr><td>Abdominal distention</td><td>0</td><td>0</td></tr>
<tr><td>Face edema</td><td>0</td><td>1 (2.4%)</td></tr>
<tr><td>Lip swelling</td><td>0</td><td>1 (2.4%)</td></tr>
</table>
<u>Study Analysis</u>
• Large SD for the mean; median more appropriately used for evaluation
• Higher percentage of patients on placebo had primary endpoint time set at 24hrs
• Patients presenting with laryngeal sx not included
• No standardized method for grading severity of HAE attack; severity of attack noted per patient as mild, moderate, severe with investigator confirmation
• Quality of life not evaluated</td>
</tr>
</table>

AE=adverse event; C1 INH=C1 inhibitor; d=day; DB=double-blind; FFP=fresh frozen plasma; HA=headache; HAE=hereditary angioedema; hrs=hours; IV=intravenous; kg=kilogram; MC=multi-center; n=number of patients; PC=placebo-controlled; pt=patient; R=randomized; SAE=serious adverse event; SD=standard deviation; sx=symptoms; tx=treatment; U=units