P&T®

PRODUCT PROFILER

Berinert®

C1 Esterase Inhibitor (Human)

For Treatment of Acute Abdominal or Facial Attacks of Hereditary Angioedema

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SECTION TWO

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The Product Profiler

The Product Profiler provides P&T committee members with current, detailed information about a specific therapeutic agent to help them manage their formularies and establish medication-related policies. The Profiler provides information about pharmacology, clinical studies and FDA-approved indications, safety, efficacy, acquisition costs, and other pharmacoeconomic variables, along with additional P&T committee considerations, in a convenient package. Articles are written by experts in the field.

About the Authors

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Disclosures

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PRODUCT PROFILER

Berinert®

C1 Esterase Inhibitor (Human)

This section of *P&T* is supported by CSL Behring.

Berinert®

C1 Esterase Inhibitor (Human)

INTRODUCTION

Type I and II hereditary angioedema (HAE) are autosomal dominant inherited disorders caused by a qualitative or quantitative deficiency of the serine protease inhibitor, C1 esterase inhibitor (C1-INH) (Agostini 2004, Frank 1976). Estimates suggest that 80% to 85% of patients are affected with type I HAE characterized by antigenic and functional plasma C1-INH levels that are 5% to 30% below normal levels (Table 1) (Frank 1976, Nzeako 2001). Among the remaining 10% to 15% of patients with type II HAE, normal or increased levels of C1-INH are produced with decreased C1 inhibitor activity attributed to secretion of a dysfunctional C1 inhibitor protein (Nzeako 2001). Deficiencies in C1-INH activate various systems including the contact system, also known as the kallikrein-kinin system (Nzeako 2001). Reduced levels of C1-INH and dysfunctional C1-INH prevent autoactivation of the C1 complement system and impair production of coagulation factors XIIa, XIIf, and XIa (Nzeako 2001). CI-INH is a direct inhibitor of activated kallikrein (Figure 1) (Agostini 2004). C1-INH deficiencies also affect the complement pathway, fibrinolytic system, and the intrinsic coagulation pathway (Frank 1976). Activation of each of these systems results in the release of vasoactive peptides, such as bradykinin, and this release of bradykinin increases the permeability of vascular tissue, resulting in angioedema (Davis 2006, Zuraw 2008). HAE typically manifests as acute attacks with nonpruritic, nonpitting, subcutaneous, or submucosal edema, with the most frequently affected areas including the arms, legs, hands, feet, bowels, genitalia, trunk, face, tongue, and larynx (Zuraw 2008).

TABLE 1
Features of HAE by Type

Type of HAE	Percentage of patients	Antigenic C1 levels	Functional C1 levels
Type I	80-85%	Low	Low
Type II	10-15%	Normal or increased	Low
Type III	<1%	Normal	Low

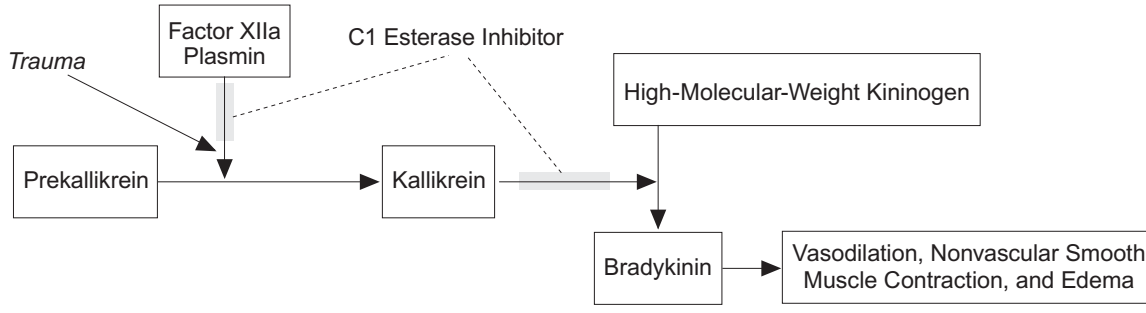
Source: Adapted from Agostini 2004.

Epidemiologic Burden

Prevalence estimates for HAE are difficult to determine due to a low awareness of the condition and the resemblance of symptoms to other disorders resulting in delayed or incorrect diagnoses (Agostini 2004). The average time between onset of first symptoms and diagnosis in 1976 was 21 years, with a recent survey of 457 patients with HAE reporting an average of 8.3 years between symptom onset and diagnosis (Frank 1976, Lunn 2010). It is currently estimated that HAE occurs in 1 in 10,000 to 1 in 50,000 individuals with no known predominance for specific ethnic groups (Bowen 2008). HAE is believed to be associated with increased risk of autoimmune disorders, particularly glomerulonephritis (Brickman 1986).

The initial symptoms of HAE usually present in childhood with exacerbations associated with the onset of puberty (Zuraw 2008). HAE persists with anywhere from fewer than one attack to more than 26 attacks per year occurring among untreated patients, although the frequency and severity of HAE events vary considerably between individuals (Agostini 2004, Winnewisser 1997).

FIGURE 1
Role of C1-INH in Production of Bradykinin



Source: Adapted from Nzeako 2001.

Acute respiratory attacks and abdominal distress are the most serious, life-threatening symptoms and leading causes of HAE-related morbidity and mortality (Craig 2009a, Nzeako 2001). Laryngeal edema can progress from mild discomfort to complete obstruction of the airway, requiring intubation and/or tracheotomy, while abdominal attacks can cause severe abdominal pain, nausea, diarrhea, and vomiting (Bork 2005, Winnewisser 1997). It is estimated that approximately 52% of patients experience laryngeal attacks at some point in their lives while recurrent abdominal attacks due to gastrointestinal (GI) wall edema are reported to affect up to 94% of patients (Bork 2006). Among untreated patients, mortality rates as high as 30% have been associated with laryngeal edema (Frank 1976).

Although there is a lack of comprehensive information, factors associated with the onset of HAE episodes include emotional stress, mechanical stress, infections, minor trauma, and minor surgical and dental procedures (Agostini 2004, Davis 1988, Zuraw 2008). Certain medications, such as angiotensin-converting-enzyme (ACE) inhibitors and exogenous estrogens, are known to increase risk of HAE although the mechanisms underlying these effects are not well understood (Agostini 2004, Frank 1976, Frank 1979).

The recurrent nature, varying severity of attacks, and the need for long-term care imposes a significant economic burden on patients and the healthcare delivery system. Recent research shows that patients with HAE incur upwards of $40,000 in direct and indirect medical costs associated with the disease with costs increasing considerably with increasing attack severity (Wilson 2010). Additionally, many patients with HAE reported significant work impairments as well as an inability to maintain full-time employment due to HAE (Wilson 2010).

Current Treatment Options

Therapeutic management of patients with HAE includes prompt treatment of acute attacks, short-term prophylactic interventions to prevent attacks, and long-term preventive interventions to decrease the frequency and severity of recurrent attacks. Epinephrine can slow progression of edema during acute attacks but its effects are transient and do not alter the course of an attack (Agostini 2004, Frank 1976, Zuraw 2008). Respiratory support should be provided as clinically needed as well as aggressive fluid replacement, antiemetics, and pain management for symptoms associated with GI edema (Agostini 2004, Craig 2009a).

Short-term prophylactic interventions are recommended for patients undergoing elective dental or surgical procedures. These rely on attenuated androgen therapy (e.g., danazol, stanozolol, and oxandrolone) at least 2 to 3 days before the procedure (Craig 2009a). However, androgens are associated with side effects including virilization, weight gain, amenorrhea, decreased libido, myalgia, fatigue, headache, hemorrhagic cystitis, arterial hypertension, lipid abnormalities, liver cell adenoma, hepatocellular cancer, and hepatic necrosis (Craig 2009a, Epstein 2008, Zuraw 2008). Antifibrinolytics, such as tranexamic acid and ε-aminocaproic acid, have not been approved by the U.S. Food and Drug Administration (FDA) to prevent acute episodes of HAE (Craig 2009a, Zuraw 2008). Berinert® is a C1 esterase inhibitor approved by the FDA for the treatment of acute facial and abdominal HAE attacks (Berinert® Prescribing Information 2009). In addition, a kallikrein inhibitor, Kalbitor®, has been approved by the FDA for treatment of acute attacks in patients 16 years and older (Kalbitor® Package Insert 2009). The FDA also has approved Cinryze™, a C1 esterase inhibitor, for routine prophylaxis of HAE in adolescent and adult patients (Cinryze™ Package Insert 2009).

Product Information

INDICATIONS AND USAGE

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

Description

Berinert® is a human plasma-derived, purified, pasteurized, lyophilized concentrate of C1 esterase inhibitor to be reconstituted for intravenous administration. Berinert® is prepared from large pools of human plasma from U.S. donors. One standard unit of C1 esterase inhibitor concentrate is equal to the amount of C1 esterase inhibitor in 1 mL of fresh citrated human plasma, which is equivalent to 270 mg/L or 2.5 M/L. There is no international laboratory standard for quantifying C1 esterase inhibitor. An in-house standard is used to assure lot-to-lot consistency with regards to product potency.

C1 esterase inhibitor is a soluble, single-chain glycoprotein containing 478 amino acid residues organized into three beta-sheets and eight or nine alpha-helices. The heavily glycosylated molecule has an apparent molecular weight of 105 kD, of which the carbohydrate chains comprise 26% to 35%.

Each vial of Berinert® contains 500 units of C1 esterase inhibitor, 50 to 80 mg of total protein, 85 to 115 mg of glycine, 70 to 100 mg of sodium chloride, and 25 to 35 mg of sodium citrate.

All plasma used in the manufacture of Berinert® is obtained from U.S. donors and is tested using serological assays for hepatitis B surface antigen and antibodies to HIV-1/2 and HCV. Additionally, the plasma is tested with Nucleic Acid Testing (NAT) for HCV and HIV-1 and found to be non-reactive (negative). In addition, the plasma is tested by NAT for HAV and Human Parvovirus B19. Only plasma that has passed virus screening is used for production, and the limit for Parvovirus B19 in the fractionation pool is set not to exceed 104 IU of Parvovirus B19 DNA per mL.

The manufacturing process for Berinert® includes mul-

TABLE 2
Mean Virus Inactivation/Reductions in Berinert®

Virus studied	Pasteurization [$\log_{10}$]	Hydrophobic interaction chromatography [$\log_{10}$]	DEAE-sephadex A50 chromatography QAE-sephadex chromatography and ammonium sulphate precipitation [$\log_{10}$]	Total cumulative [$\log_{10}$]
Enveloped viruses				
HIV-1	≥6.6	≥4.5	4.3	≥15.4
BVDV	≥9.2	≥4.6	NA	≥13.8
PRV	6.3	≥6.5	≥7.7	≥20.5
WNV	≥7.0	ND	NA	NA
Non-enveloped viruses				
HAV	≥6.4	4.5	NA	≥10.9
CPV	1.4	6.1	NA	7.5
B19V	3.9	ND	NA	NA

B19V=Human Parvovirus B19; BVDV=Bovine viral diarrhea virus, a model for HCV; CPV=Canine parvovirus; HAV=Hepatitis A virus; HIV-1=Human immunodeficiency virus type 1, a model for HIV-1 and HIV-2; NA=not applicable; ND=not determined; PRV=Pseudorabies virus, a model for large enveloped DNA viruses (eg, herpes virus); WNV=West Nile virus

Source: Berinert® Prescribing Information 2009.

tiple steps that reduce the risk of virus transmission. The virus inactivation/reduction capacity of three steps (pasteurization in aqueous solution at 60°C for 10 hours, hydrophobic interaction chromatography, and the combination of ion exchange chromatography and ammonium sulphate precipitation) was evaluated in a series of *in vitro* spiking experiments. The total mean cumulative virus inactivation/reduction is shown in Table 2.

CLINICAL PHARMACOLOGY

Mechanism of Action

C1 esterase inhibitor is a normal constituent of human plasma and belongs to the group of serine protease inhibitors (serpins) that includes antithrombin III, alpha$_1$-protease inhibitor, alpha$_2$-antiplasmin, and heparin cofactor II. As with the other inhibitors in this group, C1 esterase inhibitor has an important inhibiting potential on several of the major cascade systems of the human body, including the complement system, the intrinsic coagulation (contact) system, the fibrinolytic system, and the coagulation cascade. Regulation of these systems is performed through the formation of complexes between the proteinase and the inhibitor, resulting in inactivation of both and consumption of the C1 esterase inhibitor.

C1 esterase inhibitor, which is usually activated during the inflammatory process, inactivates its substrate by covalently binding to the reactive site. C1 esterase inhibitor is the only known inhibitor for the subcomponent of the complement component 1 (C1r), C1s, coagulation factor XIIa, and kallikrein. Additionally, C1 esterase inhibitor is the main inhibitor for coagulation factor XIa in the intrinsic coagulation cascade.

HAE patients have low levels of endogenous or functional C1 esterase inhibitor. Although the events that induce attacks of angioedema in HAE patients are not well defined, it has been postulated that increased vascular permeability and the clinical manifestation of HAE attacks may be primarily mediated through contact system activation. Suppression of contact system activation by C1 esterase inhibitor through the inactivation of plasma kallikrein and factor XIIa is thought to modulate this vascular permeability by preventing the generation of bradykinin.

Administration of Berinert® to patients with C1 esterase inhibitor deficiency replaces the missing or malfunctioning protein in patients. The plasma concentration of C1 esterase inhibitor in healthy volunteers is approximately 270 mg/L.

Pharmacokinetics

The pharmacokinetics of Berinert® were evaluated in an open-label, uncontrolled, single-center study in 40 subjects (35 adults and 5 children under 16 years of age) with either mild or severe HAE. All subjects received a single intravenous injection of Berinert® ranging from 500 units to 1,500 units. Blood samples were taken during an attack-

TABLE 3
Pharmacokinetic Parameters of Berinert® in Adult Subjects with HAE by Non-compartmental Analysis (n=35)

Parameters	Unadjusted for baseline	Adjusted for baseline
$AUC_{(0-t)}$ (hr x IU/mL)*	27.5 ± 8.5 (15.7-44.7)	12.8 ± 6.7 (3.9-34.7)
CL (mL/hr/kg)	0.60 ± 0.17 (0.34-0.96)	1.44 ± 0.67 (0.43-3.85)
V_{ss} (mL/kg)	18.6 ± 4.9 (11.1-27.6)	35.4 ± 10.5 (14.1-56.1)
Half-life (hrs)	21.9 ± 1.7 (16.5-24.4)	18.4 ± 3.5 (7.4-22.8)
MRT (hrs)	31.5 ± 2.4 (23.7-35.2)	26.4 ± 5.0 (10.7-33.0)

AUC=area under the curve; CL=clearance; MRT=mean residence time; V_{ss},=volume steady state

*Based on a 15 unit/kg dose. Numbers in parentheses are the range.

Source: Berinert® Prescribing Information 2009.

TABLE 4
Pharmacokinetic Parameters of Berinert® in Pediatric Subjects with HAE by Non-compartmental Analysis (n=5)

Parameters	Unadjusted for baseline	Adjusted for baseline
$AUC_{(0-t)}$ (hr x IU/mL)*	25.45 ± 5.8 (16.8-31.7)	9.78 ± 4.37 (4.1-15.2)
CL (mL/hr/kg)	0.62 ± 0.17 (0.47-0.89)	1.9 ± 1.1 (0.98-3.69)
V_{ss} (mL/kg)	19.8 ± 4.0 (16.7-26.1)	38.8 ± 8.9 (31.9-54.0)
Half-life (hrs)	22.4 ± 1.6 (20.3-24.4)	16.7 ± 5.8 (7.4-22.5)
MRT (hrs)	32.3 ± 2.3 (29.3-35.2)	24.0 ± 8.3 (10.7-32.4)

Source: Berinert® Prescribing Information 2009.

free period at baseline and for up to 72 hours after drug administration. Pharmacokinetic parameters were estimated using non-compartmental analysis (with or without baseline adjustment). Table 3 summarizes the pharmacokinetic parameters in 35 adult subjects with HAE.

Table 4 summarizes the pharmacokinetic parameters in 5 pediatric subjects (ages 6 through 13) with HAE. Based on adjusted baseline, compared to adults, the half-life of Berinert® was shorter and clearance was faster in this limited cohort of children. However, the clinical implication of this difference is not known.

DOSAGE AND ADMINISTRATION

For Intravenous Use Only.

Administer Berinert® at a dose of 20 units per kg body weight by intravenous injection.

Berinert® is provided as a freeze-dried powder for reconstitution with the diluent (sterile water) provided. Store the vial in the original carton in order to protect from light. Do not freeze.

Preparation and Handling

Check the expiration date on the product vial label. Do not use beyond the expiration date.

Use aseptic technique when preparing and administering Berinert®.

After reconstitution and prior to administration, inspect Berinert® visually for particulate matter and discoloration. The reconstituted solution should be colorless, clear, and free from visible particles. Do not use if the solution is cloudy, discolored, or contains particulates.

The Berinert® vial is for single use only. Berinert® contains no preservative. Any product that has been reconstituted should be used promptly. The reconstituted solution must be used within 8 hours. Discard partially used vials.

Do not freeze the reconstituted solution.

Reconstitution and Administration

Each Berinert® kit consists of one carton containing one single-use vial of Berinert®, one 10 mL vial of diluent (sterile water), one Mix2Vial™ transfer set, and one alcohol swab.

Use either the Mix2Vial transfer set provided with Berinert® or a commercially available double-ended needle and vented filter spike.

Reconstitution

The procedures below are provided as general guidelines for the reconstitution and administration of Berinert®.

Administration

Do not mix Berinert® with other medicinal products and administer by a separate infusion line.

Use aseptic technique when administering Berinert®.

Administer Berinert® by slow intravenous injection at a rate of approximately 4 mL per minute.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Berinert® is supplied in a single-use vial. Each carton contains a 500 unit vial of Berinert® for reconstitution with 10 mL of diluent containing sterile water (meets USP chemistry requirements except for pH; pH 4.5-8.5). The components used in the packaging for Berinert® are latex-free.

Each product package consists of the following:

NDC Number	Component
63833-825-02	Carton (kit) containing one 500 unit vial of Berinert® [NDC 63833-835-01], one 10 mL vial of diluent (sterile water) [NDC 63833-765-15], one Mix2Vial filter transfer set, and one alcohol swab.

Clinical Trial Summary

Efficacy of Human C1 Esterase Inhibitor Concentrate Compared with Placebo in Acute Hereditary Angioedema Attacks

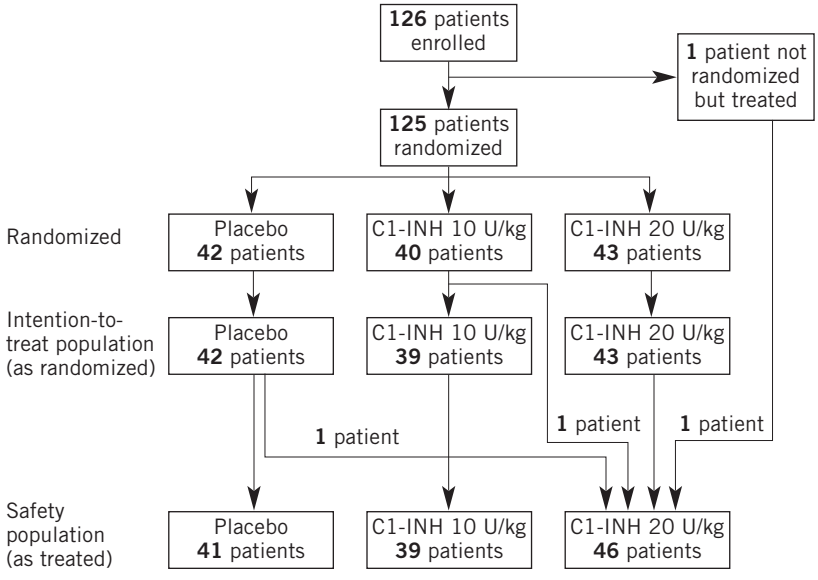
The International Multi-centre Prospective Angioedema C1-Inhibitor Trial (IMPACT-1) was a multinational, parallel-group, double-blind, randomized, placebo-controlled, 3-arm, phase 2/3 trial conducted at 36 sites in 15 countries between August 2005 and December 2007 (Craig 2009b). The primary study objective was to compare the efficacy and safety of Berinert®, a C1 esterase inhibitor (C1-INH), 20 U/kg with placebo for the treatment of acute facial or abdominal attack of HAE. The efficacy of Berinert®10 U/kg also was compared with placebo as a secondary trial objective.

Study eligibility criteria included patients 6 years of age or older with either type I or II HAE who had laboratory-confirmed C1-INH deficiency. Treatment of eligible patients was administered at the time of occurrence of an acute moderate-to-severe abdominal or facial attack of HAE within 5 hours of the attack attaining moderate intensity according to patient evaluation and confirmation by the investigators. Patients were excluded from the trial if they had a history of hypersensitivity to C1-INH concentrates, a diagnosis of acquired angioedema, all other types of angioedema, and abdominal pain not associated with C1-INH deficiency. Additional exclusion criteria included a history of routine use of narcotics or pain medications during a current HAE attack, treatment with any C1-INH concentrate or any other drug for acute angioedema, and treatment with fresh frozen or native plasma in the 7 days preceding enrollment in the IMPACT-1 trial.

Methods

Patients were randomized to intravenous infusion with C1-INH 20 U/kg, C1-INH 10 U/kg, or placebo and each patient was treated for only one abdominal or facial attack during the course of the trial. Figure 2 presents the disposition of patients by the three treatment groups for IMPACT-1. Patients were observed for at least 4 hours following initiation of treatment and discharged thereafter if their symptoms resolved. A second dose of double-blind treatment was administered as rescue medication to patients who failed to obtain relief of their symptoms within 4 hours following their initial treatment. Rescue study medications included C1-INH 20 U/kg for patients randomized to placebo, a second dose of C1-INH 10 U/kg to those randomized to the C1-INH 10 U/kg group, and treatment with placebo for patients randomized to treatment with C1-INH 20 U/kg. Viral safety assessments were performed before randomization and for up to 12 weeks following treatment.

FIGURE 2
Study Design and Patient Disposition for IMPACT-1 Trial



Source: Craig 2009b. Reprinted from Efficacy of human C1 esterase inhibitor concentrate compared with placebo in acute hereditary angioedema attacks. *J Allergy Clin Immunol*. 2009; 124:801–806. Copyright 2009, with permission from Elsevier.

Study endpoints

The primary endpoint was time to symptom relief following initiation of treatment assessed by patient responses to a standardized questionnaire conducted at appropriate time intervals for up to 24 hours following treatment initiation. Secondary efficacy endpoints included time to complete resolution of all symptoms of HAE, the proportion of patients who experienced worsening of HAE symptoms between 2 and 4 hours after treatment initiation compared with baseline with at least one HAE symptom reported at baseline, and the number of episodes of vomiting within 4 hours of treatment initiation.

Four primary safety endpoints were monitored. These included: the number and type of adverse events (AEs) that occurred up to 9 days fol-

lowing initial treatment, serious adverse events (SAEs) up to 12 weeks after treatment, vital signs (blood pressure, heart rate, respiratory rate, and body temperature) prior to treatment and up to 24 hours following initiation of therapy, and assessments of viral safety up to 12 weeks following treatment including rates of HIV 1 and 2, hepatitis, and the human B19 virus.

All efficacy analyses were based on the intention-to-treat (ITT) population defined as all patients who were treated with any blinded dose of study medication while the safety analyses included all patients who received any treatments. A Wilcoxon 1-sided, 2-sample test was performed to analyze the primary efficacy endpoint of time to onset of symptom relief by treatment group. Time to onset of symptom relief was set at 24 hours if patients required treatment with rescue medications to achieve symptom relief or were treated with analgesics, antiemetics, open-label C1-INH, or fresh frozen plasma during the first 4 to 5 hours following the start of their initial treatment. Wilcoxon 1-sided, 2-sample tests also were conducted to evaluate time to complete symptom resolution and number of vomiting episodes while a 1-sided Fischer exact test yielded the statistical comparison between the three treatment groups for the proportion of patients experiencing exacerbations in the intensity of symptoms occurring 2 and 4 hours following treatment initiation. Safety analyses included assessment of AEs that occurred in the 4 hours following initiation of treatment to provide an unbiased assessment of C1-INH compared with placebo during maximum exposure to therapy during the acute phase of each attack, which preceded administration of any rescue medications. AEs also were evaluated for all patients who received any dose of C1-INH including patients in the placebo group who required rescue therapy with C1-INH 10 U/kg. Descriptive statistics characterized vital signs and viral safety assessments.

TABLE 5
Baseline Demographic and Clinical Characteristics of Intention-to-Treat Population

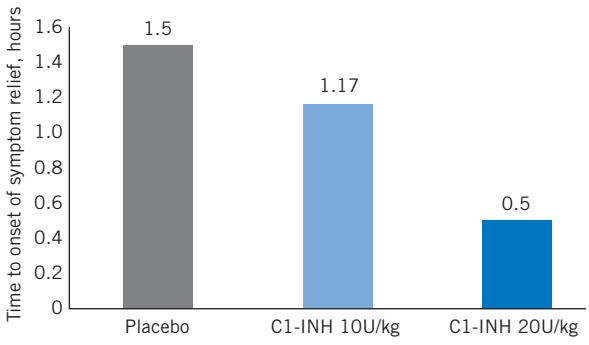
	Treatment Group			
	Placebo (n=42)	C1-INH 10 U/kg (n=39)	C1-INH 20 U/kg (n=43)	Overall (n=124)
Gender, n (%)				
Female	28 (66.7)	26 (66.7)	30 (69.8)	84 (67.7)
Male	14 (33.3)	13 (33.3)	13 (30.2)	40 (32.3)
Age, years				
Mean (SD)	31.5 (13.57)	33.1 (12.77)	34.6 (14.91)	33.1 (13.76)
Range	6 – 62	13 – 72	10 – 71	6 – 72
Race/ethnic group, n (%)				
American Indian/Alaskan Native	1 (2.4)	0 (0.0)	0 (0.0)	1 (0.8)
Asian	2 (4.8)	1 (2.6)	0 (0.0)	3 (2.4)
Black	1 (2.4)	0 (0.0)	3 (7.0)	4 (3.2)
Hispanic	1 (2.4)	2 (5.1)	2 (4.7)	5 (4.0)
White	37 (88.1)	36 (92.3)	38 (88.4)	111 (89.5)
BMI, kg/m^2				
Mean (SD)	25.3 (6.00)	26.7 (5.29)	27.0 (5.57)	26.4 (5.64)
Range	13 – 38	17 – 36	18 – 40	13 – 40
HAE type, n (%)				
Type I	38 (90.5)	35 (89.7)	35 (81.4)	108 (87.1)
Type II	4 (9.5)	3 (7.7)	8 (18.6)	15 (12.1)
Missing	0 (0.0)	1 (2.6)	0 (0.0)	1 (0.8)
Intensity of baseline attack, n (%)				
Moderate	26 (61.9	32 (82.1)	27 (62.8)	85 (68.5)
Severe	16 (38.1)	7 (17.9)	16 (37.2)	39 (31.5)

BMI=body mass index; HAE=hereditary angioedema; SD=standard deviation
Source: Adapted from Craig 2009b.

Results

A total of 125 patients were randomized to 1 of the 3 study groups with 42 treated with placebo, 40 administered C1-INH 10 U/kg, and 43 randomized to treatment with C1-INH 20 U/kg. One patient randomized to C1-INH 10 U/kg was excluded from the ITT population due to the need for open-label rescue medication before treatment with the randomized therapy. The three treatment arms were well-balanced with respect to gender, age, race, and ethnicity (Table 5). Overall, 87.1% of patients were diagnosed with type I HAE and 12.1% with Type II HAE; 0.8% had missing data. Mean age for the full study population was 33.1 years (± 13.76), 89.5% of patients were white, and mean body mass index (BMI) was 26.4 (± 5.64). The majority (79%) of patients were treated for abdominal attacks while 20.2% experienced facial attacks; 68.5% of all attack types were considered to be moderate in severity. Rescue medication was required by 57.1% of patients in the placebo group compared with 33.3% and 18.6% of those treated with C1-INH 10 U/kg and C1-INH 20 U/kg, respectively.

FIGURE 3
Median Time to Onset of Symptom Relief by Treatment Group: Intention-to-Treat Population



P=.0025 for comparison of C1-INH 20 U/kg with placebo

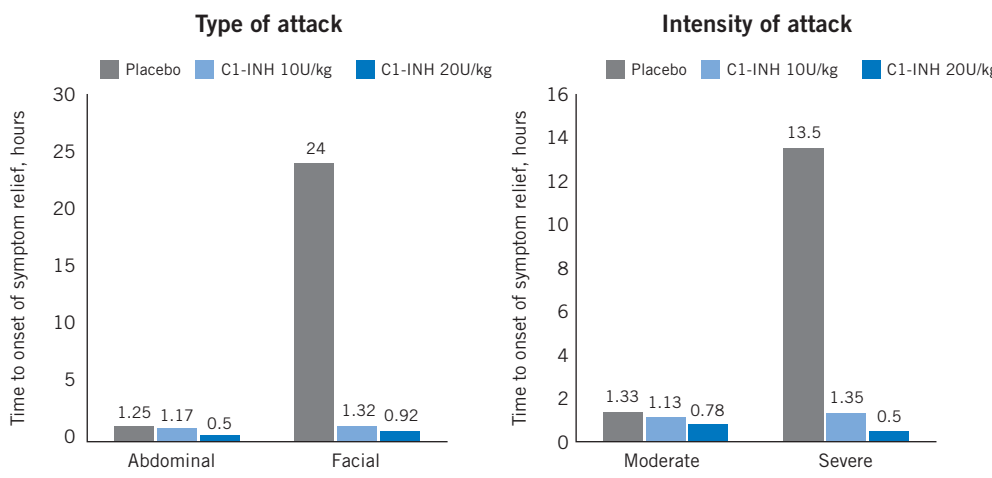
Source: Adapted from Craig 2009b.

Efficacy

Seventeen of 42 patients in the placebo group (40.5%) had time set to 24 hours for symptom relief compared with 11 of 39 (28.2%) patients treated with C1-INH 10 U/kg and 6 of 43 (14.0%) patients in the C1-INH 20 U/kg group. Under this stringent analysis, the median time to resolution of all HAE symptoms was 1.5 hours (95% confidence interval [CI], 0.20-24.0) for patients treated with placebo compared with 0.50 (95% CI, 0.17-24.0) hours for C1-INH 20 U/kg (*P*=.0025; Figure 3). A similar comparison between patients in the placebo group and those treated with C1-INH 10 U/kg did not reveal significantly shorter times to symptom resolution following treatment with median time to symptom relief for the lower dose of C1-INH of 1.17 hours (95% CI, 0.17-24.00) compared with 1.5 hours for patients who were administered placebo.

Symptom relief within 1 hour following the start of treatment was reported by more than 75% of patients administered C1-INH 20 U/kg compared with approximately 40% of those treated with placebo. A closed testing procedure for dose finding demonstrated more rapid onset of symptom relief for patients in the C1-INH 20 U/kg group compared with those in the 10 U/kg dose group (*P*=.0048) while no statistically significant differences

FIGURE 4
Median Time to Onset of Symptom Relief by Characteristics of HAE Event: Intention-to-Treat Population



Source: Adapted from Craig 2009b.

TABLE 6
Analysis of Time to Onset of Symptom Relief by Characteristics of HAE Attack for Intention-to-Treat Population*

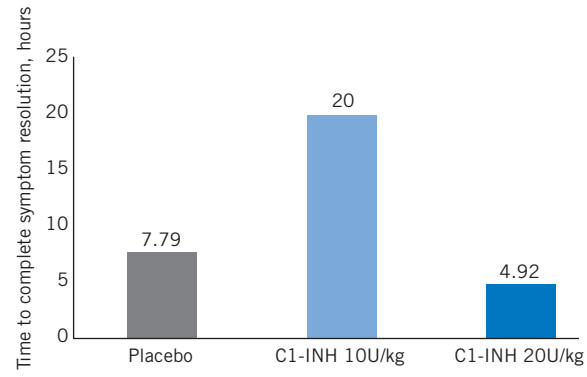
Characteristic	Treatment group		
	Placebo (n=42)	C1-INH 10 U/kg (n=39)	C1-INH 20 U/kg (n=43)
Abdominal attack			
Number	33	31	34
Mean (SD)	8.59 (11.08)	7.59 (10.68)	3.37 (7.66)
Median (range)	1.25 (0.20 – 24.00)	1.17 (0.17 – 24.00)	0.50 (0.17 – 24.00)
Facial attack			
Number	8	8	9
Mean (SD)	15.47 (11.80)	7.02 (10.53)	5.89 (10.27)
Median (range)	24.00 (0.25 – 24.00)	1.32 (0.50 – 24.00)	0.92 (0.25 – 24.00)
Moderate intensity of attack			
Number	26	32	27
Mean (SD)	8.92 (11.20)	8.12 (10.89)	4.95 (9.26)
Median (range)	1.33 (0.25 – 24.00)	1.13 (0.22 – 24.00)	0.78 (0.17 – 24.00)
Severe intensity of attack			
Number	16	7	16
Mean (SD)	12.44 (11.95)	4.50 (8.68)	2.11 (5.86)
Median (range)	13.50 (0.20 – 24.00)	1.35 (0.17 – 24.00)	0.50 (0.17 -24.00)

*Time to onset of symptom relief set to 24 hours if patients were administered rescue study medications or analgesics, antiemetics, open-label C1-INH, or fresh frozen plasma 4 hours after treatment initiation.
SD=standard deviation
Source: Adapted from Craig 2009b.

were evident for a similar comparison between patients in the C1-INH 10 U/kg and placebo groups (*P*=.2731).

Among patients treated with placebo, the median time to symptom relief for abdominal HAE events was 1.3 hours compared with 1.2 hours for C1-INH 10 U/kg and 0.5 hours for C1-INH 20 U/kg (Figure 4). The median time to onset of symptom relief for facial attacks was 24 hours for placebo, 1.3 hours for C1-INH 10 U/kg, and 0.9 hours for C1-INH 20 U/kg. Among patients considered to have experienced a severe attack, the median time to symptom resolution was 13.5 hours for the placebo group compared with 0.5 hours for patients treated with C1-INH 20 U/kg. The median time to symptom relief for moderate attacks was 1.3 hours for placebo and 0.8 hours for C1-INH 20 U/kg. However, a 2-sided test of the interaction did not reveal a significant difference in time to onset of relief by severity of attack (Table 6).

FIGURE 5
Median Time to Complete Symptom Resolution by Treatment Group: Intention-to-Treat Population



P=.0237 for comparison of C1-INH 20 U/kg with placebo

Source: Adapted from Craig 2009b.

The median time to complete resolution of HAE symptoms was significantly shorter for patients treated with C1-INH 20 U/kg at 4.9 hours compared with 7.8 hours for the placebo group (*P*=.0237; Figure 5).

In addition, the proportion of patients who experienced an exacerbation of their symptoms between 2 and 4 hours following initiation of treatment was 4.7% among those in the C1-INH 20 U/kg arm compared with 31.0% for those in the placebo arm (*P*=.0014; Figure 6). The mean num-

TABLE 7
Overall Incidence of Adverse Events in Safety Population

Adverse event	Up to 4 hours after treatment			Any time
	Placebo (n=41)	C1-INH 10 U/kg (n=39)	C1-INH 20 U/kg (n=46)	C1-INH all doses (n=108)
Total adverse events, n (%)	18 (43.9)	10 (25.6)	9 (19.6)	55 (50.9)
Possibly related adverse events, n (%)	8 (19.5)	8 (20.5)	5 (10.9)	29 (26.9)
SAE, n (%)	0 (0.0)	0 (0.0)	0 (0,0)	4 (3.7)
Adverse events leading to study D/C, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

D/C=discontinuation; SAE=serious adverse event
Source: Adapted from Craig 2009b.

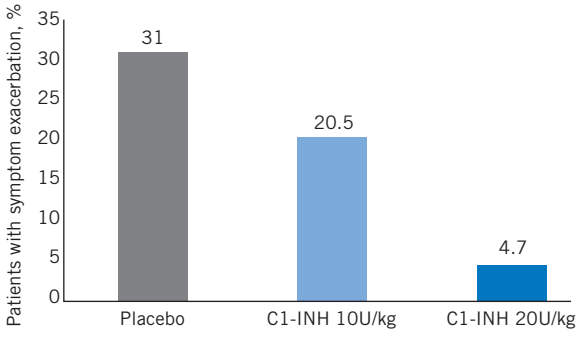
ber of vomiting episodes within the first 4 hours of treatment was 0.1 for patients treated with C1-INH 20 U/kg compared with 0.8 for the placebo group (*P*=.0329; Figure 7). Analysis of the primary efficacy endpoint and the secondary endpoints of symptom exacerbation and the rate of vomiting episodes for patients administered C1-INH 10 U/kg revealed lower treatment effects compared with the higher dose of C1-INH but greater efficacy compared with placebo.

Safety

Safety analyses included 126 patients, with 41 in the placebo group, 39 in the C1-INH 10 U/kg group, and 46 in the C1-INH 20 U/kg group. The frequency of AEs occurring within 4 hours of treatment initiation was lower for patients treated with C1-INH 20 U/kg (19.6%) compared with placebo (43.9%, Table 7). In addition, 10.9% of AEs were considered at least possibly related to treatment in the C1-INH 20 U/kg group compared with 19.5% of patients administered placebo (Table 7).

The most frequently observed AEs were GI disorders, general disorders, administration site reactions, and musculoskeletal/connective tissue disorders, with lower rates for each of these reported by patients treated with C1-INH 20 U/kg (10.9%) compared with placebo (31.7%). Overall, 25.6% of patients in the C1-INH 10 U/kg arm experienced AEs compared with 43.9% observed in the placebo arm. The most commonly reported AEs were nausea, diarrhea, abdominal pain, and muscle spasms with rates for each of these events lower among patients treated with C1-INH 20 U/kg compared with patients randomized to placebo treatment (Table 8). There were no reports of SAEs or AEs within the first 4 hours of treatment that prompted study discontinuation in any of the three treatment groups. There were also no clinically significant changes in vital signs and no seroconversions for HIV, hepatitis, or human B19 virus among patients in any of the three treatment groups.

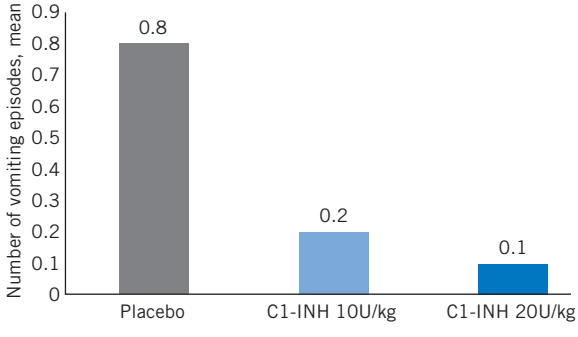
FIGURE 6
Percentage of Patients with Symptom Exacerbation between 2 and 4 Hours Following Treatment Initiation: Intention-to-Treat Population



P=.0014 for comparison of C1-INH 20 U/kg with placebo

Source: Adapted from Craig 2009b.

FIGURE 7
Mean Number of Vomiting Episodes within 4 Hours after Treatment Initiation: Intention-to-Treat Population



P=.0329 for comparison of C1-INH 20 U/kg with placebo

Source: Adapted from Craig 2009b.

TABLE 8
Adverse Events Affecting >1 Patient Overall

Adverse Event, n (%)	Up to 4 Hours after Treatment			Any time
	Placebo (n=41)	C1-INH 10 U/kg (n=39)	C1-INH 20 U/kg (n=46)	C1-INH All Doses (n=108)
HAE	0 (0.0)	0 (0.0)	0 (0.0)	14 (13.0)
Headache	2 (4.9)	1 (2.6)	0 (0.0)	13 (12.0)
Abdominal pain	3 (7.3)	1 (2.6)	2 (4.3)	7 (6.5)
Nausea	5 (12.2)	1 (2.6)	3 (6.5)	7 (6.5)
Muscle spasms	2 (4.9)	4 (10.3)	1 (2.2)	6 (5.6)
Pain	1 (2.4)	4 (10.3)	1 (2.2)	6 (5.6)
Diarrhea	4 (9.8)	1 (2.6)	0 (0.0)	5 (4.6)
Vomiting	3 (7.3)	1 (2.6)	1 (2.2)	5 (4.6)
Back pain	1 (2.4)	0 (0.0)	0 (0.0)	4 (3.7)
Dysgeusia	0 (0.0)	1 (2.6)	2 (4.3)	4.(3.7)
Peripheral edema	0 (0.0)	1 (2.6)	1 (2.2)	4 (3.7)
Abdominal distension	0 (0.0)	1 (2.6)	0 (0.0)	2 (1.9)
URTI	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.9)
Facial edema	1 (2.4)	1 (2.6)	0 (0.0)	1 (0.9)
Lip swelling	1 (2.4)	1 (2.6)	0 (0.0)	1 (0.9)

HAE=hereditary angioedema; URTI=upper respiratory tract infection
Source: Adapted from Craig 2009b.

TABLE 9
Adverse Reactions* Occurring up to 4 hours After Initial Infusion in More Than 4% of Subjects, *Irrespective of Causality*†

Adverse reactions	Number (%) of subjects reporting adverse reactions Berinert® 20 units/kg (n=43)	Number (%) of subjects reporting adverse reactions placebo group (n=42)
Nausea†	3 (7%)	5 (11.9%)
Dysgeusia	2 (4.7%)	0 (0)
Abdominal pain†	2 (4.7%)	3 (7.1%)
Vomiting†	1 (2.3%)	3 (7.1%)
Diarrhea†	0 (0)	4 (9.5%)
Headache	0 (0)	2 (4.8%)

* The study protocol specified that adverse events that began within 72 hours of blinded study medication administration were to be classified as at least possibly related to study medication (ie, adverse reactions).
† The following abdominal symptoms were identified in the protocol as associated with HAE abdominal attacks: abdominal pain, bloating, cramps, nausea, vomiting, and diarrhea.
Source: Berinert® Prescribing Information 2009.

TABLE 10
Adverse Reactions* Occurring in More Than 4% of Subjects up to 72 hours After Infusion of Initial or Rescue Medication† by Intent-to-Treat, *Irrespective of Causality*

Adverse reactions	Number (%) of subjects reporting adverse reactions†‡ Berinert® 20 units/kg (n=43)	Number (%) of subjects reporting adverse reactions†‡ placebo group (n=42)
Nausea	3 (7%)	11 (26.2%)
Headache	3 (7%)	5 (11.9%)
Abdominal pain	3 (7%)	5 (11.9%)
Dysgeusia	2 (4.7%)	1 (2.4%)
Vomiting	1 (2.3%)	7 (16.7%)
Pain	1 (2.3%)	4 (9.5%)
Muscle spasms	1 (2.3%)	4 (9.5%)
Diarrhea	0 (0)	8 (19%)
Back pain	0 (0)	2 (4.8%)
Facial pain	0 (0)	2 (4.8%)

* The study protocol specified that adverse events that began within 72 hours of blinded study medication administration were to be classified as at least possibly related to study medication (ie, adverse reactions).
† If a subject experienced no relief or insufficient relief of symptoms within 4 hours after infusion, investigators had the option to administer a blinded second infusion ("rescue" treatment) of Berinert® (20 units/kg for the placebo group or 10 units/kg for the 10 units/kg group), or placebo (for the 20 units/kg group).
‡ Adverse reactions following either initial treatment and/or blinded "rescue" treatment. Because more subjects in the placebo randomization group than in the Berinert® randomization group received rescue treatment, the median observation period in this analysis for subjects randomized to placebo was slightly longer than for subjects randomized to receive Berinert®.
Source: Berinert® Prescribing Information 2009.

SAFETY

Contraindications

Berinert® is contraindicated in individuals who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations.

Warnings and Precautions

Severe hypersensitivity reactions may occur. Epinephrine should be immediately available for treatment of acute severe hypersensitivity reactions. The signs and symptoms of hypersensitivity reactions may include hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and/or anaphylaxis during or after injection of Berinert®.

Because hypersensitivity reactions may have symptoms similar to HAE attacks, treatment methods should be carefully considered. In case of suspected hypersensitivity, immediately discontinue administration of Berinert® and institute appropriate treatment.

Thrombotic events have been reported in association with Berinert® when used for off-label and at higher than labeled doses. Animal studies have confirmed the risk of thrombosis from intravenous administration of C1 esterase inhibitor.

Transmission of Infectious Agents

Because Berinert® is made from human blood, it may contain infectious agents (eg, viruses and, theoretically, the Creutzfeldt-Jakob disease [CJD] agent) that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by processes demonstrated to inactivate and/or remove certain viruses during manufacturing.

Despite these measures, such products may still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products.

Since 1979, a few suspected cases of viral transmission have been reported with the use of Berinert® outside the U.S., including cases of acute hepatitis C. From the incomplete information available from these cases, it was not possible to determine with certainty if the infections were or were not related to prior administration of Berinert®.

The physician should discuss the risks and benefits of this product with the patient before prescribing or administering it to the patient.

All infections thought by a physician possibly to have been transmitted by Berinert® should be reported by lot number, by the physician, or other healthcare provider to the CSL Behring Pharmacovigilance Department at 1-866-915-6958.

Adverse Reactions

The most serious adverse reaction reported in subjects enrolled in clinical studies who received Berinert® was an increase in the severity of pain associated with HAE.

The most common adverse reactions that have been reported in greater than 4% of the subjects who received Berinert® in clinical studies were subsequent HAE attack, headache, abdominal pain, nausea, muscle spasm, pain, diarrhea, and vomiting.

Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Placebo-controlled Clinical Study

In the placebo-controlled clinical study, referred to as the randomized clinical trial (RCT), 124 subjects experiencing an acute moderate to severe abdominal or facial HAE attack were treated with Berinert® (either a 10 unit per kg body weight or a 20 unit per kg body weight dose), or placebo (physiological saline solution).

The treatment-emergent serious adverse reactions/events that occurred in 5 subjects in the RCT were laryngeal edema, facial attack with laryngeal edema, swelling (shoulder and chest), exacerbation of hereditary angioedema, and laryngospasm.

Table 11 lists the adverse events that occurred in more than 4% of the subjects 7 to 9 days after the end of a Berinert® infusion, irrespective of causality.

TABLE 11
Adverse Events Occurring in More Than 4% of Subjects* Receiving Berinert® at Either 10 Units/kg or 20 units/kg 7 to 9 Days after Infusion, *Irrespective of Causality*

Adverse events	Number (%) of subjects reporting adverse events (n=108)
Hereditary angioedema	12 (11.1%)
Headache	12 (11.1%)
Abdominal pain†	7 (6.5%)
Nausea†	7 (6.5%)
Muscle spasms	6 (5.6%)
Pain	6 (5.6%)
Diarrhea†	5 (4.6%)
Vomiting†	5 (4.6%)

* Includes subjects in the placebo group who received Berinert® 20 units/kg as rescue study medication.
† These symptoms were identified in the protocol as related to the underlying disease. Any increase in intensity or new occurrence of these symptoms after study medication administration was considered to be an adverse event.
Source: Berinert® Prescribing Information 2009.

Subjects were tested at baseline and after 3 months for possible exposure to Parvovirus B19, hepatitis B, hepatitis C, and HIV-1 and HIV-2. No subject who underwent testing evidenced seroconversion or treatment-emergent positive polymerase chain reaction testing for these pathogens.

Extension Study

In an interim safety analysis of the ongoing open-label extension study, 56 subjects with 559 acute moderate-to-severe abdominal, facial, peripheral, and/or laryngeal attacks received a 20 unit/kg body weight dose of Berinert®. This study provides additional safety data in subjects who received multiple infusions of the product for sequential HAE attacks (one infusion per attack).

Table 12 lists the adverse events that occurred in this interim safety analysis of the ongoing open-label extension study in more than 4% of subjects up to 72 hours or 9 days after the end of a Berinert® infusion, irrespective of causality.

Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

Adverse reactions reported in Europe since 1979 in patients receiving Berinert® for treatment of HAE include hypersensitivity/anaphylactic reactions, a few suspected cases of viral transmission, including cases of acute hepatitis C, injection-site pain, injection-site redness, chills, and fever.

The following adverse reactions, identified by system organ class, have been attributed to Berinert® during postapproval use outside the U.S.

Immune System Disorder: Hypersensitivity/anaphylactic.

General/Body as a Whole: Pain on injection, redness at injection site, chills, and fever.

TABLE 12
Incidence of Adverse Events by Descending Frequency Occurring in More Than 4% of Subjects Receiving Berinert® up to 72 Hours or 9 Days After Infusion, *Irrespective of Causality*

Adverse events	Number (%) of subjects reporting adverse events up to 72 hours (n=56)	Number (%) of subjects reporting adverse events up to 9 days (n=56)
Headache	3 (5.4%)	4 (7.1%)
Abdominal pain	3 (5.4%)	3 (5.4%)
Hereditary angioedema	2 (3.6%)	4 (7.1%)
Nasopharyngitis	2 (3.6%)	3 (5.4%)

Source: Berinert® Prescribing Information 2009.

P&T Committee Considerations

As a human C1 esterase inhibitor, the proposed mechanism of action of Berinert® is the replacement of the missing or dysfunctional human protein that contributes to the pathogenesis of HAE (Berinert® Prescribing Information 2009). Berinert® has been approved as an on-demand therapy for patients experiencing acute abdominal or facial HAE attacks (Berinert® Prescribing Information 2009). Berinert® employs weight-based dosing with a recommended dose of 20 U/kg of body weight (Berinert® Prescribing Information 2009).

Education of patients in recognizing prodromal symptoms prior to an acute attack, such as flu-like symptoms, headache, nausea, non-itchy rash, tingling sensation, and diarrhea, may allow healthcare professionals to administer Berinert® for on-demand use. Berinert® is intended for administration by intravenous infusion by healthcare providers in a variety of settings including hospitals, physicians' offices, or home healthcare settings (Berinert® Prescribing Information 2009). Berinert® does not require refrigeration, which increases patients' ability and convenience in storing Berinert® in the home setting or taking it with them to have available as quickly as possible following the onset of acute facial or abdominal HAE attack (Berinert® Prescribing Information 2009).

The IMPACT-1 trial established the efficacy of Berinert® for the treatment of acute onset of facial and abdominal HAE attacks with median time to onset of symptom relief reported as 0.50 (range, 0.17-24.00) hours for Berinert® 20 U/kg compared with 1.50 (range, 0.20-24.00) hours for the placebo group (P=.0025) (Craig 2009b). Median time to symptom relief for abdominal attacks was 0.5 hours for Berinert® 20 U/Kg compared with 1.25 hours for placebo and 0.92 hours for Berinert® 20 U/kg compared with 24 hours for placebo among patients who experienced facial attacks. Further, the IMPACT-1 trial demonstrated that 75% of patients treated with Berinert® 20 U/kg experienced symptom relief within 1 hour following initiation of treatment compared with 40% of those treated with placebo (Craig 2009b). There was no statistically significant difference in median time to onset of symptom relief between moderate and severe attacks with Berinert® 20 U/kg (0.78 [range, 0.17-24.00] hours vs. 0.50 [range, 0.17-24.00] hours, respectively; P=.463). Additionally, there was no statistically significant difference in median time to onset of symptom relief between abdominal and facial attacks (0.50 [range, 0.17-24.00] hours vs. 0.92 [range, 0.25-24.00] hours, respectively). This suggests that the efficacy of Berinert® 20 U/kg is equivalent between affected body locations and for attacks of varying severity (Craig 2009b).

The half-life of Berinert® is 21.9 hours (16.5 to 24.4 hours) with a median residence time of 31.5 hours (23.7 to 35.2 hours), which may potentially reduce the need for a second dose in order to achieve 24-hour symptom control (Berinert® Prescribing Information 2009). Results from IMPACT-1 revealed that the median time to complete resolution of all symptoms was significantly shorter for patients treated with Berinert® 20 U/kg at 4.92 hours compared with 7.79 hours for the placebo group (P=.0237) (Craig 2009b). The IMPACT-1 trial also found that 31.0% of patients who received placebo experienced symptom exacerbations between 2 and 4 hours following treatment compared with 4.7% of patients treated with Berinert® 20 U/kg (P=.0014). Among patients who received Berinert® 20 U/kg, no new attacks occurred before the complete resolution of the previous attack, which demonstrates that Berinert® is not associated with rebound angioedema (Craig 2009b).

The safety results from the IMPACT-1 trial demonstrated that Berinert® 20 U/kg was well-tolerated. Notably, no patients experienced increased severity of HAE symptoms in the Berinert® 20 U/kg arm while 28.6% of patients treated with placebo experienced increased intensity of HAE symptoms between 2 and 4 hours following treatment (Craig 2009b). The IMPACT-1 trial also revealed significantly lower rates of AEs within 4 hours of treatment initiation for patients administered Berinert® 20 U/kg (19.6%) compared with placebo (43.9%). The most frequent AEs observed in the IMPACT-1 trial were nausea, diarrhea, abdominal pain, and muscle spasms with lower frequencies for each of these events among patients treated with Berinert® 20 U/kg compared with those in the placebo arm (Craig 2009b).

The need for new therapeutic options to treat patients with HAE, particularly those experiencing acute attacks, was recently reported in results from a recent voluntary, web-based survey conducted by the U.S. Hereditary Angioedema Association. The survey was conducted to assess the economic burden imposed by the treatment of acute HAE attacks and long-term treatment of patients with HAE (Wilson 2010). Demographic and clinical questions assessed the severity, location, duration, and treatment of patients' most recent HAE event as well as the average severity of HAE attacks, medical resource utilization, indirect costs associated with HAE due to travel and childcare, missed time from work, and average frequency of attacks in the year preceding the survey. In addition, the Work Productivity and Impairment–General Health (WPAI-GH) questionnaire was included to determine the impact of HAE on work productivity and activ-

TABLE 13
Direct and Indirect Economic Costs (U.S. Dollars) for Acute Hereditary Angioedema Attacks by Severity of Attack

Costs	Overall population	Severity of most recent HAE attack		
		mild	moderate	severe
Direct medical costs				
Number of patients	419	118	189	112
Clinical care*	1,166	427	469	3,220
ED visits/ hospitalizations	19,938	570	5,041	65,482
Medications	235	44	254	404
Indirect medical costs				
Number of patients	419	118	189	112
Childcare and travel†	444	19	97	1,549
Missed work	3,402	940	3,987	5,109

*Clinical care includes clinic or physician office visit and treatment including procedures or tests (ie, intubation, magnetic resonance imaging, ultrasonography, x-rays, endoscopy, blood work, and abdominal surgery).
†Patient-reported out-of-pocket costs for childcare and travel including bus fare, taxi, parking, and hotel.
Source: Adapted from Wilson 2010.

ity impairment during the preceding week with results expressed as percentages. Higher percentages were associated with increased work impairment and decreased productivity.

Eligible respondents (N=457) were 18 years old (19 years old in Alabama or Nebraska), had a diagnosis of HAE, and were able to complete an online survey in English. Patients reported a mean of 26.9 HAE attacks per year and 94% had at least 1 HAE attack in the year prior to completing the survey with 56.5% of these being abdominal episodes and 24.5% experiencing a laryngeal attack. The majority (69.4%) of patients did not seek medical interventions for their most recent attack although 12.5% were seen at emergency departments (EDs) and 58.9% of these were admitted to the hospital. Slightly more than half (50.8%) of respondents indicated that they received long-term care from allergists or immunologists for their HAE with 26.3% receiving such care from family practitioners, internists, or primary care physicians, and 10.5% relied on emergency medical physicians for their care. More than two-thirds of respondents (68.3%) required treatment with medications in the previous year to manage their HAE episodes.

The average annual direct medical cost per patient was $25,884 with $21,339 (82.4%) of this total attributed to care for acute HAE attacks. Hospitalization for treatment of acute attacks was the primary component of all direct medical costs at 67.0% with 10.1% of total direct costs for acute attacks associated with ED visits, and 9.8% for routine visits.

Respondents indicated that HAE significantly affected their ability to work with 50.6% reporting they had missed at least 1 day of work during their most recent attack and lost an average of 3.3 workdays. This was estimated to be associated with approximately $525 in lost wages for each HAE attack. The average annual cost of missed work due to acute HAE attacks was estimated at $3,402. Responses to the WPAI-GH indicated a mean impairment of 33.5% while working, and it was estimated that an average cost of $5,750 was incurred per patient year due to work impairments. Inability to maintain full-time employment due to HAE was reported by 16.4% of respondents. The annual average per-patient cost of lost wages for not being able to work full-time was estimated at $6,512. The largest proportion of indirect costs for the average patient with HAE was attributed to the inability to work full-time (40.4%) while an additional 37.5% of indirect costs were associated with decreased work productivity. Direct medical costs increased with the severity of HAE events ranging from total annual costs of $14,379 for mild attacks to $26,914 and $95,460 for moderate and severe attacks, respectively. A summary of direct and indirect costs for acute HAE attacks is presented in Table 13.

This study provides a comprehensive assessment of the direct and indirect medical and economic burden imposed by HAE with substantial costs associated with acute attacks as well as long-term management. The total annual cost for an average patient with HAE was estimated at $42,000 including both indirect and direct expenditures. Notably, costs associated with the treatment of severe attacks were almost three times greater than the costs of medical care for patients who experienced attacks of moderate severity, and treatment costs for moderate HAE episodes were almost double those for care of patients who experienced mild attacks. ED visits and hospitalizations accounted for about 48% of the total annual cost of care for patients with acute HAE attacks.

These results confirm that HAE imposes a significant economic burden on patients, their families, employers, and the healthcare delivery system in the U.S. Acute HAE episodes were associated with the highest direct medical costs (particularly for patients with moderate and severe acute attacks) as well as indirect costs associated with lost time at work, decreased productivity, and an inability to maintain full-time employment. These results underscore the need for new therapies to improve the management of patients experiencing acute HAE attacks in order to reduce the overall economic burden of this disease for both the patient and the healthcare system.

Another recent online survey of 80 U.S. physicians

including 94% who were self-identified as allergists and 6% as immunologists assessed their perceptions of HAE and the need to screen patients and their family members with suspected HAE (Lunn 2010). The investigators also conducted an e-mail and postal survey of U.S. and European patients with HAE to assess healthcare utilization from presentation to diagnosis, identify treatment differences between countries, and assess patients' perceptions of the effectiveness of prevention and acute treatment for HAE.

The physician survey revealed that respondents provided care for a mean of 7 patients with HAE and a mean of 4.8 patients were currently treated with androgens. In addition, approximately 84% of physicians reported relying on C1-INH levels and function to establish the diagnosis of HAE while only 63.8% relied on C4 levels for screening and diagnosis of patients with symptoms frequently associated with HAE, such as angioedema or abdominal pain. Less than two-thirds of physicians retested their patients with only 12.2% conducting annual retests of their patients to verify and monitor the status and progression of HAE.

Among 313 patients who completed the online survey, 43% reported that they had waited more than 1 year after their first HAE episode before seeking medical care. Strikingly, the mean time between onset of first symptom(s) of HAE and diagnosis was 8.3 years and patients sought care from an average of 4.4 physicians before receiving a diagnosis of HAE. Sixty-five percent of patients indicated they had received a misdiagnosis of their condition and 19% of U.S. respondents and 24% of those in Europe reported having unnecessary surgical procedures attributed to a misdiagnosis. The patients reported an average of 2 immediate and 2 extended blood relatives who also were diagnosed with HAE, although only 48% of first-degree and 26% of extended family members had been tested for HAE. Only 32% of patients reported that all of their family members had been tested for the condition.

These findings emphasize the imperative for physician education about screening, diagnosis, and treatment of patients with suspected HAE including family members of patients with HAE. Screening of C4 levels was identified as an important strategy to establish a differential diagnosis of HAE, which would result in more rapid and accurate diagnosis as well as initiation of appropriate follow-up and treatment. Such educational efforts also should include patients. Patient and physician education, combined with guidelines for the diagnosis of HAE, were suggested by the investigators to have the potential to improve clinical outcomes for patients.

THE BERINERT® EXPERT NETWORK

The Berinert® Expert Network (B.E.N.™) program provides ongoing information and support to patients every day, 24 hours per day via a toll-free number (CSL Behring 2010). The program offers patients assistance with identification of physicians with expertise in the treatment of HAE and initiation of treatment with Berinert® by helping providers develop treatment plans that are appropriate for the individual patient. In addition, patients and physicians can contact the B.E.N.™ to identify specialty pharmacies that have been approved to provide Berinert®. The program also can be contacted to identify hospitals near patient locations that have access and the ability to administer Berinert® according to approved indications (CSL Behring 2010). This can facilitate access by patients and family members to programs, resources, and services developed by and for individuals with HAE. The B.E.N.™ program also provides assistance with insurance issues and questions by addressing prior treatment authorizations, coverage appeals, and letters of medical necessity. In addition, the provision of the Assurance and Assistance Program helps patients gain access to Berinert® if they experience a lapse in third-party, private insurance coverage as well as assistance in obtaining Berinert® for patients who are uninsured, under-insured, or cannot afford to pay for Berinert®.

Conclusion

While HAE affects only a small proportion of the general population in the United States, the frequency, severity, and potentially life-threatening symptoms associated with HAE impose a significant burden on patients and the healthcare system. Additionally, it is estimated that 50% of HAE patients remain undiagnosed. Patients and physicians report diminished quality of life (QOL), impaired social relationships, reduced ability to work full-time, decreased work productivity, and significant direct and indirect costs that increase with the severity and frequency of attacks. The economic impact is particularly high for patients requiring treatment for acute HAE attacks with more than 80% of direct medical expenditures attributed to the care of patients experiencing acute HAE events.

Furthermore, treatment options for HAE in the United States have been limited, although three new agents were approved in 2009 for the condition. Many patients are not adequately managed with approved therapies or are at increased risk of serious side effects when they require long-term treatment with such agents as attenuated androgens, which have been the mainstay of HAE care for decades. Effective treatments for acute HAE attacks are essential to reduce the high economic costs associated with the direct and indirect economic burden of acute episodes.

Replacement of C1-INH with Berinert®, a pasteurized, lyophilized, human, plasma-derived C1-INH concentrate, repairs the underlying biochemical dysfunction that characterizes HAE. Furthermore, results from IMPACT-1 establish that treatment of acute abdominal and facial HAE attacks with Berinert® 20 U/kg significantly reduced median time to symptom resolution, decreased rates of symptom exacerbations, and was associated with significantly fewer vomiting episodes compared with placebo. There was no evidence of rebound angioedema among patients treated with Berinert®. Furthermore, Berinert® 20 U/kg was well-tolerated by patients and associated with lower rates of AEs compared with those observed in patients treated with placebo. The most common AEs observed by ≥4% of subjects after Berinert® treatment were subsequent HAE attacks, headache, abdominal pain, nausea, muscle spasm, pain, diarrhea, and vomiting (Berinert® Prescribing Information 2009). The IMPACT-1 trial establishes that the treatment of acute abdominal and facial HAE events with intravenous Berinert® 20 U/kg is safe and effective for rapid relief of symptoms.

Evaluation of Berinert® for inclusion on a formulary by P&T committees must include consideration of the efficacy of this agent, safety issues, and acquisition and monitoring costs. Results from IMPACT-1 demonstrate a favorable benefit-risk profile for Berinert®, although this ratio must be evaluated for individual patients by their healthcare professionals. P&T committees may be able to develop a protocol and identify patient populations for whom this drug will offer clinical benefit based on a review of findings from the randomized controlled trial reviewed in this Product Profiler. Although improved methods for diagnosis of HAE coupled with new therapies and improvements in supportive care for patients experiencing acute HAE attacks has resulted in reduced mortality, HAE remains a significant cause of morbidity and diminished QOL. New therapeutic options such as Berinert® offer the potential to significantly reduce the impact of acute HAE episodes on both patients and managed care organizations.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Berinert safely and effectively. See full prescribing information for Berinert.

Berinert [C1 Esterase Inhibitor (Human)]
For intravenous use. Freeze-Dried Powder for Reconstitution.
Initial U.S. Approval: 2009

----------INDICATIONS AND USAGE----------

Berinert is a plasma-derived C1 Esterase Inhibitor (Human) indicated for the treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adult and adolescent patients (1).
The safety and efficacy of Berinert for prophylactic therapy have not been established (1).

----------DOSAGE AND ADMINISTRATION----------

For intravenous use only.

- Store the vial in the original carton in order to protect from light. Store at 2-25°C (36-77°F). Do not freeze (2).
- Administer 20 units per kg body weight (2).
- Reconstitute Berinert prior to use using the diluent (sterile water) provided (2.1).
- Administer at room temperature within 8 hours of reconstitution (2.1).
- Inject at a rate of approximately 4 mL per minute (2.2).
- Do not mix Berinert with other medicinal products or solutions (2.2).

----------DOSAGE FORMS AND STRENGTHS----------

500 units lyophilized concentrate in a single-use vial for reconstitution with 10 mL of diluent (sterile water) (3).

----------CONTRAINDICATIONS ----------

- Do not use in patients with a history of life-threatening immediate hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations (4).

----------WARNINGS AND PRECAUTIONS----------

- Hypersensitivity reactions may occur. Epinephrine should be immediately available to treat any acute severe hypersensitivity reactions following discontinuation of administration (5.1).
- Thrombotic events have occurred in patients receiving off-label high doses of Berinert. Monitor patients with known risk factors for thrombotic events (5.2).
- Berinert is made from human plasma and may contain infectious agents, eg, viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent (5.3).

----------ADVERSE REACTIONS----------

- The most serious adverse reaction reported in subjects who received Berinert was an increase in the severity of pain associated with HAE (6.1).
- The most common adverse reactions observed by ≥4% of subjects after Berinert treatment were subsequent HAE attack, headache, abdominal pain, nausea, muscle spasm, pain, diarrhea and vomiting (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact the CSL Behring Pharmacovigilance Department at 1-866-915-6958 or to the FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

No drug interaction studies have been conducted (7).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: No animal data. Limited human data. Use only if clearly needed (8.1).
- Children: Safety and effectiveness in children ages 0 through 12 have not been established. Berinert was evaluated in 5 children (ages 3 through 12) and in 8 adolescent subjects (ages 13 through 16) [8.4].
- Compared to adults, the half-life of Berinert was shorter and clearance was faster in children. The clinical implication of this difference is not known (12.3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: November 2009

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

Berinert® [C1 Esterase Inhibitor (Human)]
Freeze-dried powder

1 INDICATIONS AND USAGE

Berinert is a plasma-derived concentrate of C1 Esterase Inhibitor (Human) indicated for the treatment of acute abdominal or facial attacks of hereditary angioedema (HAE) in adult and adolescent patients.

The safety and efficacy of Berinert for prophylactic therapy have not been established.

2 DOSAGE AND ADMINISTRATION

For Intravenous Use Only.

Administer Berinert at a dose of 20 units per kg body weight by intravenous injection.

Berinert is provided as a freeze-dried powder for reconstitution with the diluent (sterile water) provided. Store the vial in the original carton in order to protect from light. Do not freeze.

2.1 Preparation and Handling

- Check the expiration date on the product vial label. Do not use beyond the expiration date.
- Use aseptic technique when preparing and administering Berinert *(see Reconstitution and Administration [2.2])*.
- After reconstitution and prior to administration, inspect Berinert visually for particulate matter and discoloration. The reconstituted solution should be colorless, clear, and free from visible particles. Do not use if the solution is cloudy, discolored, or contains particulates.
- The Berinert vial is for single use only. Berinert contains no preservative. Any product that has been reconstituted should be used promptly. The reconstituted solution must be used within 8 hours. Discard partially used vials.
- Do not freeze the reconstituted solution.

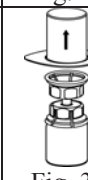
2.2 Reconstitution and Administration

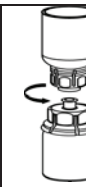
Each Berinert kit consists of one carton containing one single-use vial of Berinert, one 10 mL vial of diluent (sterile water), one Mix2Vial™ transfer set, and one alcohol swab.

Use either the Mix2Vial transfer set provided with Berinert (*see How Supplied [16.1]*) or a commercially available double-ended needle and vented filter spike.

Reconstitution

The procedures below are provided as general guidelines for the reconstitution and administration of Berinert.

1. Ensure that the Berinert vial and diluent vial are at room temperature. Use aseptic technique during the reconstitution procedure.	
2. Place the Berinert vial, diluent vial and Mix2Vial transfer set on a flat surface.	
3. Remove the flip caps from the Berinert and diluent vials. Treat the vial stoppers with the alcohol swab provided and allow to dry prior to opening the Mix2Vial transfer set package.	
4. Open the Mix2Vial transfer set package by peeling away the lid (Fig. 1). Leave the Mix2Vial transfer set in the clear package.	 Fig. 1
5. Place the diluent vial on a flat surface and hold the vial tightly. Grip the Mix2Vial transfer set together with the clear package and snap the blue end of the Mix2Vial transfer set onto the diluent vial stopper at a 90° angle (Fig. 2).	 Fig. 2
6. Carefully remove the clear package from the Mix2Vial transfer set. Make sure that you pull up only the clear package, and not the Mix2Vial transfer set (Fig. 3).	 Fig. 3
7. With the Berinert vial placed firmly on a flat surface, invert the diluent vial with the Mix2Vial transfer set attached and snap the transparent adapter onto the Berinert vial stopper at a 90° angle (Fig. 4). The diluent will automatically transfer into the Berinert vial.	 Fig. 4
8. With the diluent and Berinert vial still attached to the Mix2Vial transfer set, gently swirl the Berinert vial to ensure that the Berinert is fully dissolved (Fig. 5). Do not shake the vial.	 Fig. 5

9. With one hand, grasp the Berinert-side of the Mix2Vial transfer set and with the other hand grasp the blue diluent-side of the Mix2Vial transfer set and unscrew the set into two pieces. (Fig. 6).	 Fig. 6
10. Draw air into an empty, sterile syringe. While the Berinert vial is upright, screw the syringe to the Mix2Vial transfer set. Inject air into the Berinert vial. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly. (Fig. 7).	 Fig. 7
11. Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the plunger facing down) and unscrew the syringe from the Mix2Vial transfer set (Fig. 8). Attach the syringe to a suitable intravenous (IV) administration set.	 Fig. 8
12. If the same patient is to receive more than one vial, the contents of multiple vials may be pooled in a single administration device (eg, syringe). A new unused Mix2Vial transfer set should be used for each Berinert vial.	
13. Do not refrigerate after reconstitution. When reconstitution is carried out using aseptic technique, administration may begin within 8 hours, provided the solution has been stored at up to 25ºC (77ºF). Do not refrigerate or freeze the reconstituted solution.	

Administration

Do not mix Berinert with other medicinal products and administer by a separate infusion line.

Use aseptic technique when administering Berinert.

Administer Berinert by slow intravenous injection at a rate of approximately 4 mL per minute.

3 DOSAGE FORMS AND STRENGTHS

- Berinert is available in a single-use vial that contains 500 units of C1 esterase inhibitor as a lyophilized concentrate.
- Each vial must be reconstituted with 10 mL of diluent (sterile water) provided.

4 CONTRAINDICATIONS

Berinert is contraindicated in individuals who have experienced life-threatening hypersensitivity reactions, including anaphylaxis, to C1 esterase inhibitor preparations.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

Severe hypersensitivity reactions may occur. Epinephrine should be immediately available for treatment of acute severe hypersensitivity reaction *(see Patient Counseling Information [17])*. The signs and symptoms of hypersensitivity reactions may include hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and/or anaphylaxis during or after injection of Berinert.

Because hypersensitivity reactions may have symptoms similar to HAE attacks, treatment methods should be carefully considered. In case of suspected hypersensitivity, immediately discontinue administration of Berinert and institute appropriate treatment.

5.2 Thrombotic Events

Thrombotic events have been reported in association with Berinert when used off-label and at higher than labeled doses.[1] Animal studies have confirmed the risk of thrombosis from intravenous administration of C1 esterase inhibitor products[2] (*see Overdosage [10] and Animal Toxicology and/or Pharmacology [13.2]).*

5.3 Transmission of Infectious Agents

Because Berinert is made from human blood, it may contain infectious agents (eg, viruses and, theoretically, the Creutzfeldt-Jakob disease [CJD] agent) that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by processes demonstrated to inactivate and/or remove certain viruses during manufacturing (*see Description [11] and Patient Counseling Information [17]*).

Despite these measures, such products may still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products.

Since 1979, a few suspected cases of viral transmission have been reported with the use of Berinert outside the US, including cases of acute hepatitis C. From the incomplete information available from these cases, it was not possible to determine with certainty if the infections were or were not related to prior administration of Berinert.

The physician should discuss the risks and benefits of this product with the patient before prescribing or administering it to the patient. *(See Patient Counseling Information [17.1]).*

All infections thought by a physician possibly to have been transmitted by Berinert should be reported by lot number, by the physician, or other healthcare provider to the CSL Behring Pharmacovigilance Department at 1-866-915-6958.

6 ADVERSE REACTIONS

The most serious adverse reaction reported in subjects enrolled in clinical studies who received Berinert was an increase in the severity of pain associated with HAE.

The most common adverse reactions that have been reported in greater than 4% of the subjects who received Berinert in clinical studies were subsequent HAE attack, headache, abdominal pain, nausea, muscle spasm, pain, diarrhea and vomiting.

6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Placebo-controlled Clinical Study

In the placebo-controlled clinical study, referred to as the randomized clinical trial (RCT) (*see Clinical Studies [14]*), 124 subjects experiencing an acute moderate to severe abdominal or facial HAE attack were treated with Berinert (either a 10 unit per kg body weight or a 20 unit per kg body weight dose), or placebo (physiological saline solution).

The treatment-emergent serious adverse reactions/events that occurred in 5 subjects in the RCT were laryngeal edema, facial attack with laryngeal edema, swelling (shoulder and chest), exacerbation of hereditary angioedema, and laryngospasm.

Table 1: Adverse Reactions* Occurring up to 4 hours After Initial Infusion in More Than 4% of Subjects, *Irrespective of Causality*†

Adverse Reactions	Number (%) of Subjects Reporting Adverse Reactions Berinert 20 units/kg (n = 43)	Number (%) of Subjects Reporting Adverse Reactions Placebo Group (n = 42)
Nausea†	3 (7%)	5 (11.9%)
Dysgeusia	2 (4.7%)	0 (0)
Abdominal Pain†	2 (4.7%)	3 (7.1%)
Vomiting†	1 (2.3%)	3 (7.1%)
Diarrhea†	0 (0)	4 (9.5%)
Headache	0 (0)	2 (4.8%)

* The study protocol specified that adverse events that began within 72 hours of blinded study medication administration were to be classified as at least possibly related to study medication (ie, adverse reactions).

† The following abdominal symptoms were identified in the protocol as associated with HAE abdominal attacks: abdominal pain, bloating, cramps, nausea, vomiting, and diarrhea.

Table 2: Adverse Reactions* Occurring in More Than 4% of Subjects up to 72 hours After Infusion of Initial or Rescue Medication† by Intent-to-Treat, *Irrespective of Causality*

Adverse Reactions	Number (%) of Subjects Reporting Adverse Reactions†‡ Berinert 20 units/kg (n = 43)	Number (%) of Subjects Reporting Adverse Reactions†‡ Placebo Group (n = 42)
Nausea	3 (7%)	11 (26.2%)
Headache	3 (7%)	5 (11.9%)
Abdominal Pain	3 (7%)	5 (11.9%)
Dysgeusia	2 (4.7%)	1 (2.4%)
Vomiting	1 (2.3%)	7 (16.7%)
Pain	1 (2.3%)	4 (9.5%)
Muscle spasms	1 (2.3%)	4 (9.5%)
Diarrhea	0 (0)	8 (19%)
Back pain	0 (0)	2 (4.8%)
Facial pain	0 (0)	2 (4.8%)

* The study protocol specified that adverse events that began within 72 hours of blinded study medication administration were to be classified as at least possibly related to study medication (ie, adverse reactions).

† If a subject experienced no relief or insufficient relief of symptoms within 4 hours after infusion, investigators had the option to administer a blinded second infusion ("rescue" treatment) of Berinert (20 units/kg for the placebo group or 10 units/kg for the 10 units/kg group), or placebo (for the 20 units/kg group).

‡ Adverse reactions following either initial treatment and/or blinded "rescue" treatment. Because more subjects in the placebo randomization group than in the Berinert randomization group received rescue treatment, the median observation period in this analysis for subjects randomized to placebo was slightly longer than for subjects randomized to receive Berinert.

Table 3 lists the adverse events that occurred in more than 4% of the subjects 7 to 9 days after the end of a Berinert infusion, *irrespective of causality.*

Table 3: Adverse Events Occurring in More Than 4% of Subjects* Receiving Berinert at Either 10 Units/kg or 20 units/kg 7 to 9 Days after Infusion, *Irrespective of Causality*

Adverse Events	Number (%) of Subjects Reporting Adverse Events (n=108)
Hereditary angioedema	12 (11.1%)
Headache	12 (11.1%)
Abdominal pain†	7 (6.5%)
Nausea†	7 (6.5%)
Muscle spasms	6 (5.6%)
Pain	6 (5.6%)
Diarrhea†	5 (4.6%)
Vomiting†	5 (4.6%)

* Includes subjects in the placebo group who received Berinert 20 units/kg as rescue study medication.
† These symptoms were identified in the protocol as related to the underlying disease. Any increase in intensity or new occurrence of these symptoms after study medication administration was considered to be an adverse event.

Subjects were tested at baseline and after 3 months for possible exposure to Parvovirus B19, hepatitis B, hepatitis C, and HIV-1 and HIV-2. No subject who underwent testing evidenced seroconversion or treatment-emergent positive polymerase chain reaction testing for these pathogens.

Extension Study

In an interim safety analysis, of the ongoing open-label extension study, 56 subjects with 559 acute moderate to severe abdominal, facial, peripheral, and/or laryngeal attacks received a 20 unit/kg body weight dose of Berinert (*see Clinical Studies [14]*). This study provides additional safety data in subjects who received multiple infusions of the product for sequential HAE attacks (one infusion per attack).

Table 4 lists the adverse events that occurred in this interim safety analysis of the ongoing open-label extension study in more than 4% of subjects up to 72 hours or 9 days after the end of a Berinert infusion, *irrespective of causality.*

Table 4: Incidence of Adverse Events by Descending Frequency Occurring in More Than 4% of Subjects Receiving Berinert up to 72 Hours or 9 Days After Infusion, *Irrespective of Causality*

Adverse Events	Number (%) of Subjects Reporting Adverse Events up to 72 hours (n=56)	Number (%) of Subjects Reporting Adverse Events up to 9 Days (n=56)
Headache	3 (5.4%)	4 (7.1%)
Abdominal pain	3 (5.4%)	3 (5.4%)
Hereditary angioedema	2 (3.6%)	4 (7.1%)
Nasopharyngitis	2 (3.6%)	3 (5.4%)

6.2 Postmarketing Experience

Because postmarketing reporting of adverse reactions is voluntary and from a population of uncertain size, it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

Adverse reactions reported in Europe since 1979 in patients receiving Berinert for treatment of HAE include hypersensitivity/anaphylactic reactions, a few suspected cases of viral transmission, including cases of acute hepatitis C, injection-site pain, injection-site redness, chills, and fever.

The following adverse reactions, identified by system organ class, have been attributed to Berinert during post-approval use outside the US.

- *Immune System Disorder: Hypersensitivity/anaphylactic reactions, and shock*
- *General/Body as a Whole: Pain on injection, redness at injection site, chills, and fever*

7 DRUG INTERACTIONS

No drug interaction studies have been conducted.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with Berinert. It is not known whether Berinert can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Berinert should be given to a pregnant woman only if clearly needed. In a retrospective case collection study, 20 pregnant women ranging in age from 20 to 35 years received Berinert with repeated doses up to 3,500 units per attack; these women reported no complications during delivery and no harmful effects on their 34 neonates.

8.2 Labor and Delivery

The safety and effectiveness of Berinert administration prior to or during labor and delivery have not been established. Use only if clearly needed.

8.3 Nursing Mothers

It is not known whether Berinert is excreted in human milk. Because many drugs are excreted in human milk, use only if clearly needed when treating a nursing woman.

8.4 Pediatric Use

Safety and efficacy of Berinert in children (ages 0 through 12) have not been established. The clinical studies included an insufficient number of subjects in this age group to determine whether they respond differently from older subjects. The safety and efficacy of Berinert were evaluated in 5 children (ages 3 through 12) and in 8 adolescent subjects (ages 13 through 16) (*see Pharmacokinetics [12.3]*).

8.5 Geriatric Use

Safety and efficacy of Berinert in the geriatric population have not been established. Clinical studies with Berinert included four subjects older than 65 years. The clinical studies included an insufficient number of subjects in this age group to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

The development of thrombosis has been reported after doses exceeding 20 units/kg body weight of Berinert when used off-label[1] in newborns and young children with congenital heart anomalies during or after cardiac surgery under extracorporeal circulation.

The maximum dose administered in clinical studies in hereditary angioedema was 20 units/kg body weight. Overdosage did not occur in connection with treatment of HAE.

11 DESCRIPTION

Berinert is a human plasma-derived, purified, pasteurized, lyophilized concentrate of C1 esterase inhibitor to be reconstituted for intravenous administration. Berinert is prepared from large pools of human plasma from US donors. One standard unit of C1 esterase inhibitor concentrate is equal to the amount of C1 esterase inhibitor in 1 mL of fresh citrated human plasma, which is equivalent to 270 mg/L or 2.5 μM/L. No international laboratory standard for quantifying C1 esterase inhibitor. An in-house standard is used to assure lot-to-lot consistency in product potency.

C1 esterase inhibitor is a soluble, single-chain glycoprotein containing 478 amino acid residues organized into three beta-sheets and eight or nine alpha-helices.[3] The heavily glycosylated molecule has an apparent molecular weight of 105 kD, of which the carbohydrate chains comprise 26% to 35%.[4]

Each vial of Berinert contains 500 units C1 esterase inhibitor, 50 to 80 mg total protein, 85 to 115 mg glycine, 70 to 100 mg sodium chloride, and 25 to 35 mg sodium citrate.

All plasma used in the manufacture of Berinert is obtained from US donors and is tested using serological assays for hepatitis B surface antigen and antibodies to HIV-1/2 and HCV. Additionally, the plasma is tested with Nucleic Acid Testing (NAT) for HCV and HIV-1 and found to be non-reactive (negative). In addition, the plasma is tested by NAT for HAV and Human Parvovirus B19. Only plasma that has passed virus screening is used for production, and the limit for Parvovirus B19 in the fractionation pool is set not to exceed 10^4 IU of Parvovirus B19 DNA per mL.

The manufacturing process for Berinert includes multiple steps that reduce the risk of virus transmission. The virus inactivation/reduction capacity of three steps (pasteurization in aqueous solution at 60°C for 10 hours, hydrophobic interaction chromatography, and the combination of ion exchange chromatographies and ammonium sulphate precipitation) was evaluated in a series of *in vitro* spiking experiments. The total mean cumulative virus inactivation/reduction is shown in Table 5.

Table 5: Mean Virus Inactivation/Reductions in Berinert

Virus Studied	Pasteurization [log_{10}]	Hydrophobic Interaction Chromatography [log_{10}]	DEAE-Sephadex A50 Chromatography QAE-Sephadex Chromatography and Ammonium Sulphate Precipitation [log10]	Total Cumulative [log_{10}]
Enveloped Viruses				
HIV-1	≥6.6	≥4.5	4.3	≥15.4
BVDV	≥9.2	≥4.6	NA	≥13.8
PRV	6.3	≥6.5	≥7.7	≥20.5
WNV	≥7.0	ND	NA	NA
Non-Enveloped Viruses				
HAV	≥6.4	4.5	NA	≥10.9
CPV	1.4	6.1	NA	7.5
B19V	3.9	ND	NA	NA

HIV-1, Human immunodeficiency virus type 1, a model for HIV-1 and HIV-2
BVDV, Bovine viral diarrhea virus, a model for HCV
PRV, Pseudorabies virus, a model for large enveloped DNA viruses (eg, herpes virus)
WNV, West Nile virus
HAV, Hepatitis A virus
CPV, Canine parvovirus
B19V, Human Parvovirus B19
ND, Not determined
NA, Not applicable

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

C1 esterase inhibitor is a normal constituent of human plasma and belongs to the group of serine protease inhibitors (serpins) that includes antithrombin III, alpha$_1$-protease inhibitor, alpha$_2$-antiplasmin, and heparin cofactor II. As with the other inhibitors in this group, C1 esterase inhibitor has an important inhibiting potential on several of the major cascade systems of the human body, including the complement system, the intrinsic coagulation (contact) system, the fibrinolytic system, and the coagulation cascade. Regulation of these systems is performed through the formation of complexes between the proteinase and the inhibitor, resulting in inactivation of both and consumption of the C1 esterase inhibitor.

C1 esterase inhibitor, which is usually activated during the inflammatory process, inactivates its substrate by covalently binding to the reactive site. C1 esterase inhibitor is the only known inhibitor for the subcomponent of the complement component 1 (C1r), C1s, coagulation factor XIIa, and kallikrein. Additionally, C1 esterase inhibitor is the main inhibitor for coagulation factor XIa of the intrinsic coagulation cascade.

HAE patients have low levels of endogenous or functional C1 esterase inhibitor. Although the events that induce attacks of angioedema in HAE patients are not well defined, it has been postulated that increased vascular permeability and the clinical manifestation of HAE attacks may be primarily mediated through contact system activation. Suppression of contact system activation by C1 esterase inhibitor through the inactivation of plasma kallikrein and factor XIIa is thought to modulate this vascular permeability by preventing the generation of bradykinin.[5]

Administration of Berinert to patients with C1 esterase inhibitor deficiency replaces the missing or malfunctioning protein in patients. The plasma concentration of C1 esterase inhibitor in healthy volunteers is approximately 270 mg/L.[6]

12.3 Pharmacokinetics

The pharmacokinetics of Berinert were evaluated in an open-label, uncontrolled, single-center study in 40 subjects (35 adults and 5 children under 16 years of age) with either mild or severe HAE. All subjects received a single intravenous injection of Berinert ranging from 500 units to 1500 units. Blood samples were taken during an attack-free period at baseline and for up to 72 hours after drug administration. Pharmacokinetic parameters were estimated using non-compartmental analysis (with or without baseline adjustment). Table 6 summarizes the pharmacokinetic parameters in 35 adult subjects with HAE.

Table 6: Pharmacokinetic Parameters of Berinert in Adult Subjects with HAE by Non-compartmental Analysis (n=35)

Parameters	Unadjusted for baseline	Adjusted for baseline
$AUC_{(0-t)}$ (hr x IU/mL)*	27.5 ± 8.5 (15.7-44.7)	12.8 ± 6.7 (3.9-34.7)
CL (mL/hr/kg)	0.60 ± 0.17 (0.34-0.96)	1.44 ± 0.67 (0.43-3.85)
V_{ss} (mL/kg)	18.6 ± 4.9 (11.1-27.6)	35.4 ± 10.5 (14.1-56.1)
Half-life (hrs)	21.9 ± 1.7 (16.5-24.4)	18.4 ± 3.5 (7.4-22.8)
MRT (hrs)	31.5 ± 2.4 (23.7-35.2)	26.4 ± 5.0 (10.7-33.0)

AUC: Area under the curve
CL: Clearance
$V_{ss:}$ Volume steady state
MRT: Mean residence time
*Based on a 15 unit/kg dose. Numbers in parenthesis are the range.

Table 7 summarizes the pharmacokinetic parameters in 5 pediatric subjects (ages 6 through 13) with HAE. Based on adjusted baseline, compared to adults, the half-life of Berinert was shorter and clearance was faster in this limited cohort of children. However, the clinical implication of this difference is not known.

Table 7: Pharmacokinetic Parameters of Berinert in Pediatric Subjects with HAE by Non-compartmental Analysis (n=5)

Parameters	Unadjusted for baseline	Adjusted for baseline
$AUC_{(0-t)}$ (hr x IU/mL)*	25.45 ± 5.8 (16.8-31.7)	9.78 ± 4.37 (4.1-15.2)
CL (mL/hr/kg)	0.62 ± 0.17 (0.47-0.89)	1.9 ± 1.1 (0.98-3.69)
V_{ss} (mL/kg)	19.8 ± 4.0 (16.7-26.1)	38.8 ± 8.9 (31.9-54.0)
Half-life (hrs)	22.4 ± 1.6 (20.3-24.4)	16.7 ± 5.8 (7.4-22.5)
MRT (hrs)	32.3 ± 2.3 (29.3-35.2)	24.0 ± 8.3 (10.7-32.4)

AUC: Area under the curve
CL: Clearance
$V_{ss:}$ Volume steady state
MRT: Mean residence time
*Based on a 15 unit/kg dose. Numbers in parenthesis are the range.

Studies have not been conducted to evaluate the pharmacokinetics of Berinert in special patient populations identified by gender, race, geriatric age, or the presence of renal or hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No animal studies have been completed to evaluate the effects of Berinert on carcinogenesis, mutagenesis, and impairment of fertility.

13.2 Animal Toxicology and/or Pharmacology

Acute intravenous toxicity of Berinert was performed in mice at 1500, 3000, and 6000 units/kg and in rats at 1000, 2000, and 3000 units/kg. Berinert was well tolerated and no signs of toxicity were observed up to the highest dose administered.

Repeat intravenous dose toxicity was studied in a 14-day repeat dose study in rats at doses of 20, 60, and 200 units/kg/day. Berinert was well tolerated and no toxicity was observed up to the highest dose administered. No antibody response against C1 esterase inhibitor could be demonstrated in this study after multiple dosing with Berinert.

In a safety pharmacology study, Berinert was administered to beagle dogs intravenously at a cumulative dose of 3500 units/kg. No adverse effects were seen on the cardiovascular and respiratory system. There was a drop in body temperature, reduced coagulation time, and a decrease in thrombocyte aggregation.

Local intravenous tolerance of Berinert was evaluated in rabbits at 1500 units. No pathological changes were noted at the time of injection or during the following 24 hours. No pathological signs were noted during necropsy.

Thrombotic events have been reported in association with C1 esterase inhibitor products when used off-label and at higher than labeled doses[1] (*see Overdosage [10]).* Animal studies have confirmed the risk of thrombosis from intravenous administration of C1 esterase inhibitor products.[2]

14 CLINICAL STUDIES

The safety and efficacy of Berinert in the treatment of acute abdominal or facial attacks in subjects with hereditary angioedema were demonstrated in a placebo-controlled, double-blind, prospective, multinational, randomized, parallel-group, dose-finding, three-arm, clinical study, referred to as the randomized clinical trial (RCT). The RCT assessed the efficacy and safety of Berinert in 124 adult and pediatric subjects with C1 esterase inhibitor deficiency who were experiencing an acute moderate to severe attack of

abdominal or facial HAE. Subjects ranged in age from six to 72 years of age; 67.7% were female and 32.3% were male; and approximately 90% were Caucasian.

The study objectives were to evaluate whether Berinert shortens the time to onset of relief of symptoms of an abdominal or facial attack compared to placebo and to compare the efficacy of two different doses of Berinert. The time to onset of relief of symptoms was determined by the subject's response to a standard question posed at appropriate time intervals for as long as 24 hours after start of treatment, taking into account all single HAE symptoms. In addition the severity of the single HAE symptoms was assessed over time.

Subjects were randomized to receive a single 10 unit/kg body weight dose of Berinert (39 subjects), a single 20 unit/kg dose of Berinert (43 subjects), or a single dose of placebo (42 subjects) by slow intravenous infusion (recommended to be given at a rate of approximately 4 mL per minute) within 5 hours of an HAE attack. At least 70% of the subjects in each treatment group were required to be experiencing an abdominal attack.

If a subject experienced no relief or insufficient relief of symptoms by 4 hours after infusion, investigators had the option to administer a second infusion of Berinert (20 units/kg for the placebo group, 10 units/kg for the 10 units/kg group), or placebo (for the 20 units/kg group). This masked (blinded) "rescue study medication" was administered to subjects and they were then followed until complete resolution of symptoms was achieved. Adverse events were collected for up to 7 to 9 days following the initial administration of Berinert or placebo.

In the rare case that a subject developed life-threatening laryngeal edema after inclusion into the study, immediate start of open-label treatment with a 20 unit/kg body weight dose of Berinert was allowed.

All subjects who received confounding medication (rescue medication) before symptom relief were regarded as "non-responders." Therefore, time to onset of symptom relief was set at 24 hours if a subject received any rescue medication (ie, rescue study medication, narcotic analgesics, non-narcotic analgesics, anti-emetics, open-label C1 inhibitor, androgens at increased dose, or fresh frozen plasma) between 5 hours before administration of blinded study medication until time to onset of relief.

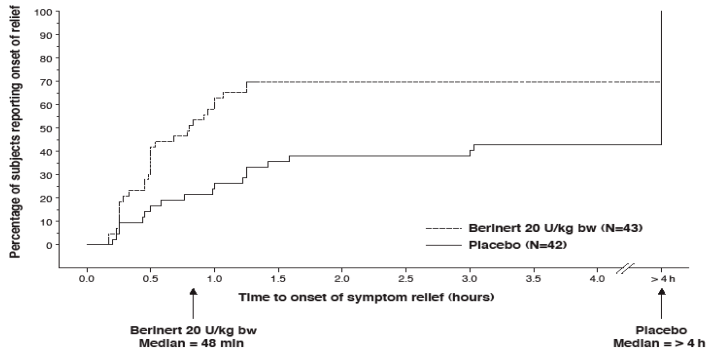
For the trial to be considered successful, the study protocol specified the following criteria for the differences between the Berinert 20 units/kg and the placebo group:

- The time to onset of relief of symptoms of the HAE attack had to achieve a one-sided p-value of less than 0.0249 for the final analysis, and at least one of the following criteria had to demonstrate a trend in favor of Berinert with a one-sided p-value of less than 0.1:
  - The proportion of subjects with increased intensity of clinical HAE symptoms between 2 and 4 hours after start of treatment with study medication compared to baseline, or
  - The number of vomiting episodes within 4 hours after start of study treatment.

Subjects treated with 20 units/kg body weight of Berinert experienced a significant reduction (p=0.0016; "Wilcoxon Rank Sum test") in time to onset of relief from symptoms of an HAE attack as compared to placebo (median of 48 minutes for Berinert 20 units/kg body weight, as compared to a median of >4 hours for placebo). The time to onset of relief from symptoms of an HAE attack for subjects in the 10 unit/kg dose of Berinert was not statistically significantly different from that of subjects in the placebo group.

Figure 9 is a Kaplan-Meier curve showing the percentage of subjects reporting onset of relief of HAE attack symptoms as a function of time. Individual time points beyond 4 hours are not presented on the graph, because the protocol permitted blinded rescue medication, analgesics, and/or anti-emetics to be administered starting 4 hours after randomized blinded study medication had been administered.

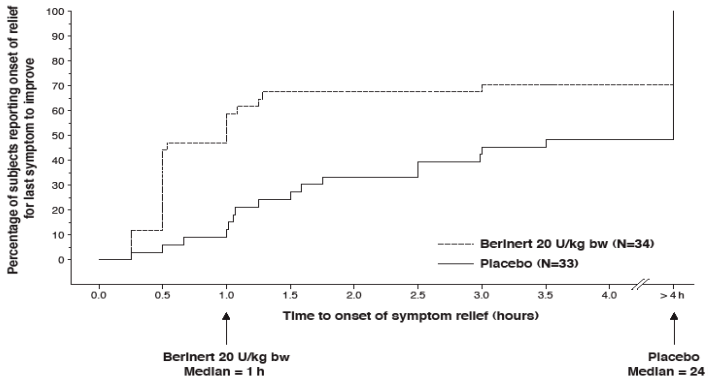
Figure 9: Time to Onset of Symptom Relief With Imputation to >4 Hours for Subjects Who Received any Rescue Medication* or Non-narcotic Analgesics Before Start of Relief



* Included rescue study medication (as blinded C1 inhibitor or placebo given as rescue medication), open-label C1 inhibitor, narcotic and non-narcotic analgesics, anti-emetics, androgens at increased dose or fresh frozen plasma.

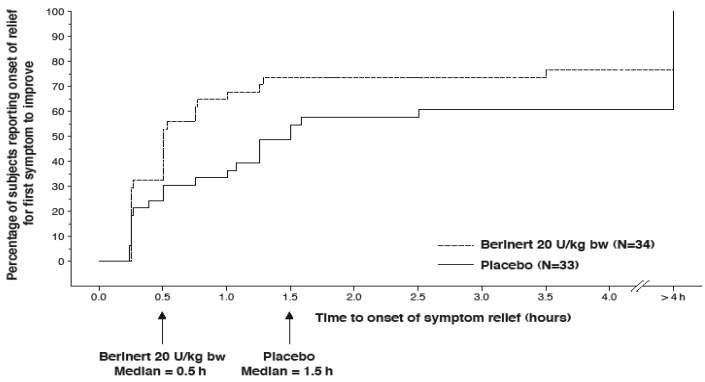
In addition, the efficacy of Berinert 20 units/kg body weight could be confirmed by observing a reduction in the intensity of single HAE symptoms at an earlier time compared to placebo. For abdominal attacks Figure 10a shows the time to start of relief of the *last* symptom to improve that was already present at baseline. Pre-defined abdominal HAE symptoms included pain, nausea, vomiting, cramps and diarrhea. Figure 10b shows the respective time to start of relief of the *first* symptom to improve that was already present at baseline.

Figure 10a: Time to Start of Relief of the *Last* Symptom to Improve (Abdominal Attacks) with Imputation to >4 Hours for Subjects Who Received any Rescue Medication* Before Start of Relief



* Included rescue study medication (as blinded C1 inhibitor or placebo given as rescue medication), open-label C1 inhibitor, narcotic and non-narcotic analgesics, anti-emetics, androgens at increased dose or fresh frozen plasma.

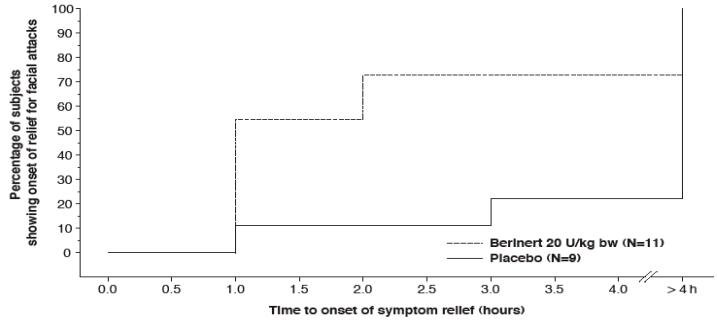
Figure 10b: Time to Start of Relief of the *First* Symptom to Improve (Abdominal Attacks) With Imputation to >4 Hours for Subjects Who Received Any Rescue Medication* Before Start of Relief



* Included rescue study medication (as blinded C1 inhibitor or placebo given as rescue medication), open-label C1 inhibitor, narcotic and non-narcotic analgesics, anti-emetics, androgens at increased dose or fresh frozen plasma.

For facial attacks, single HAE symptoms were recorded. In addition, photos were taken at pre-determined time points and assessed by the members of an independent Data Safety Monitoring Board (DSMB), who were blinded as to treatment, center and other outcome measures. The change in the severity of the edema when compared to baseline was assessed on a scale with outcomes "no change", "better", "worse" and "resolved". Figure 11 shows the time to start of relief from serial facial photographs by DSMB assessment.

Figure 11: Time to Start of Relief From Serial Facial Photographs*



* Includes facial attacks in subjects with concomitant abdominal attacks.

Table 8 compares additional endpoints, including changes in HAE symptoms and use of rescue medication in subjects receiving Berinert at 20 units/kg body weight and placebo.

Table 8: Changes in HAE Symptoms and Use of Rescue Medication in Subjects Receiving Berinert 20 units/kg Body Weight vs. Placebo

Additional Endpoints	Number (%) of Subjects Berinert 20 units/kg Body Weight Group (n=43)	Number (%) of Subjects Placebo Group (n=42)
Onset of symptom relief within 60 minutes after administration of study medication *(post-hoc)*	27 (62.8%)	11 (26.2%)
Onset of symptom relief within 4 hours after administration of study medication	30 (69.8%)	18 (42.9%)
Number of vomiting episodes within 4 hours after start of study treatment*	6 episodes	35 episodes
Worsened intensity of clinical HAE symptoms between 2 and 4 hours after administration of study medication compared to baseline†	0 (0%)	12 (28.6%)
Number (percent) of combined abdominal and facial attack subjects receiving rescue study medication, analgesics, or anti-emetics at any time prior to initial relief of symptoms	13 (30.2%)	23 (54.8%)
At least one new HAE symptom not present at baseline and starting within 4 hours after administration of study medication	2 (4.6%)	6 (14.3%)

* p-value = 0.033
† p-value = 0.00008

Both the proportion of subjects with increased intensity of clinical HAE symptoms between 2 and 4 hours after start of treatment compared to baseline, and the number of vomiting episodes within 4 hours after start of study treatment demonstrated trends in favor of Berinert in comparison to placebo (p-values <0.1). Tables 9 through 12 present additional information regarding responses to treatment.

Table 9: Proportion of Subjects Experiencing Start of Self-Reported Relief of Symptoms by 4 Hours by Attack Type

Attack Type	Berinert 20 units/kg Body Weight (Abdominal Subjects =34) (Facial Subjects = 9) (Other subjects = 0)	Placebo Group (Abdominal Subjects = 33) (Facial Subjects = 8) (Other subjects = 1)*
Abdominal	24 (70.6%)	15 (45.5%)
Facial	6 (66.7%)	3 (37.5%)

* Laryngeal edema initially classified as facial edema.

Table 10: Proportion of Subjects Experiencing Reduction in Severity of at Least One Individual HAE Attack Symptom by 4 Hours

Attack Type	Berinert 20 units/kg Body Weight (Abdominal Subjects = 34) (Facial Subjects = 9)	Placebo Group (Abdominal Subjects = 33) (Facial Subjects = 8)
Abdominal	33 (97.1%)	29 (87.9%)
Facial	6 (66.7%)	4 (50%)

Table 11: Proportion of Subjects with Facial Attacks Demonstrating Improvement in Serial Facial Photographs by 4 hours*

Attack Type	Berinert 20 units/kg Body Weight (Subjects = 9)	Placebo Group (Subjects = 8)
Facial	7 (77.8%)	2 (25%)

* Based on masked (blinded) evaluation by data safety monitoring board.

Table 12: Proportion of Subjects with Abdominal and Facial Attacks Receiving Rescue Study Medication at any Time Prior to *Complete Relief of Symptoms*

Attack Type	Berinert 20 U/kg Body Weight (Abdominal Subjects = 34) (Facial Subjects = 9)	Placebo Group (Abdominal Subjects = 33) (Facial Subjects = 8)
Abdominal	7 (20.6%)	17 (51.5%)
Facial	1 (11.1%)	6 (75%)

No subjects treated with Berinert at 20 units/kg body weight reported worsening of symptoms at 4 hours after administration of study medication compared to baseline.

The study demonstrated that the Berinert 20 unit/kg body weight dose was significantly more efficacious than the Berinert 10 unit/kg body weight dose or placebo.

Open-Label Extension Study

Berinert was evaluated in a prospective, open-label, uncontrolled, multicenter extension study conducted at 10 centers in the US and Canada in subjects who had participated in the RCT study for the treatment of acute abdominal or facial attacks in subjects with hereditary angioedema.

The purpose of this ongoing extension study is to provide Berinert to subjects who had participated in the RCT study and who experienced any type of subsequent HAE attack (ie, abdominal, facial, peripheral, or laryngeal).

In a non-pre-specified interim safety analysis of the ongoing open-label extension study, a total of 56 subjects (19 males and 37 females, age range: 10 to 53 years) with 559 HAE attacks treated with 20 unit/kg body weight dose of Berinert per attack, were observed at the study site until onset of relief of HAE symptoms, and were followed up for adverse events for 7 to 9 days following treatment of each HAE attack (see *Adverse Reactions, Clinical Trials Experience [6.1]*). There were 49 subjects with abdominal attacks, 11 subjects with facial attacks, 28 subjects with peripheral attacks, and 12 subjects with laryngeal attacks.

15 REFERENCES

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16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Berinert is supplied in a single-use vial. Each carton contains a 500 unit vial of Berinert for reconstitution with 10 mL of diluent containing sterile water (meets USP chemistry requirements except for pH; pH 4.5-8.5). The components used in the packaging for Berinert are latex-free.

Each product package consists of the following:

NDC Number	Component
63833-825-02	Carton (kit) containing one 500 unit vial of Berinert [NDC 63833-835-01], one 10 mL vial of diluent (sterile water) [NDC 63833-765-15], one Mix2Vial filter transfer set, and one alcohol swab.

16.2 Storage and Handling

When stored at temperatures of 2-25°C (36-77°F), Berinert is stable for the period indicated by the expiration date on the carton and vial label (up to 30 months). Keep Berinert in its original carton until ready to use. Do not freeze. Protect from light.

17 PATIENT COUNSELING INFORMATION

Inform patients to immediately report the following to their physician:

- Signs and symptoms of allergic hypersensitivity reactions, such as hives, urticaria, tightness of the chest, wheezing, hypotension and/or anaphylaxis experienced during or after injection of Berinert *(see WARNINGS AND PRECAUTIONS/Hypersensitivity [5.1])*
- Signs and symptoms of thrombosis, such as new onset swelling and pain in the limbs or abdomen, new onset chest pain, shortness of breath, loss of sensation or motor power, or altered consciousness, vision, or speech *(see WARNINGS AND PRECAUTIONS/Thrombotic Events [5.2])*

Advise female patients to notify their physician if they become pregnant or intend to become pregnant during the treatment of acute abdominal or facial attacks of HAE with Berinert.

Advise patients to notify their physician if they are breastfeeding or plan to breastfeed.

Advise patients to consult with their healthcare professional prior to travel.

Advise patients that, because Berinert is made from human blood, it may carry a risk of transmitting infectious agents, eg, viruses, and, theoretically, the Creutzfeldt-Jakob (CJD) agent *(see WARNINGS AND PRECAUTIONS/Transmission of Infectious Agents [5.3] and Description [11])*. Inform patients of the risks and benefits of Berinert before prescribing or administering it to the patient.

17.1 FDA-Approved Patient Labeling – Patient Product Information (PPI)

Berinert (BEAR-ĭ-nert)
C1 Esterase Inhibitor (Human)
Freeze-Dried Powder for Reconstitution

This leaflet summarizes important information about BERINERT. Please read it carefully before using Berinert and each time you get a refill. There may be new information provided. This information does not take the place of talking with your healthcare provider, and it does not include all of the important information about BERINERT. If you have any questions after reading this, ask your healthcare provider.

What is BERINERT?

BERINERT is an injectable medicine used to treat swelling and/or painful attacks in adults and adolescents with hereditary angioedema (HAE). HAE is caused by the poor functioning or lack of a protein called C1 that is present in your blood and helps control inflammation (swelling) and parts of the immune system. Berinert contains C1 esterase inhibitor, a protein that helps control C1.

Who should not use BERINERT?

You should not use BERINERT if you have experienced life-threatening immediate hypersensitivity reactions, including anaphylaxis to the product.

What should I tell my healthcare provider before BERINERT is given?

Tell your healthcare provider about all of your medical conditions, including if you:

- Are pregnant or planning to become pregnant. It is not known if BERINERT can harm your unborn baby.
- Are breastfeeding or plan to breastfeed. It is not known if BERINERT passes into your milk and if it can harm your baby.
- Have a history of blood clotting problems. Blood clots (thrombosis) have occurred in patients receiving large amounts of Berinert. Very high doses of C1 esterase inhibitor could increase the risk of blood clots.

Tell your healthcare provider and pharmacist about all of the medicines you take, including all prescription and non-prescription medicines such as over-the-counter medicines, supplements, or herbal remedies.

How is BERINERT given?

Your healthcare provider will infuse BERINERT into your vein (intravenous injection). Before infusing, he or she must dissolve the BERINERT powder using the sterile water provided. Your healthcare provider will prescribe the dose that you should be given.

What are the possible side effects of BERINERT?

Allergic reactions may occur with BERINERT. Call your healthcare provider or the emergency department right away if you have any of the following symptoms after using BERINERT:

- **wheezing**
- **difficulty breathing**
- **chest tightness**
- **turning blue (look at lips and gums)**
- **fast heartbeat**
- **swelling of the face**
- **faintness**
- **rash**
- **hives**

Signs of a blood clot include:

- new onset of swelling and pain in the limbs or abdomen
- new onset of chest pain
- shortness of breath
- loss of sensation or control of muscles/muscle weakness on one side of the body
- altered consciousness, vision, or speech.

In clinical studies, the most severe side effect reported in subjects who received BERINERT was an increase in the severity of pain associated with HAE.

Other side effects patients experienced during clinical research studies include:

- subsequent HAE attack
- headache
- abdominal pain
- nausea
- muscle spasms
- pain
- diarrhea
- vomiting

Because BERINERT is made from human blood, it may carry a risk of transmitting infectious agents, eg, viruses, and, theoretically, the Creutzfeldt-Jakob (CJD) agent.

These are not all the possible side effects of BERINERT.

Tell your healthcare provider about any side effect that bothers you or that does not go away. You can also report side effects to the FDA at 1-800-FDA-1088.

What else should I know about BERINERT?

Medicines are sometimes prescribed for purposes other than those listed here. Do not use BERINERT for a condition for which it is not prescribed. Do not share BERINERT with other people, even if they have the same symptoms that you have.

This leaflet summarizes the most important information about BERINERT. If you would like more information, talk to your healthcare provider. You can ask your healthcare provider or pharmacist for information about BERINERT that was written for healthcare professionals.

Talk to your healthcare provider before traveling.

This Patient Package Insert has been approved by the US Food and Drug Administration.

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