

National PBM Drug Monograph C1 Inhibitor (Cinryze™) June 2009

VHA Pharmacy Benefits Management Services and the Medical Advisory Panel

The purpose of VACO PBM-MAP 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 Documents will be placed in the Archive section when the information is deemed to be no longer current.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

- **Indications:** C1 inhibitor (human) Cinryze™ was approved by the FDA for routine prophylaxis against angioedema attacks in adolescent and adult patients with hereditary angioedema (HAE).
- **Efficacy:** In a 12 week placebo-controlled cross-over trial of patients with HAE (unpublished data), prophylaxis with C1 inhibitor 1000 units twice per week significantly reduced the number of attacks per patient (means 6.1 vs. 13.5) and decreased the severity and duration of attacks, as well as the number of days of swelling. The efficacy of C1 inhibitor for acute treatment (off-label use) was evaluated in a placebo-controlled trial (unpublished data) of patients with HAE attacks, with a reduction in the median time to onset of relief reduced in patients treated with C1 inhibitor (2.0 hours) compared to placebo (greater than 4 hours). There was also a reduction in the median time to complete resolution of symptoms in the C1 inhibitor treatment group compared to placebo (12.3 vs. 31.6 hours, respectively). Another trial was conducted in patients instructed on the self-administration of C1 inhibitor. Patients in the on-demand treatment group for acute symptoms experienced a significant reduction in the time from symptom onset to treatment (1.4 vs. 3.4 hours), time to symptom relief, and time to symptom resolution (5.9 vs. 13.8 hours), compared to historical controls. Self-administration of treatment prophylaxis with C1 inhibitor in patients with a history of frequent severe attacks of angioedema significantly reduced the number of attacks to a mean of 0.3 per month compared to historical control of 4 per month.
- **Safety:** The most frequently occurring adverse events (reported in $\geq 5\%$) in patients receiving C1 inhibitor included upper respiratory tract infection, sinusitis, rash, and headache. Serious adverse events that have been reported in clinical trials with C1 inhibitor (but considered not related to the medication) include death (due to non-catheter related foreign body embolus), preeclampsia resulting in delivery by emergency caesarean section, stroke, and HAE attack exacerbation. The use of C1 inhibitor has also been associated with severe hypersensitivity reactions including anaphylaxis, hives, urticaria, chest tightness, wheezing, and hypotension. Since C1 inhibitor (Cinryze™) is derived from human blood, it has the potential risk 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 administration, this should be reported by the provider to the manufacturer. The risk vs. benefit of treatment with C1 inhibitor should also be discussed with the patient.
- **Dose:** C1 inhibitor should be administered as a total dose of 1000 units (2 vials should be reconstituted for one dose with a concentration of 100 units/ml) intravenously over 10 minutes at a rate of 1 ml/minute. The recommended dose for routine prophylaxis of angioedema attacks in patients with HAE is 1000 units administered every 3 to 4 days. Once reconstituted, the dose must be administered within 3 hours.
- **Conclusions:** C1 inhibitor appears to be effective for prophylaxis in patients with HAE and frequent attacks (≥ 2 attacks per month; patients may also have been on prophylaxis with 17-alpha alkylated androgens or antifibrinolytic agents prior to enrollment and during the study) by reducing the number of angioedema attacks, and decreasing the severity and duration of attacks. The efficacy of C1 inhibitor was also evaluated for acute treatment of HAE attacks, and reduced the time to onset of relief compared to placebo. Select patients may also benefit from self-administration of C1 inhibitor for prophylaxis or treatment of acute HAE attacks after extensive education regarding the disease and administration of the medication. Treatment with C1 inhibitor appears to be well-tolerated with the most frequently occurring adverse events including upper respiratory tract infection, sinusitis, rash, and headache. Since treatment with C1 inhibitor has been associated with severe hypersensitivity reactions and the prophylaxis trial conducted in the U.S. only included those patients who had received an initial dose in a medical treatment facility as part of the acute treatment trial, consideration should be given to administering the first dose under medical supervision, or only after extensive education on the proper administration of C1 inhibitor and management of a hypersensitivity reaction if it were to occur. C1 inhibitor 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. In patients with HAE, treatment with C1 inhibitor has not been compared to other treatments used for prophylaxis of angioedema attacks or evaluated against current treatment of acute angioedema attacks. C1 inhibitor should be reserved for treatment of prophylaxis of angioedema attacks in patients with HAE who have an inadequate response to or intolerable side effects or contraindications to current VA National Formulary agents (e.g., danazol, epsilon aminocaproic acid). In these patients, treatment with C1 inhibitor as on-demand therapy (note: off-label; patient requires extensive education on self-administration and management of hypersensitivity if it were to occur) could be considered. If the patient continues to experience frequent attacks (e.g., > 1 per 10 days) then routine prophylaxis may be appropriate. C1 inhibitor has not been studied in short-term prophylaxis; although, it has been recommended outside the U.S. as an option (danazol, fresh frozen plasma have also been recommended) as prophylaxis for major procedures or those requiring intubation. The risk vs. benefit of off-label use of C1 inhibitor for short-term prophylaxis or in the management of acute HAE attacks should be evaluated on a case by case basis. There is insufficient evidence to recommend treatment with C1 inhibitor for ACEI induced angioedema at this time.

June 2009

Updated versions may be found at www.pbm.va.gov or <http://vaww.pbm.va.gov>

National PBM Drug Monograph C1 Inhibitor (Cinryze™) June 2009

VHA Pharmacy Benefits Management Services and the Medical Advisory Panel

Introduction¹⁻⁸

C1 inhibitor (human) (Cinryze™, ViroPharma) was approved by the FDA October 14, 2008 for routine prophylaxis against angioedema attacks in adolescent and adult patients with hereditary angioedema (HAE).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 is 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 which can occur on average every 1 to 2 weeks. Some patients rarely will experience an attack while others have them on a more frequent basis.^{2,3}

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.² 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; although, attacks may occur without a precipitating factor.³ 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 (refer to discussion in Pathophysiology/Pharmacology below).^{3,4}

Management of HAE includes treatment of acute symptoms, and short and long-term prophylaxis.^{3,4} Use of C1 inhibitor has been found to be effective in the treatment of acute attacks. Fresh frozen plasma that contains C1 inhibitor has also been used for acute attacks although it has been suggested that an exacerbation may occur in some patients due to the potential for bradykinin production. Symptom control includes narcotic analgesics for abdominal pain, and antiemetics and hydration. Intubation may be necessary in patients with oropharyngeal involvement if closure of the airway occurs.³ For short-term prophylaxis, treatment with C1 inhibitor (not studied with Cinryze™) has been recommended 1 hour prior to a procedure or event that may trigger an attack. Administration of 17-alpha alkylated androgens (e.g., danazol) or fresh frozen plasma has also been used for short-term prophylaxis.^{3,4} It is recommended that long-term prophylaxis be considered for patients with frequent or severe attacks. Treatment with androgens (e.g., danazol) or antifibrinolytic agents (e.g., epsilon aminocaproic acid, tranexamic acid) reduces the frequency of attacks compared to placebo.³⁻⁷ On-demand treatment or prophylaxis with C1 inhibitor has been shown to be effective in reducing the number of attacks and decreasing their severity and duration.^{1,2,8}

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.³ There is insufficient evidence to recommend treatment with C1 inhibitor for ACEI induced angioedema at this time.

Pathophysiology/Pharmacology¹⁻³

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.³

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 factors XII and XIIa, and kallikrein, preventing the release of bradykinin, which is thought to be responsible for the symptoms associated with HAE and increased vascular permeability.^{2,3}

Pharmacokinetics^{1,2}

Dose*	C baseline (U/ml)	Cmax (U/ml)	Tmax (hrs)	AUC (U hr/ml)	CL (ml/min)	T _{1/2} (hrs)
Single dose	0.31±0.20	0.68±0.08	3.9±7.3	74.5±30.3	0.85±1.07	56±36
Double Dose	0.33±0.20	0.85±0.12	2.7±1.9	95.9±19.6	1.17±0.78	62±38

*Single dose=1,000 units; Double dose=1,000 units followed by additional 1,000 units 60 minutes later

FDA Approved Indication(s) and Off-Label Uses^{1,2}

C1 inhibitor is FDA approved for the routine prophylaxis against angioedema attacks in adolescent and adult patients with HAE.¹

Current VA National Formulary Alternatives^{3,4}

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 epsilon aminocaproic acid (EACA) have been used for long-term prophylaxis in patients with HAE, but it is not 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.

Dosage and Administration^{1,2,4}

General Recommendations: C1 inhibitor (Cinryze™) is available as a freeze-dried powder that should be protected from light prior to reconstitution and stored at 36°F to 77°F (2°C to 25°C). The powder and sterile water for injection should be brought to room temperature prior to reconstitution. A double-ended transfer needle should be inserted into a 5ml vial of sterile water for injection, then the opposite end of the needle in the inverted vial of sterile water should be inserted into the upright but tilted vial of C1 inhibitor; the vacuum in the medication vial will draw in the sterile water. The contents should be dissolved by gently swirling the bottle (do not shake as this will denature the protein⁴). The 5ml of reconstituted solution should be a colorless to a slightly bluish clear solution that will contain a concentration of 100 units/ml (500 units) C1 inhibitor. Two vials should be reconstituted for one dose using a filter needle to draw up the contents of the 2 vials into a syringe. After discarding the filter needle, a needle for injection or infusion set should be attached and the dose administered intravenously over 10 minutes at a rate of 1 ml/minute. Once reconstituted, the dose must be administered within 3 hours.

Recommended Dose of C1 Inhibitor for Routine Prophylaxis for HAE Attacks

Availability	Dose	Initial Infusion Rate	Maintenance Infusion Rate
500 units single dose vial (5ml reconstituted)	1000 units (2 vials) IV every 3 to 4 days	1 ml/min over 10 minutes	1 ml/min over 10 minutes as tolerated

Product Access

C1 inhibitor (Cinryze™) is available via a limited distribution system called Cinryze*Solutions* established by ViroPharma Incorporated (additional information available by calling 877-945-1000).²

Adverse Events^{1,2}

The most common adverse events ($\geq 5\%$) reported with C1 inhibitor (Cinryze™) include upper respiratory tract infection, sinusitis, rash, and headache. Serious adverse events that have been reported in clinical trials with C1 inhibitor (but considered not related to the medication) include death (due to non-catheter related foreign body embolus), preeclampsia resulting in delivery by emergency caesarean section, stroke, and HAE attack exacerbation. Adverse events reported in two or more patients enrolled in a study are included in the table below.

Adverse Event ^a	Number of Adverse Events	Number of Patients (n=24)
Sinusitis	8	5
Rash	7	5
Headache	4	4
Upper respiratory tract infection (URI)	3	3
Viral URI	5	3
Bronchitis	2	2
Limb injury	2	2
Back pain	2	2
Pain in extremity	2	2
Pruritus	2	2

^aAdverse events reported in at least 2 patients

The manufacturer reports that over 180 patients administered 9000 doses of C1 inhibitor were evaluated and were negative for seroconversion to parvovirus B19, Hepatitis B, Hepatitis C, and HIV.

Look-alike/Sound-alike Error Risk Potential

As part of a pilot program, the VA PBM and Center for Medication Safety queried a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonological similarities, as well as similarities in dosage form, strength and route of administration. By incorporating similarity scores as well as clinical judgment, it was determined that the following drug names may pose as potential sources of drug name confusion.

Drug Name	Potential Name Confusion
C1 Inhibitor (Human) 500 units single dose vial (per 5 ml when reconstituted) for IV injection	Carnitor (200 mg, inj)
	Carnitor SF (1 gm, oral solution)
Cinryze (brand) 500 units single dose vial (per 5 ml when reconstituted) for IV injection	Cerezyme (200 units, inj)
	Cinacalcet (30 mg tablets)
	Clindesse (2% vaginal cream)
	Sinemet (10 mg tablets)
	Synercid (350 mg, inj)

Contraindications^{1,2}

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

Warnings^{1,2}

Hypersensitivity: The use of C1 inhibitor 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 at high doses has been associated with thrombotic events.

General: Since C1 inhibitor is derived from human blood it has the potential risk 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 administration, this should be reported by the provider to the manufacturer. The risk vs. benefit of treatment with C1 inhibitor should also be discussed with the patient.

Precautions^{1,2}

Pregnancy: C1 inhibitor is Pregnancy Category C. The use of C1 inhibitor in pregnant females has not been adequately studied and there are no available data in animals. Since it is unknown as to whether C1 inhibitor may cause harm to the fetus or if there are untoward effects on reproduction, the risk vs. benefit should be considered before administering C1 inhibitor to a pregnant women.

Nursing Mothers: It is unknown if C1 inhibitor is excreted in human milk. Caution should be used if C1 inhibitor is given to a nursing female.

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

Patient Information: Patients should be instructed to immediately report any sign or symptoms of hypersensitivity (hives, urticaria, chest tightness, wheezing, hypotension, anaphylaxis) or thrombosis (new onset swelling or pain in limbs or abdomen, new onset chest pain or shortness of breath, loss of feeling or mobility, or altered speech or consciousness) to their healthcare provider. The risk for transmission of infection from C1 inhibitor has been minimized through screening, testing, and manufacturer processing. Regarding administration, the patient or caregiver should be informed of the following: C1 inhibitor should be protected from light; the contents of 2 vials should be used for 1 dose; the product should be reconstituted according to manufacturer instructions provided; the reconstituted solution should be a colorless to a slightly bluish clear solution and should not be administered if cloudy or if it contains particulates; once reconstituted, the solution should be administered intravenously as directed within 3 hours; any unused solution, used vials, needles, and syringes should be disposed of properly.

Demographics (Age): According to the manufacturer, there were three patients under the age of 18 included in one of the clinical trials and an inadequate number of patients over the age of 65 were studied to determine if there was a difference in safety or effectiveness based on the patient's age.

Nonclinical Toxicology^{1,2}

Carcinogenesis, Mutagenesis, Fertility Impairment: The manufacturer states that there have not been any animal studies evaluating C1 inhibitor in these areas.

Animal Toxicology/Pharmacology: Signs of toxicity were not apparent in a single dose study of 1, 7, and 28 times the normal dose in rats. The manufacturer reported that in a repeated dose study after 7 days, only the 28 times the normal dose was associated with a significant neutralizing antibody response between days 1 and 14. A potential for clot formation was noted when 14 times the normal dose (> 200 units/kg) was administered as part of in vitro and in vivo thrombogenicity studies and thrombotic events have been reported with the use of C1 inhibitors at high dose for off-label indications.

Drug Interactions^{1,2}

The manufacturer reports that there are not drug interaction studies that have been conducted with C1 inhibitor.

Efficacy Measures¹

Primary Endpoints

- Number of attacks per patient (prophylaxis)
- Time to beginning of treatment effect (acute)

Secondary and Other Endpoints

- Severity of attacks (prophylaxis)
- Duration of attacks (prophylaxis)
- Number of days of swelling (prophylaxis)
- Percent of patients with onset relief within 4 hours (acute)
- Median time to symptom resolution (acute)
- Time to treatment (on-demand)
- Time to onset relief (on-demand)
- Time to symptom resolution (on-demand)
- Safety and tolerability

Clinical Trial Data

A literature search was performed on PubMed/Medline using the search terms C1 inhibitor, Cinryze, and hereditary angioedema through 04302009. The search was limited to clinical trials performed in humans and published in the English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All controlled trials published in peer-reviewed journals evaluating treatment with C1 inhibitor (human derived) Cinryze™ (or comparable formulations, Ceter[®]) were included.

Prophylaxis

CHANGE Trial Part B (Unpublished Data)^{1,2}

The efficacy and safety of C1 inhibitor (Cinryze™) was evaluated in a Phase 3, multicenter, randomized, double-blind, placebo-controlled, crossover trial of 24 patients (mean age 38.1 years, range 9 to 73; 90.9% female; 95.5% Caucasian) with HAE (low C4 and a low C1 inhibitor antigenic level, or normal C1 inhibitor antigenic level and low C1 inhibitor functional level, or known HAE C1 inhibitor mutation), normal C1q levels, and frequent attacks of angioedema (≥ 2 per month), enrolled to receive 12 weeks of treatment prophylaxis with C1 inhibitor 1000 units and 12 weeks placebo. Doses were administered twice weekly. Only patients who had previously been enrolled in the CHANGE Trial Part A (acute treatment trial discussed below) were eligible to participate. Patients were permitted to continue their treatment with either danazol or EACA; although, dose adjustments were not allowed. Two patients dropped from the trial. Treatment with C1 inhibitor significantly ($p < 0.0001$) reduced the primary endpoint of the number of attacks per patient (defined as swelling reported by the patient when swelling was not reported on the previous day) (refer to Table below).^{1,2}

Number of Attacks (per patient)	C1 Inhibitor	Placebo
Range	0 to 17	6 to 22
Mean	6.1 \pm 5.4	12.7 \pm 4.8
Median	6.0	13.5

The secondary endpoints of the severity and duration of attacks and the number of days of swelling were significantly reduced in patients treated with C1 inhibitor compared to placebo (refer to Table below).^{1,2}

Secondary Endpoints	C1 Inhibitor	Placebo	p value
Mean Severity (score 1 to 3) ^a	1.3 \pm 0.85	1.9 \pm 0.36	0.0006
Mean Duration (days)	2.1 \pm 1.13	3.4 \pm 1.4	0.0023
Swelling (days)	10.1 \pm 10.73	29.6 \pm 16.9	<0.0001

^a1=mild, 2=moderate, 3=severe

Treatment emergent adverse events occurred in 87% of patients who received treatment with C1 inhibitor; no serious treatment related adverse events were reported. The following adverse events were reported in at least 2

June 2009

Updated versions may be found at www.pbm.va.gov or <http://vaww.pbm.va.gov>

patients: sinusitis (n=5), rash (n=5), headache (n=4), upper respiratory tract infection (n=3), viral upper respiratory tract infection (n=3), bronchitis (n=2), limb injury (n=2), back pain (n=2), extremity pain (n=2), pruritus (n=2).

Acute Treatment

CHANGE Trial Part A (Unpublished Data)^{1,2}

The efficacy and safety of C1 inhibitor (Cinryze™) was evaluated in a Phase 3 multicenter, randomized, double-blind, placebo-controlled trial of 71 patients with HAE attacks (inclusion criteria as described in CHANGE Trial Part B above). Patients were instructed to return to the treatment center within 4 hours of the onset of an acute attack. Patients experiencing symptoms involving the abdomen, genitourinary area, or face were randomized to treatment with C1 inhibitor 1000 units or placebo. If patients were not responding after one hour, a second dose could be administered. Patients with laryngeal edema were treated with open-label C1 inhibitor and were not included in the analysis. Approximately 70% of patients presented with an attack involving the abdomen. In the intent-to-treat group, the primary endpoint of median time to onset of relief of the defining symptom (first of 3 reports of symptom relief or resolution) in patients treated with C1 inhibitor (n=36) was 2.0 hours compared to greater than 4 hours with placebo (n=35). The success ratio for patients in the C1 inhibitor treatment group was 2.048 (95% CI 1.008 to 4.164; p=0.048) compared to placebo. The secondary endpoint of patients who experienced symptom relief within 4 hours was 58.3% of patients who received C1 inhibitor and 42.8% of patients in the placebo group. The median time to complete symptom resolution was 12.3 hours with C1 inhibitor and 31.6 hours with placebo, with a success ratio of 2.717 (95% CI 1.471 to 5.020). Fourteen patients in the C1 inhibitor treatment group received open-label C1 inhibitor as rescue therapy compared to 21 in the placebo group. Among the 83 (71 plus 12 open-label) patients who received C1 inhibitor, 13 reported a treatment emergent adverse event. Sinusitis, decreased blood pressure, and nausea were each reported in 2 patients. Three patients experienced a severe treatment emergent adverse event but this was thought not to be related to the study drug.^{1,2}

Prophylaxis and On-Demand (Self-Administration)

Levi M, et al (J Allergy Clin Immunol 2006)⁸

This trial was conducted to determine whether self-administration of C1 inhibitor (Cetor®; Sanquin, Amsterdam, The Netherlands) would decrease the time to treatment, symptom relief, and resolution of symptoms in patients with frequent severe acute attacks of angioedema; and decrease the number of attacks in patients receiving prophylaxis with C1 inhibitor. Patients received extensive education on the disease, indications for treatment with C1 inhibitor, documentation of symptoms, and proper preparation and administration of C1 inhibitor. Thirty-one patients were enrolled in treatment on-demand, and 12 patients received prophylaxis with C1 inhibitor 1000 units on a weekly basis. The details and results of this trial are available in Appendix 1. In summary, patients in the on-demand treatment group experienced a reduction in the time from symptom onset to treatment (1.4 vs. 3.4 hours; p=0.01), time to symptom relief (p=0.015), and time to symptom resolution (5.9 vs. 13.8 hours; p<0.05), compared to historical controls. Treatment prophylaxis with C1 inhibitor in patients with a history of frequent severe attacks of angioedema significantly reduced the number of attacks to a mean of 0.3 per month compared to historical control of 4 per month. Patients were reported to be successful in the self-administration of C1 inhibitor and treatment was generally well-tolerated.⁸

Acquisition Cost

Dose/Regimen	Price/Dose	Price/Patient/Month	Annual Price/Patient
C1 Inhibitor 500 units per vial			
Prophylaxis: 1000 units every 3 to 4 days ^{1,2}	\$2,978.82	\$23,830.56	\$285,966.72
Acute: 1000 units X 1 (may repeat) ²	\$2,978.82	NA	NA

Price Comparison

Drug/Dose ^a	Price ^b /Patient/Month	Annual Price/Patient
Danazol 200 mg daily	\$102.90	\$1,234.80
EACA 2 gm three times daily	\$253.26	\$3,039.12

^a Usual dose for long-term prophylaxis³

^b Prices as of 05012009 (danazol: open market; EACA: Low2000)

June 2009

Updated versions may be found at www.pbm.va.gov or <http://vaww.pbm.va.gov>

Cost-Effectiveness Analysis²

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

Conclusions

Per unpublished data, C1 inhibitor (Cinryze™) appears to be effective for prophylaxis in patients with HAE and frequent attacks (≥ 2 attacks per month; patients may also have been on prophylaxis with 17-alpha alkylated androgens or antifibrinolytic agents prior to enrollment and during the study) by reducing the number of angioedema attacks, and decreasing the severity and duration of attacks. The efficacy of C1 inhibitor was also evaluated for acute treatment of HAE attacks, and reduced the time to onset of relief compared to placebo. According to one published trial, select patients may benefit from self-administration of C1 inhibitor for prophylaxis or treatment of acute HAE attacks after extensive education regarding the disease and administration of the medication. Treatment with C1 inhibitor appears to be well-tolerated with the most frequently occurring adverse events including upper respiratory tract infection, sinusitis, rash, and headache. Since treatment with C1 inhibitor has been associated with severe hypersensitivity reactions and the prophylaxis trial conducted in the U.S. only included those patients who had received an initial dose in a medical treatment facility as part of an acute treatment trial, consideration should be given to administering the first dose under medical supervision, or only after extensive education on the proper administration of C1 inhibitor and management of a hypersensitivity reaction if it were to occur. C1 inhibitor 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. In patients with HAE, treatment with C1 inhibitor has not been compared to other treatments used for prophylaxis of angioedema attacks or evaluated against current treatment of acute angioedema attacks. C1 inhibitor should be reserved for treatment of prophylaxis of angioedema attacks in patients with HAE who have an inadequate response to or intolerable side effects or contraindications to current VA National Formulary agents (e.g., danazol, epsilon aminocaproic acid). In these patients, treatment with C1 inhibitor as on-demand therapy (note: off-label; patient requires extensive education on self-administration and management of hypersensitivity if it were to occur) could be considered. If the patient continues to experience frequent attacks (e.g., > 1 per 10 days) then routine prophylaxis may be appropriate. C1 inhibitor has not been studied in short-term prophylaxis; although, it has been recommended outside the U.S. as an option (danazol, fresh frozen plasma have also been recommended) as prophylaxis for major procedures or those requiring intubation. The risk vs. benefit of off-label use of C1 inhibitor for short-term prophylaxis or in the management of acute HAE attacks should be evaluated on a case by case basis. There is insufficient evidence to recommend treatment with C1 inhibitor for ACEI induced angioedema at this time.

References

1. Cinryze™ (C1 inhibitor [human]) prescribing information. New York, NY:Lev Pharmaceuticals, Inc.; 2008 Oct.
2. AMCP Formulary Dossier. Submission of clinical and economic data supporting formulary consideration of: Cinryze™ C1 inhibitor (human). ViroPharma Incorporated: Exton, PA. January 12, 2009:1-52.
3. Zuraw BL. Hereditary angioedema. *N Engl J Med* 2008;359:1027-36.
4. 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.
5. Nzeako UC, Frigas E, Tremaine WJ. Hereditary angioedema: a broad review for clinicians. *Arch Intern Med* 2001;161:2417-29.
6. Frank MM, Sergent JS, Kane MA, Alling DW. Epsilon aminocaproic acid therapy of hereditary angioneurotic edema: a double-blind study. *N Engl J Med* 1972;286:808-812.
7. 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.
8. 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.

Prepared (May 2009)/Contact Person: Elaine M. Furnaga, Pharm.D, Clinical Pharmacy Specialist, VHA PBM Services

June 2009

Updated versions may be found at www.pbm.va.gov or <http://vaww.pbm.va.gov>

Appendix: Published Clinical Trials

Trial	Inclusion/Exclusion	Endpoints/Treatment	Results	AEs/Limitations/Conclusions																																																																															
<p>Levi M et al, 2006⁹</p> <p>Observational study</p> <p>The Netherlands</p> <p>n=31 (on-demand); n=12 (prophylaxis); n=10 (control)</p> <p>Mean f/u: 3.5yrs (on-demand) 3.8yrs (prophylaxis)</p>	<p>Diagnosis of Hereditary or Acquired Angioedema</p> <p>Hereditary angioedema: Clinical presentation, recurrent attacks, C1 INH < 0.5 U/ml, C4 < 100 mg/L, family hx (optional)</p> <p>Acquired angioedema: Age onset > 25yrs, C1q < 80 IU/ml, C1 INH < 0.5 U/ml, C4 < 100 mg/L, anti-C1-esterase antibodies (optional), diagnosis lymphoproliferative disorder (optional)</p> <p>Inclusion Criteria</p> <p>On demand: Severe angioedema despite preventive tx (> 1 per 3wks), requiring C1 INH on demand X > 2yrs</p> <p>Prophylaxis: Frequent attacks (> 1 per 10d) despite preventive tx or w/o tx due to intolerance</p> <p>Exclusion Criteria</p> <p>Not reported</p> <p>Severe Angioedema: Orofacial area, upper airway, or severe abdominal attack (severe pain w/NV) Attacks w/swelling of extremities or angioedema of the GU area were recorded as less severe</p>	<p>Endpoints</p> <p>On-demand: Time from onset severe angioedema to time received C1 INH (ATT) Time to sx improvement Time to sx resolution Reported above for 5 episodes prior to study (hx control)</p> <p>Prophylaxis: Number of attacks angioedema per month on tx vs. prior to tx phase</p> <p>Control Group (no C1 INH): Patients w/angioedema due to C1 INH deficiency not on self-administration tx</p> <p>Preventive Tx (All pts)</p> <p>Danazol 100-400 mg/d ± Tranexamic acid 2-3 gm/d (imminent attack or daily if danazol not tolerated)</p> <p>On-demand</p> <p>C1 INH 1000 U IV</p> <p>Prophylaxis</p> <p>C1 INH 1000 U IV every 5-7d</p> <p>Patients received education on disease, indications for tx w/C1 INH, documentation of sx, proper preparation and administration C1 INH</p>	<p>Baseline</p> <p>On-demand: hereditary angioedema (n=28), acquired (n=3); mean age 43yrs; attack frequency 1 per 16.6d; Prophylaxis: hereditary angioedema (n=10), acquired (n=2); mean age 38yrs; attack frequency 1 per 7.9d</p> <table border="1"> <thead> <tr> <th>Location of Attacks</th> <th>On-Demand</th> <th>Prophylaxis</th> </tr> </thead> <tbody> <tr> <td>Orofacial</td> <td>15%</td> <td>18%</td> </tr> <tr> <td>Laryngeal</td> <td>2%</td> <td>1%</td> </tr> <tr> <td>Abdominal</td> <td>31%</td> <td>37%</td> </tr> <tr> <td>GU</td> <td>8%</td> <td>10%</td> </tr> <tr> <td>Extremities</td> <td>44%</td> <td>34%</td> </tr> <tr> <td colspan="3">Preventive Tx</td> </tr> <tr> <td>Danazol</td> <td>94%</td> <td>58%</td> </tr> <tr> <td>Tranexamic acid</td> <td>16%</td> <td>50%</td> </tr> </tbody> </table> <p>Results</p> <table border="1"> <thead> <tr> <th></th> <th>On-demand</th> <th>Prophylaxis</th> <th></th> </tr> </thead> <tbody> <tr> <td>Mean no. inj/pt</td> <td>21.4±5.3</td> <td>185.3±28.4</td> <td></td> </tr> <tr> <td>Tech fail rate</td> <td>1.8%</td> <td>0.8%</td> <td></td> </tr> <tr> <td></td> <th>Self-administered</th> <th>Hx control</th> <th>p</th> </tr> <tr> <td>ATT (hrs)</td> <td>1.4±1.0</td> <td>3.4±2.1</td> <td>0.01</td> </tr> <tr> <td>Mean T relief onset (min)</td> <td>NR</td> <td>171</td> <td>0.015</td> </tr> <tr> <td>Mean T resolution (hrs)</td> <td>5.9±2.2</td> <td>13.8±2.9</td> <td><0.05</td> </tr> <tr> <td>Mean no. attacks per month (Prophylaxis)</td> <td>0.3</td> <td>4.0</td> <td><0.001</td> </tr> <tr> <td></td> <th>After inj</th> <th>48hrs</th> <th>5d</th> </tr> <tr> <td>Mean plasma C1 INH (U/ml)</td> <td>1.1±0.2</td> <td>0.7±0.2</td> <td>0.3±0.1</td> </tr> </tbody> </table> <ul style="list-style-type: none"> No difference in clinical response between patients with hereditary or acquired angioedema Similar response between hx control and control group Mean time between inj (Prophylaxis) 6.8±1.0d 	Location of Attacks	On-Demand	Prophylaxis	Orofacial	15%	18%	Laryngeal	2%	1%	Abdominal	31%	37%	GU	8%	10%	Extremities	44%	34%	Preventive Tx			Danazol	94%	58%	Tranexamic acid	16%	50%		On-demand	Prophylaxis		Mean no. inj/pt	21.4±5.3	185.3±28.4		Tech fail rate	1.8%	0.8%			Self-administered	Hx control	p	ATT (hrs)	1.4±1.0	3.4±2.1	0.01	Mean T relief onset (min)	NR	171	0.015	Mean T resolution (hrs)	5.9±2.2	13.8±2.9	<0.05	Mean no. attacks per month (Prophylaxis)	0.3	4.0	<0.001		After inj	48hrs	5d	Mean plasma C1 INH (U/ml)	1.1±0.2	0.7±0.2	0.3±0.1	<p>AEs/Limitations/Conclusions</p> <p>Adverse Events</p> <p>No serious AEs reported</p> <table border="1"> <thead> <tr> <th>AE</th> <th>% inj</th> </tr> </thead> <tbody> <tr> <td>Skin irritation (inj site)</td> <td>2.1%</td> </tr> <tr> <td>Minor hematoma (inj site)</td> <td>1.6%</td> </tr> <tr> <td>Dizziness (at time of inj)</td> <td>0.3%</td> </tr> <tr> <td>Mild extremity pain (after inj)</td> <td>0.3%</td> </tr> <tr> <td>Increase temp (subfebrile)</td> <td>0.1%</td> </tr> </tbody> </table> <p>Study Limitations</p> <ul style="list-style-type: none"> Observational study Historical control Exclusion criteria not stated Actual mean time to relief onset in self-administered tx group not stated in publication Number of pts to determine mean plasma C1 INH levels unknown <p>Study Conclusions</p> <p>On-demand treatment with self-administration of C1 INH is an option in patients with C1 INH deficiency who experience frequent, serious angioedema attacks.</p> <p>With on-demand treatment, there was a decrease in the time to administration after onset of the attack, with a reduction in the time to onset of relief of symptoms as well as time to symptom resolution. Based on the accelerated time to resolution of symptoms, the authors suggested that earlier administration could reduce the duration and severity of attacks.</p> <p>Prophylaxis with weekly C1 INH in patients with very frequent angioedema attacks despite or in patients unable to tolerate preventive therapy substantially reduces the number of attacks with the elimination of attacks in some patients.</p>	AE	% inj	Skin irritation (inj site)	2.1%	Minor hematoma (inj site)	1.6%	Dizziness (at time of inj)	0.3%	Mild extremity pain (after inj)	0.3%	Increase temp (subfebrile)	0.1%
Location of Attacks	On-Demand	Prophylaxis																																																																																	
Orofacial	15%	18%																																																																																	
Laryngeal	2%	1%																																																																																	
Abdominal	31%	37%																																																																																	
GU	8%	10%																																																																																	
Extremities	44%	34%																																																																																	
Preventive Tx																																																																																			
Danazol	94%	58%																																																																																	
Tranexamic acid	16%	50%																																																																																	
	On-demand	Prophylaxis																																																																																	
Mean no. inj/pt	21.4±5.3	185.3±28.4																																																																																	
Tech fail rate	1.8%	0.8%																																																																																	
	Self-administered	Hx control	p																																																																																
ATT (hrs)	1.4±1.0	3.4±2.1	0.01																																																																																
Mean T relief onset (min)	NR	171	0.015																																																																																
Mean T resolution (hrs)	5.9±2.2	13.8±2.9	<0.05																																																																																
Mean no. attacks per month (Prophylaxis)	0.3	4.0	<0.001																																																																																
	After inj	48hrs	5d																																																																																
Mean plasma C1 INH (U/ml)	1.1±0.2	0.7±0.2	0.3±0.1																																																																																
AE	% inj																																																																																		
Skin irritation (inj site)	2.1%																																																																																		
Minor hematoma (inj site)	1.6%																																																																																		
Dizziness (at time of inj)	0.3%																																																																																		
Mild extremity pain (after inj)	0.3%																																																																																		
Increase temp (subfebrile)	0.1%																																																																																		

AE=adverse event; ATT=attack to treatment time; d=day; GU=genitourinary; hx=history; inj=injection; n=number of patients; no.=number; NR=not reported; pt=patient; sx=symptoms; T=time; tech fail rate=technical failure rate; temp=temperature; tx=treatment; wks=weeks; yrs=years