

CEPROTIN

[Protein C Concentrate (Human)]

Lyophilized Powder for Solution for Injection

Initial U.S. Approval: 2007

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

INDICATIONS AND USAGE

CEPROTIN is indicated for patients with severe congenital Protein C deficiency for the prevention and treatment of venous thrombosis and purpura fulminans. CEPROTIN is indicated as a replacement therapy for pediatric and adult patients. (1.1)

DOSAGE AND ADMINISTRATION

Initiate treatment under the supervision of a physician experienced in using coagulation factors/inhibitors where monitoring of Protein C activity is feasible. (2.1)

CEPROTIN Dosing Schedule for Acute Episodes, Short-term Prophylaxis and Long-term Prophylaxis*			
	Initial Dose**	Subsequent 3 Doses**	Maintenance Dose**
Acute Episode/Short-term Prophylaxis***	100–120 IU/kg	60–80 IU/kg Q 6 hours	45–60 IU/kg Q 6 or Q 12 hours
Long-term Prophylaxis	NA	NA	45–60 IU/kg Q 12 hours

* Dosing is based upon a pivotal clinical trial of 15 patients

** The dose regimen should be adjusted according to the pharmacokinetic profile for each individual. (2.1, 2.2)

*** CEPROTIN should be continued until desired anticoagulation is achieved.

NA = Not Applicable, Q = Every

Store at 2°C–8°C (36°F–46°F) and protect from light. Avoid freezing. Administer via intravenous injection within 3 hours of reconstitution. (16)

• Dosage Forms And Strengths

BLUE BAR: Approximately 500 IU/vial (3)

GREEN BAR: Approximately 1000 IU/vial (3)

Each single-dose vial contains the following excipients: 8 mg/mL human albumin, 4.4 mg/mL trisodium citrate dihydrate and 8.8 mg/mL sodium chloride when reconstituted with the appropriate amount of diluent. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS/PRECAUTIONS

- Discontinue administration if symptoms of hypersensitivity/allergic reactions occur. (2.1, 5.1, 6.1)
- Made from pooled human plasma. The possibility of transmitting infectious agents cannot be ruled out. (5.2, 11)
- Simultaneous administration with tPA and/or anticoagulants may increase risk of bleeding. (5.3)
- Contains heparin. If heparin-induced thrombocytopenia is suspected, check platelet counts immediately and discontinue administration. (5.4)
- Contains sodium >200 mg. Patients on a low-sodium diet and/or patients with renal impairment should be informed. (5.5)

ADVERSE REACTIONS

- The most serious and common adverse reactions observed in clinical trials were rash, itching and lightheadedness. (2.1, 5.1, 6.1)
- The most serious adverse reactions post-marketing were hemothorax and hypotension. (6.2)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare Corporation at 1-866-888-2472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- None known. (7)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Not studied. (8.1)
- Labor and Delivery: Not studied. (8.2)
- Nursing Mothers: Not studied. (8.3)
- Pediatric Use: Recommended for neonate and pediatric use. (2.1, 8.4, 12.3)
- Renal/Hepatic Impairment: Not studied. (8.6)

See 17 for PATIENT COUNSELING INFORMATION AND FDA APPROVED PATIENT LABELING.

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

CEPROTIN [Protein C Concentrate (Human)] Lyophilized Powder for Solution for Injection

FULL PRESCRIBING INFORMATION

1. INDICATIONS AND USAGE

1.1 Severe Congenital Protein C Deficiency

CEPROTIN is indicated for patients with severe congenital Protein C deficiency for the prevention and treatment of venous thrombosis and purpura fulminans. CEPROTIN is indicated as a replacement therapy for pediatric and adult patients.

2. DOSAGE AND ADMINISTRATION

2.1 General

Treatment with CEPROTIN should be initiated under the supervision of a physician experienced in replacement therapy with coagulation factors/inhibitors where monitoring of protein C activity is feasible.

CEPROTIN is administered by intravenous injection after reconstitution of the powder for solution for injection with Sterile Water for Injection. Allergic type hypersensitivity reactions are possible. See **WARNINGS/PRECAUTIONS: Hypersensitivity/Allergic Reactions (5.1)**.

The dose, administration frequency and duration of treatment with CEPROTIN depends on the severity of the protein C deficiency, the patient's age, the clinical condition of the patient and the patient's plasma level of protein C. **Therefore, the dose regimen should be adjusted according to the pharmacokinetic profile for each individual patient.** See **DOSAGE AND ADMINISTRATION: Protein C Activity Monitoring (2.2)**.

Table 1 provides the CEPROTIN dosing schedule for acute episodes, short-term prophylaxis and long-term prophylaxis.

	Initial Dose**	Subsequent 3 Doses**	Maintenance Dose**
Acute Episode/Short-term Prophylaxis***	100–120 IU/kg	60–80 IU/kg Q 6 hours	45–60 IU/kg Q 6 or Q 12 hours
Long-term Prophylaxis	NA	NA	45–60 IU/kg Q 12 hours

* Dosing is based upon a pivotal clinical trial of 15 patients

** The dose regimen should be adjusted according to the pharmacokinetic profile for each individual. (2.1, 2.2)

*** CEPROTIN should be continued until desired anticoagulation is achieved.

NA = Not Applicable, Q = Every

An initial dose of 100–120 IU/kg for determination of recovery and half-life is recommended for acute episodes and short-term prophylaxis. Subsequently, the dose should be adjusted to maintain a target peak protein C activity of 100%. After resolution of the acute episode, continue the patient on the same dose to maintain trough protein C activity level above 25% for the duration of treatment.

In patients receiving prophylactic administration of CEPROTIN, higher peak protein C activity levels may be warranted in situations of an increased risk of thrombosis (such as infection, trauma, or surgical intervention). Maintenance of trough protein C activity levels above 25% is recommended.

These dosing guidelines are also recommended for neonatal and pediatric patients. See **USE IN SPECIFIC POPULATIONS: Pediatric Use (8.4)** and **CLINICAL PHARMACOLOGY: Pharmacokinetics (12.3)**.

2.2 Protein C Activity Monitoring

The measurement of protein C activity using a chromogenic assay is recommended for the determination of the patient's plasma level of protein C before and during treatment with CEPROTIN. The half-life of CEPROTIN may be shortened in certain clinical conditions such as acute thrombosis, purpura fulminans and skin necrosis. See **CLINICAL PHARMACOLOGY: Pharmacokinetics (12.3)**. In the case of an acute thrombotic event, it is recommended that protein C activity measurements be performed immediately before the next injection until the patient is stabilized. After the patient is stabilized, continue monitoring the protein C levels to maintain the trough protein C level above 25%.

Patients treated during the acute phase of their disease may display much lower increases in protein C activity. Coagulation parameters should also be checked; however, in clinical trials data were insufficient to establish correlation between protein C activity levels and coagulation parameters.

2.3 Initiation of Vitamin K Antagonists

In patients starting treatment with oral anticoagulants belonging to the class of vitamin K antagonists, a transient hypercoagulable state may arise before the desired anticoagulant effect becomes apparent. This transient effect may be explained by the fact that protein C, itself a vitamin K-dependent plasma protein, has a shorter half-life than most of the vitamin K-dependent proteins (i.e. Factor II, IX and X).

In the initial phase of treatment, the activity of protein C is more rapidly suppressed than that of the procoagulant factors. For this reason, if the patient is switched to oral anticoagulants, protein C replacement must be continued until stable anticoagulation is obtained. Although warfarin-induced skin necrosis can occur in any patient during the initiation of treatment with oral anticoagulant therapy, individuals with severe congenital protein C deficiency are particularly at risk.

During the initiation of oral anticoagulant therapy, it is advisable to start with a low dose of the anticoagulant and adjust this incrementally, rather than use a standard loading dose of the anticoagulant.

2.4 Preparation of CEPROTIN [Protein C Concentrate (Human)]

Reconstitution: Use Aseptic Technique

1. Bring the CEPROTIN (powder) and Sterile Water for Injection, USP (diluent) to room temperature.
2. Remove caps from the CEPROTIN and diluent vials.
3. Cleanse stoppers with germicidal solution, and allow them to dry prior to use.
4. Remove protective covering from one end of the double-ended transfer needle and insert exposed needle through the center of the diluent vial stopper.
5. Remove protective covering from the other end of the double-ended transfer needle. Invert diluent vial over the upright CEPROTIN vial; then rapidly insert the free end of the needle through the CEPROTIN vial stopper at its center. The vacuum in the vial will draw in the diluent. If there is no vacuum in the vial, do not use the product, and contact Baxter Customer Service at 1-888-CEPROTIN (237-7684).
6. Disconnect the two vials by removing the needle from the diluent vial stopper. Then, remove the transfer needle from the CEPROTIN vial. Gently swirl the vial until all powder is dissolved. Be sure that CEPROTIN is completely dissolved; otherwise, active materials will be removed by the filter needle.

2.5 Administration of CEPROTIN [Protein C Concentrate (Human)]

Administration: Use Aseptic Technique

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

After reconstitution, the solution is colorless to slightly yellowish and clear to slightly opalescent and essentially free from visible particles. Do not use the product if the solution does not meet these criteria. CEPROTIN should be administered at room temperature not more than 3 hours after reconstitution.

1. Attach the filter needle to a sterile, disposable syringe and draw back the plunger to admit air into the syringe.
2. Insert the filter needle into the vial of reconstituted CEPROTIN.
3. Inject air into the vial and then withdraw the reconstituted CEPROTIN into the syringe.
4. Remove and discard the filter needle in a hard-walled Sharps container for proper disposal. Filter needles are intended to filter the contents of a single vial of CEPROTIN only.
5. Attach a suitable needle or infusion set with winged adapter, and inject intravenously as instructed below under Administration by Infusion.

Administration by Infusion

CEPROTIN should be administered at a maximum injection rate of 2 mL per minute except for children with a body weight of <10 kg, where the injection rate should not exceed a rate of 0.2 mL/kg/minute.

3. DOSAGE FORMS AND STRENGTHS

CEPROTIN is available in single-dose vials that contain nominally 500 (blue color bar) or 1000 (green color bar) International Units (IU) human protein C and is reconstituted with 5 mL and 10 mL of Sterile Water for Injection, respectively to provide a single dose of human Protein C at a concentration of 100 IU/mL.

CEPROTIN, when reconstituted with the appropriate volume of diluent, contains the following excipients: 8 mg/mL human albumin, 4.4 mg/mL trisodium citrate dihydrate and 8.8 mg/mL sodium chloride.

4. CONTRAINDICATIONS

None.

5. WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity/Allergic Reactions

CEPROTIN may contain traces of mouse protein and/or heparin as a result of the manufacturing process. Allergic reactions to mouse protein and/or heparin cannot be ruled out. If symptoms of hypersensitivity/allergic reaction occur, discontinue the injection/infusion. In case of anaphylactic shock, the current medical standards for treatment are to be observed.

5.2 Transmission of Infectious Agents

CEPROTIN is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, 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 inactivating and/or removing a broad range of viruses during manufacture. See DESCRIPTION (11).

Despite these measures, such products can still potentially transmit disease. Because this product is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. **ALL infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Baxter Healthcare Corporation, at 1-866-888-2472. The physician should discuss the risks and benefits of this product with the patient.**

Some viruses, such as Human Parvovirus B19 (B19V) or Hepatitis A, are particularly difficult to remove or inactivate. B19V most seriously affects pregnant women (fetal infection), or immune-compromised individuals. Symptoms of B19V infection include fever, drowsiness, chills and runny nose followed about two weeks later by a rash and joint pain. Evidence of Hepatitis A may include several days to weeks of poor appetite, tiredness, and low-grade fever followed by nausea, vomiting and abdominal pain. Dark urine and a yellowed complexion are also common symptoms. Patients should be encouraged to consult their physician if such symptoms appear.

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular and/or repeated receipt of human plasma-derived Protein C.

5.3 Bleeding Episodes

Several bleeding episodes have been observed in clinical studies. Concurrent anticoagulant medication may have been responsible for these bleeding episodes. However, it cannot be completely ruled out that the administration of CEPROTIN further contributed to these bleeding events.

Simultaneous administration of CEPROTIN and tissue plasminogen activator (tPA) may further increase the risk of bleeding from tPA.

5.4 Heparin-induced Thrombocytopenia (HIT)

CEPROTIN contains trace amounts of heparin which may lead to Heparin-induced Thrombocytopenia. The platelet count should be determined immediately and discontinuation of CEPROTIN should be considered.

5.5 Low-Sodium Diet/Renal Impairment

Patients on a low-sodium diet should be informed that the quantity of sodium in the maximum daily dose of CEPROTIN exceeds 200 mg. Patients with renal impairment should be monitored more closely for sodium overload.

6. ADVERSE REACTIONS

6.1 Clinical Studies Experience

The most serious and common adverse reactions related to CEPROTIN treatment observed were hypersensitivity or allergic reactions (itching and rash) and lightheadedness.

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

The safety profile of CEPROTIN was based on 121 patients from clinical studies and compassionate use in severe congenital Protein C deficiency. Duration of exposure ranged from 1 day to 8 years. One patient experienced hypersensitivity/allergic reactions (itching and rash) and lightheadedness which were determined by the investigator to be related to CEPROTIN.

No inhibiting antibodies to CEPROTIN have been observed in clinical studies. However, the potential for developing antibodies cannot be ruled out.

6.2 Post-marketing Experience

The following adverse reactions have been identified during postapproval use of CEPROTIN: hemothorax, hypotension, hyperhydrosis, fever and restlessness. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7. DRUG INTERACTIONS

No formal drug interaction studies have been conducted.

See **WARNINGS AND PRECAUTIONS: Bleeding Episodes (5.3)** for information regarding simultaneous administration of CEPROTIN and tissue plasminogen activator (tPA).

See **DOSAGE AND ADMINISTRATION: Initiation of Vitamin K Antagonists (2.3)** for information regarding use of CEPROTIN and vitamin K antagonists.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproduction studies have not been conducted with CEPROTIN. It is also not known whether CEPROTIN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. CEPROTIN has not been studied for use in pregnancy.

8.2 Labor and Delivery

There has been one report of CEPROTIN exposure during labor and delivery with no adverse outcome. CEPROTIN has not been studied for use during labor and delivery.

8.3 Nursing Mothers

It is not known whether CEPROTIN is excreted in human milk. CEPROTIN has not been studied for use in nursing mothers.

8.4 Pediatric Use

Neonatal and pediatric subjects were included in several retrospective and prospective studies, evaluating the safety and effectiveness of CEPROTIN. Subjects were enrolled from as early as 2 days old throughout adolescence.

8.5 Geriatric Use

Clinical studies of CEPROTIN did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

8.6 Renal/Hepatic Impairment

No experience in the treatment of patients with renal and/or hepatic impairment is available.

10. OVERDOSAGE

No symptoms of overdose with CEPROTIN have been reported.

The maximum infusion rate administered in clinical studies were doses of up to 600 IU/kg body weight (BW)/day (150 IU/kg BW every 6 hours) of CEPROTIN. There have been no overdoses of CEPROTIN reported during clinical studies. In long-term prophylactic treatment of doses up to 291.7 IU/kg BW/day, no adverse events were reported.

11. DESCRIPTION

CEPROTIN [Protein C Concentrate (Human)] is manufactured from human plasma purified by a combination of filtration and chromatographic procedures, including a column of immobilized mouse monoclonal antibodies on gel beads. See **WARNINGS/PRECAUTIONS: Transmission of Infectious Agents (5.2)**.

The manufacturing process for CEPROTIN includes processing steps designed to reduce the risk of viral transmission. Screening against potentially infectious agents begins with the donor selection process and continues throughout plasma collection and plasma preparation. Each individual plasma donation used in the manufacture of CEPROTIN is collected only at FDA-approved blood establishments and is tested by FDA licensed serological tests for Hepatitis B Surface Antigen (HBsAg), and for antibodies to Human Immunodeficiency Virus (HIV-1/HIV-2) and Hepatitis C Virus (HCV) in accordance with U.S. regulatory requirements. As an additional safety measure, plasma pools for manufacturing are tested for the presence of HIV-1 and HCV by FDA licensed Nucleic Acid Testing (NAT) and found negative.

To further improve the margin of safety, two dedicated, independent and effective virus inactivation steps (Polysorbate 80 [P80] treatment and vapor heating) have been integrated into the manufacturing process in addition to other purification steps such as immunoaffinity chromatography.

Comprehensive virus clearance studies have been performed for the following steps: P80 treatment alone or coupled with an ion exchange chromatography step (IEX I), immunoaffinity chromatography (IAX) and vapor heating. In each study, the validity of the downscaled process has been confirmed by measuring process and biochemical parameters and comparing these with data from the large-scale manufacturing process. Where applicable (i.e. for P80 treatment and for vapor heating), the robustness of virus clearance has also been investigated by adjusting critical process parameters to levels least favorable for virus inactivation (e.g. temperature and incubation time for vapor heating).

Virus clearance studies for CEPROTIN have demonstrated that the process provides for a robust overall virus clearance capacity. A summary of log₁₀ virus reduction factors per virus and manufacturing step is presented in Table 2.

Manufacturing Step	HIV-1	HCV Model Viruses		PRV	HAV	MMV
		BVDV	TBEV			
P80 Treatment	>5.1	>4.7	n.d.	2.5*	>3.8*	1.4*
IAX	5.7	n.d.	4.8	5.4	3.1	3.6
Vapor Heating	4.6	>5.9	n.d.	5.9	>4.2	1.2

*Coupled with IEX. I

Abbreviations: IEX = Ion Exchange Chromatography; IAX = Immunoaffinity Chromatography; HIV-1 = Human Immunodeficiency Virus Type I; TBEV = Tick-Borne Encephalitis Virus (model for hepatitis C virus); BVDV = Bovine Viral Diarrhea Virus (model virus for HCV and other small, enveloped RNA viruses); PRV = Pseudorabies Virus (model virus for enveloped DNA viruses, e.g. HBV, Hepatitis B Virus); HAV = Hepatitis A Virus; MMV = Mice Minute Virus (model for Human Parvovirus B19 and for non-enveloped viruses); n.d. = not done.

CEPROTIN is supplied as a sterile, white or cream colored, lyophilized powder for IV injection. It has a pH between 6.7 and 7.3 and an osmolality not lower than 240 mosmol/kg. One International Unit (IU) of protein C corresponds to the amidolytically measured activity of protein C in 1 mL of normal plasma. The potency (IU) is determined using a chromogenic substrate method referenced against the World Health Organization (WHO) International Standard (86/622).

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Protein C is the precursor of a vitamin K-dependent anticoagulant glycoprotein (serine protease) that is synthesized in the liver. See **DOSAGE AND ADMINISTRATION: Initiation of Vitamin K Antagonists (2.3)**. It is converted by the thrombin/thrombomodulin-complex on the endothelial cell surface to activated Protein C (APC). APC is a serine protease with potent anticoagulant effects, especially in the presence of its cofactor protein S. APC exerts its effect by the inactivation of the activated forms of factors V and VIII, which leads to a decrease in thrombin formation. APC has also been shown to have profibrinolytic effects.

The Protein C pathway provides a natural mechanism for control of the coagulation system and prevention of excessive procoagulant responses to activating stimuli. A complete absence of protein C is not compatible with life. A severe deficiency of this anticoagulant protein causes a defect in the control mechanism and leads to unchecked coagulation activation, resulting in thrombin generation and intravascular clot formation with thrombosis.

12.2 Pharmacodynamics

In clinical studies, the intravenous administration of CEPROTIN demonstrated a temporary increase, within approximately half an hour of administration, in plasma levels of protein C. Replacement of protein C in protein C-deficient patients is expected to control or, if given prophylactically, to prevent thrombotic complications.

12.3 Pharmacokinetics

Table 3 provides pharmacokinetic results for asymptomatic and symptomatic subjects with protein C deficiency.

PK Parameter	N	Median	95% CI for Median	Min	Max
C _{max} [IU/dL]	21	110	106 to 127	40	141
T _{max} [h]	21	0.50	0.50 to 1.05	0.17	1.33
Incremental recovery [(IU/dL)/(IU/kg)]	21	1.42	1.32 to 1.59	0.50	1.76
Initial half-life [h]	21	7.8	5.4 to 9.3	3.0	36.1
Terminal half-life [h]	21	9.9	7.0 to 12.4	4.4	15.8
Half-life by the non-compartmental approach [h]	21	9.8	7.1 to 11.6	4.9	14.7
AUC _{0-infinity} [IU*h/dL]	21	1500	1289 to 1897	344	2437
MRT [h]	21	14.1	10.3 to 16.7	7.1	21.3
Clearance [dL/kg/h]	21	0.0533	0.0428 to 0.0792	0.0328	0.2324
Volume of distribution at steady state [dL/kg]	21	0.74	0.70 to 0.89	0.44	1.65

C_{max} = Maximum concentration after infusion; T_{max} = Time at maximum concentration; AUC_{0-infinity} = Area under the curve from 0 to infinity; MRT = Mean residence time; Incremental recovery = Maximum increase in Protein C concentration following infusion divided by dose.

The protein C plasma activity was measured by chromogenic and/or clotting assay. The maximum plasma concentrations (C_{max}) and area under the plasma concentration time curve (AUC) appeared to increase dose-linearly between 40 and 80 IU/kg. The median incremental recovery was 1.42 [(IU/dL)/(IU/kg)] after intravenous administration of CEPROTIN. The median half-lives, based on non-compartmental method, ranged from 4.9 to 14.7 hours, with a median of 9.8 hours. In patients with acute thrombosis, both the increase in protein C plasma levels as well as half-life may be considerably reduced. No formal study or analysis has been performed to evaluate the effect of covariates such as race and gender on the pharmacokinetics of CEPROTIN.

The pharmacokinetic profile in pediatric patients has not been formally assessed. Limited data suggest that the pharmacokinetics of CEPROTIN may be different between very young children and adults. The systemic exposure (C_{max} and AUC) may be considerably reduced due to a faster clearance, a larger volume of distribution, and/or a shorter half-life of protein C in very young children than in older subjects. This fact must be considered when a dosing regimen for children is determined. Doses should be individualized based upon protein C activity levels. See *DOSAGE AND ADMINISTRATION: Protein C Activity Monitoring (2.2)*.

13. NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Protein C contained in CEPROTIN is a normal constituent of human plasma and acts like endogenous protein C. Studies in heterologous species to evaluate carcinogenicity, reproductive toxicology and developmental toxicology have not been performed.

CEPROTIN has not demonstrated mutagenic potential in the *Salmonella Thyphimurium* reverse mutation assay (Ames test).

13.2 Animal Toxicity and/or Pharmacology

Safety Pharmacology:

Cardio-respiratory studies performed in dogs evaluating mean arterial pressure, cardiac output, systemic vascular resistance, heart rate, QT interval changes, pulmonary artery pressure, respiratory rate and respiratory minute volume demonstrated no adverse effects at a maximum dose of 500 IU/kg. Anaphylactoid reactions as determined by measurement of bronchospastic activity in guinea pigs demonstrated no adverse effects at the maximum dose of 300 IU/kg. Thrombogenic potential was evaluated in rabbits using the Wessler stasis model and demonstrated no adverse effects at 200 IU/kg. Overall, safety pharmacology studies evaluating cardio-respiratory function, acute dose anaphylactoid potential and thrombogenicity demonstrated no adverse effects in a range of doses from 1.6 to 4.2 times the maximum single human dosage per kilogram body weight.

Acute Dose Toxicity:

Toxicity testing in rats and mice following single dosing of 2000 IU/kg or 1500 IU/kg, respectively, demonstrated no adverse clinical effects or gross pathology at 14 days post dosing.

Repeated Dose Toxicity:

Studies were not conducted to evaluate repeated-dose toxicity in animals. Prior experience with CEPROTIN has suggested immunogenic response in heterologous species following repeated dosing of this human derived protein. Thus, the long-term toxicity potential of CEPROTIN following repeated dosing in animals is unknown.

Local Tolerance Testing:

Investigation of route of injection tolerance demonstrated that CEPROTIN did not result in any local reactions after intravenous, intra-arterial injections of 500 IU/kg (5 mL) and paravenous injections of 100 IU/kg (1 mL) in rabbits.

Citrate Toxicity:

CEPROTIN contains 4.4 mg of Trisodium Citrate Dihydrate (TCD) per mL of reconstituted product. Studies in mice evaluating 1000 IU vials reconstituted with 10 mL vehicle followed by dosing at 30 mL/kg (132 mg/kg TCD) and 60 mL/kg (264 mg/kg TCD) resulted in signs of citrate toxicity (dyspnea, slowed movement, hemoperitoneum, lung and thymus hemorrhage and renal pelvis dilation).

14. CLINICAL STUDIES

14.1 Pivotal Study

This was a multi-center, open-label, non-randomized, phase 2/3 study in 3 parts which evaluated the safety and efficacy of CEPROTIN in subjects with severe congenital protein C deficiency for the (on-demand) treatment of acute thrombotic episodes, such as purpura fulminans (PF), warfarin-induced skin necrosis (WISN) and other thromboembolic events, and for short-term or long-term prophylaxis. Eighteen subjects (9 male and 9 female), ages ranging from 0 (newborn) to 25.7 years participated in this study.

The clinical endpoint of the study was to assess whether episodes of PF and/or other thromboembolic events were treated effectively, effectively with complications, or not treated effectively. Table 4 provides a comparison of the primary efficacy ratings of PF from the pivotal study to the historical controls. Inadequate data is available for treatment of WISN.

Episode Type	Primary Efficacy Rating	Protein C Concentrate (Human)		Historical Controls	
		N	%	N	%
Purpura Fulminans	Effective	17	94.4	11	52.4
	Effective with Complication	1	5.6	7	33.3
	Not Effective	0	0.0	3	14.3
	Total	18	100.0	21	100.0

N = Number of episodes

Of 18 episodes of PF (6 severe, 11 moderate, 1 mild) treated with CEPROTIN for the primary efficacy rating, 17 (94.4%) were rated as effective, and 1 (5.6%) was rated as effective with complications; none (0%) were rated not effective. When compared with the efficacy ratings for 21 episodes of PF (historical control group), subjects with severe congenital protein C deficiency were more effectively treated with CEPROTIN than those treated with modalities such as fresh frozen plasma or conventional anticoagulants.

Table 5 provides a summary of the secondary treatment ratings for treatment of skin lesions and other thrombotic episodes from part one of the study.

Rating Category	Purpura Fulminans Skin Necrosis								Other Thrombotic Events		Total	
	Mild		Moderate		Severe		Total		Total			
	N	%	N	%	N	%	N	%	N	%	N	%
Excellent	1	5.6	7	38.9	5	27.8	13	72.2	4	80.0	17	73.9
Good	0	0.0	4	22.2	0	0.0	4	22.2	1	20.0	5	21.7
Fair	0	0.0	0	0.0	1	5.6	1	5.6	0	0	1	4.3
Total	1	5.6	11	61.1	6	33.3	18	100.0	5	100.0	23	100.0

N = Number of episodes

In a secondary efficacy rating, 13 (72.2%) of the 18 episodes of PF treated with CEPROTIN were rated as excellent, 4 (22.2%) were rated as good, and 1 (5.6%) episode of severe PF was rated as fair; all were rated as effective. Four (80%) of the 5 episodes of venous thrombosis had treatment ratings of excellent, while 1 (20%) was rated as good.

CEPROTIN was also demonstrated to be effective in reducing the size and number of skin lesions. Non-necrotic skin lesions healed over a maximum 12-day (median 4-day) period and necrotic skin lesions healed over a maximum 52-day (median 11-day) period of CEPROTIN treatment, as shown in Table 6.

Lesion Type	Number of Episodes (Number of Subjects)	Mean	Median	Minimum	Maximum
Non-necrotic	16 (9 subjects)	4.6	4.0	1	12
Necrotic	7 (5 subjects)	21.1	11.0	5	52

Changes in the extent of venous thrombus were also measured for the 5 thromboembolic episodes. CEPROTIN prevented an increase in the extent of thrombus during 4 (80%) of the thromboembolic episodes by Day 3 of treatment, and 1 (20%) episode by Day 5 of treatment.

All seven of the short-term prophylaxis treatments with CEPROTIN were free of complications of PF or thromboembolic events, as shown in Table 7.

Reason for Treatment	Number of Treatments	Presentation of Purpura Fulminans During Treatment Episodes		Thromboembolic Complications During Treatment Episodes		Number of Treatments Free of Complications	
		N	%	N	%	N	%
Anticoagulation Therapy	3	0	0.0	0	0.0	3	100.0
Surgical Procedure	4	0	0.0	0	0.0	4	100.0
Total	7	0	0.0	0	0.0	7	100.0

No episodes of PF occurred in four subjects ranging from 42 to 338 days of long-term prophylactic treatment with CEPROTIN, as shown in Table 8. When not on prophylactic treatment and receiving CEPROTIN on-demand, the same four subjects experienced a total of 13 (median of 3) episodes of PF over a range of 19 to 323 days. The time to first episode of PF after exiting from long-term prophylaxis treatment ranged from 12 to 32 days for these four subjects.

Summary Statistic	Long-Term Prophylactic Treatment			While On-Demand*			Time to First Episode After Exiting Long-Term Prophylaxis
	Number of Episodes per Subject	Number of Days Receiving Prophylactic Treatment	Monthly Rate of Episodes	Number of Episodes per Subject	Number of Days Not Receiving Study Drug	Monthly Rate of Episodes	
Mean	0	229	0.0	3.3	165	1.91	23.3
Median	0	268	0.0	3.0	159	0.49	24.5
Minimum	0	42	0.0	1.0	19	0.25	12.0
Maximum	0	338	0.0	6.0	323	6.40	32.0

* Total number of episodes while subjects were On-Demand was 13.

14.2 Retrospective Analysis

A retrospective study to capture dosing information and treatment outcome data in subjects with severe congenital protein C deficiency who were treated with CEPROTIN under an emergency use IND was also conducted. Eleven subjects (6 male and 5 female), ages ranging from 2.1 to 23.8 years participated in this study.

There were 28 acute episodes of PF/WISN and vascular thrombus reported in which time to resolution ranged from 0 to 46 days. The treatment outcome for these episodes was rated effective in all cases except one.

16. HOW SUPPLIED/STORAGE AND HANDLING

CEPROTIN is available in single-dose vials that contain the following nominal product strengths:

BLUE BAR: 500 IU per vial: (NDC: 0944-4175-05)
GREEN BAR: 1000 IU per vial: (NDC: 0944-4175-10)

Actual potency is printed on the vial label.

One package of CEPROTIN contains one glass vial of CEPROTIN powder, one glass vial of Sterile Water for Injection, USP, one transfer needle, one filter needle, one full prescribing physician insert and one patient package insert.

CEPROTIN, packaged for sale, is stable for 3 years when stored refrigerated at 2°C–8°C (36°F–46°F). Do not freeze in order to prevent damage to the diluent vial. Store the vial in the original carton to protect it from light. The reconstituted solution should be used within 3 hours of reconstitution. Do not use beyond the expiration date on the CEPROTIN vial.

17. PATIENT COUNSELING INFORMATION

Patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis, as the risk of an allergic type hypersensitivity reaction cannot be excluded. In addition, CEPROTIN may contain traces of mouse protein or heparin as a result of the manufacturing process. Allergic reactions to mouse protein or heparin cannot be ruled out. If symptoms of hypersensitivity/allergic reaction occur, patients should immediately discontinue the injection/infusion and inform their physician as soon as possible.

Prior to reconstitution, CEPROTIN should be protected from light.

Reconstitute the lyophilized CEPROTIN powder with the supplied diluent (Sterile Water for Injection) using the sterile transfer needle. Gently swirl the vial until all powder is dissolved.

Visually inspect the solution for discoloration and particulate matter. The reconstituted solution should be colorless to slightly yellowish and clear to slightly opalescent and essentially free from visible particles. CEPROTIN should not be administered if discoloration or particulate matter is observed. The solution is drawn through the sterile filter needle into a sterile disposable syringe.

The reconstituted solution contains no preservatives and is intended for single use only. Once reconstituted, it is recommended that the product be administered by intravenous injection within 3 hours. All unused solution, empty vials and used needles must be discarded appropriately.

The attached CEPROTIN (Protein C Concentrate [Human]) "Information For Patients" contains more detailed instructions on the preparation of CEPROTIN.