SUMMARY BASIS OF APPROVAL

Protein C Concentrate (Human)

CEPROTIN™

Sponsor: **Baxter Healthcare Corporation**
One Baxter Way
Westlake Village, CA 91362

TABLE OF CONTENTS

SUMMARY BASIS OF APPROVAL

1. GENERAL INFORMATION

Trade Name:	CEPROTIN®
Product Name:	Protein C Concentrate (Human)
Other Names:	Human Protein C, Protein C (Human)
Name and Address of Sponsor:	Baxter Healthcare Corporation One Baxter Way Westlake Village, California 91362
Biologics License Application Tracking Number:	STN BL 125234/0
Orphan Drug Designation:	92-653
Date of Submission:	28 September 2006
Date of Filing:	17 November 2006
Review Designation:	Priority Review
Date of Licensure:	XX-Mar-2007

2. INDICATION FOR USE

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.

3. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE

3.1 Dosage Form

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 Sterile Water for Injection, contains the following excipients: 8 mg/mL human albumin, 4.4 mg/mL trisodium citrate dihydrate and 8.8 mg/mL sodium chloride.

3.2 Route of Administration

CEPROTIN is administered by intravenous injection after the powder is reconstituted with the appropriate volume of Sterile Water for Injection.

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.

3.3 Recommended Dosage

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.

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.** Table 3-1 provides the CEPROTIN dosing schedule for acute episodes, short-term prophylaxis, and long-term prophylaxis.

Table 3-1
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 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.
*** 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. Limited data suggest that the pharmacokinetics of CEPROTIN may be different between

very young children and adults. Doses should be individualized based upon Protein C activity levels.

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. 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, Protein C levels should be monitored continuously and the trough Protein C level maintained 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.

4. MANUFACTURING, CHEMISTRY AND CONTROLS

4.1 Manufacturing Process Overview

Protein C concentrate is purified from --------------- Plasma by a combination ----------- ---------------, and chromatographic procedures including an immunoaffinity chromatographic step using the monoclonal antibody -------- immobilized on -------------. The manufacturing process is briefly summarized as follows:

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4.2 Validation of Systems, Equipment and Methods

Utility systems, manufacturing equipment, manufacturing processes and analytical methodologies used in the production of CEPROTIN have been validated according to established written procedures. Procedures are in place to ensure the regular maintenance of equipment and the regular monitoring of environmental conditions within the production facilities.

The test parameters, test methods and release specifications for CEPROTIN are provided in Table 4-1. The specifications have been set in accordance with pharmacopoeia requirements as well as based on the analysis of the product manufactured in support of this project.

Table 4-1		
Test	**Test Method**	**Specification**
Test performed on the Lyophilized Product		
Appearance	---	---
Residual moisture	---	---
---	---	---
Tests performed on the Reconstituted Product **Reconstitute with the volume of sWFI stated on the label**		
Protein C Activity	---	---
Protein Content	---	---
Sodium Chloride ---	---	---
---	---	---
---	---	---
---	---	---
Safety Tests		

Table 4-1		
Test	**Test Method**	**Specification**
Test performed on the Lyophilized Product		
Sterility (21 CFR 610.12)	Membrane Filtration	Sterile
Pyrogens (21 CFR 610.13b)	Temperature rise in rabbit ----------	Pyrogen-free

CEPROTIN conformance lots were manufactured to validate the commercial scale production of CEPROTIN at Baxter's manufacturing facilities in ----------. Validation studies were performed in order to provide documented evidence that the formulation, filling and lyophilization of CEPROTIN FDP 500 IU and 1000 IU, consistently adheres to predetermined process parameters, and that the product complies with predetermined specifications and quality requirements. Several studies were performed to validate the process of pharmaceutical production of CEPROTIN FDP. The formulation and sterilizing filtration were covered under the first study. The minimum batch size was later validated under a separate protocol. As the formulation and sterilizing filtration are identical for both CEPROTIN FDP 500 IU and 1000 IU filling sizes, the studies were performed to cover them both. A batch size of ----------. ----------. ----------. ----------, ----------.

4.3 Validation of Viral Safety

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 ion exchange chromatography and 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 results 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 an overall virus clearance capacity and corresponding margins of safety with respect to adventitious viruses. A summary of $\log_{10}$ virus reduction factors per virus and manufacturing step is presented in the Table 4-1.

Table 4-1
Summary of Mean Log_{10} Virus Reduction Factors for the CEPROTIN Manufacturing Process

Manufact-uring 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.

4.4 Stability Studies

The stability of the bulk drug substance has been investigated in ------ batches for up to - months. Data to date indicate that the drug substance is stable for - months when maintained at ------°C.

The stability of the final drug product has been investigated in three batches at each of the respective potencies (one lot of the 500 IU and two lots of the 1000 IU nominal potencies). Thirty-six months of real-time data at +2°C to +8°C have been collected. The real-time data, along with the data from accelerated studies at ----°C indicate that the drug product is stable for 3 years when maintained at +2°C to + 8°C (36°F - 46°F).

The stability of the reconstituted product was investigated in 3 batches which were incubated for - hours at room temperature after reconstitution. It is recommended that the reconstituted product be administered within 3 hours to assure aseptic use.

4.5 Labeling

The labeling consists of a package insert (full prescribing information), a patient package insert, vial labels and unit cartons. The package inserts, container (vial) and package (carton) labels are in compliance with 21 CFR 201 Subparts A and B and 21 CFR 610.60, 610.61 and 610.62. The trade name, CEPROTIN, is not known to be in conflict with or easily confused with the trademark of any other licensed pharmaceutical product.

4.6 Establishment Inspections

CEPROTIN is manufactured at Baxter facilities located in ----------. The FDA pre-approval inspection was performed 24 January 2007 through 01 February 2007. No FDA 483 was issued.

4.7 Environmental Assessment

Baxter Healthcare Corporation filed a request for a categorical exclusion under 21 CFR 25.31(c) from an Environmental Assessment. This request was found to be justifiable.

5. PHARMACOLOGY AND TOXICOLOGY

5.1 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).

5.2 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 maximum dose of 500 IU/kg. Anaphylactoid reactions as determined by measurement of bronchospastic activity in guinea pigs demonstrated no adverse effects at maximum evaluated 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 anaphalactoid potential and thombogenicity 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.

5.3 Pharmacokinetics

No animal studies were performed to address pharmacokinetics, distribution, biodegradation or excretion. However, clinical pharmacokinetic data are available.

Toxicology

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).

6. CLINICAL

6.1 Efficacy

6.1.1 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. Subjects with confirmed diagnosis of congenital Protein C deficiency (genetic testing, family history) and a with documented functional protein C level of <20% were enrolled in the study. Eighteen subjects (9 male and 9 female), ages ranging from 0 (newborn) to 25.7 years participated in this study.

The primary 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. Effective treatment was defined as resolution of skin lesions (stabilization and regression of existing lesions) and/or stabilization of thrombi and effective establishment of long-term oral or parenteral anticoagulation. Complications referred to adverse drug reactions interfering with the treatment regimen (resulting in change of dose or frequency of dosing), forcing discontinuation of treatment, or introducing pathogenic viral infection. Table 6-1 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.

Table 6-1
Comparison of Primary Efficacy Ratings of Episodes of Purpura Fulminans in the Protein C Concentrate (Human) Pivotal Study to Historical Controls

		Protein C Concentrate (Human)		Historical Controls	
Episode Type	**Primary Efficacy Rating**	**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. One of the secondary efficacy variable was to analyze the percent of episodes of PF and thrombotic events in which the efficacy of treatment was rated as excellent, good, fair or

none based on predefined scale (see Appendix1). Table 6-2 provides a summary of the secondary treatment ratings for treatment of skin lesions and other thrombotic episodes from part one of the study.

Table 6-2
Summary of Secondary Treatment Ratings for Treatment of Skin Lesions and Other Thrombotic Episodes –
Protein C Concentrate (Human) Pivotal Study Part 1

	Purpura Fulminans Skin Necrosis								Other Thrombotic Events		Total	
	Mild		Moderate		Severe		Total		Total			
Rating Category	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 period (median 4-day) and necrotic skin lesions healed over a maximum 52-day (median 11-day) period of CEPROTIN treatment, as shown in Table 6-3.

Table 6-3
Number of Days to Complete Healing of Skin Lesions in the Protein C Concentrate (Human) Pivotal Study

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 the 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 6-4.

Table 6-4
Summary of Complications During Short Term Prophylaxis in the Protein C Concentrate (Human) Pivotal Study

Reason for Treatment	Number of Treatments	Presentation of Purpura Fulminans During Treatment Episodes		Thromboembolic Complications During Treatment Episode		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 6-5. 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.

Table 6-5
Number and Rate of Episodes of Skin Lesions or Thrombosis for Four Subjects Who Received Long-Term Prophylactic Treatment and Were Treated On-Demand in the Protein C Concentrate (Human) Pivotal Study

Summary Statistic	Long-Term Prophylactic Treatment			While On-Demand [a]			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

[a] Total number of episodes while subjects were On-Demand was 13.

6.1.2 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.

6.2 Pharmacokinetics

Table 6-6 provides pharmacokinetic results for asymptomatic and symptomatic subjects with Protein C deficiency.

Table 6-6
Pharmacokinetics of CEPROTIN in Subjects with Severe Congenital 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
$AUC_{0\text{-Infinity}}$ [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; $AUC_{0\text{-Infinity:}}$ Area under the curve from 0 to infinity; MRT: Mean residence time; and 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 Protein C.

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.

6.3 Safety

6.3.1 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.

6.3.2 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. POSTMARKETING COMMITMENTS

7.1 Manufacturing

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7.2 Clinical

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APPENDIX

Table 9.5-1 Secondary Treatment Efficacy Rating for Part 1		
Rating	**Purpura Fulminans or Coumarin-Induced Skin Necrosis**	**Thrombotic Episodes (Extent of Thrombus)**
Excellent	➢ No new skin lesions after 48h of treatment **and** ➢ Complete resolution[a] of non-necrotic skin lesions by Day 5 of treatment with no further progression while on Protein C Concentrate until successful establishment of adequate anticoagulation[b] **and** ➢ Resolution[c] of necrotic lesions by Day 14 (± 2) of treatment.	➢ The extent of thrombus at Day 2-3 ≤ Baseline and no extension of thrombus after Day 2-3 while on Protein C Concentrate until successful establishment of adequate anticoagulation.
Good	➢ No new skin lesions after 48h of treatment **and** ➢ Complete resolution of non-necrotic skin lesions between Day 6 and Day 14 of treatment with no further progression while on Protein C Concentrate until successful establishment of adequate anticoagulation; **and** ➢ Resolution of necrotic lesions between Day 14 (± 2) and Day 28 (± 2) of treatment.	➢ The extent of thrombus at Day 4-5 ≤ Day 2-3 and no extension of thrombus after Day 4-5 while on Protein C Concentrate until successful establishment of adequate anticoagulation.
Fair	➢ No new skin lesions after 48h of treatment **and** ➢ Complete resolution of non-necrotic skin lesions after more than 14 (± 2) Days of treatment with no further progression while on Protein C Concentrate until successful establishment of adequate anticoagulation; **and** ➢ Resolution of necrotic lesions after more than 28 (± 2) Days of treatment.	➢ No extension of thrombus after Day 4-5 while on Protein C Concentrate until successful establishment of adequate anticoagulation.[d]

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Table 9.5-1 Secondary Treatment Efficacy Rating for Part 1		
Rating	**Purpura Fulminans or Coumarin-Induced Skin Necrosis**	**Thrombotic Episodes (Extent of Thrombus)**
Continued		
Not Effective	➢ Treatment discontinued due to a serious adverse event possibly or probably related to treatment with Protein C Concentrate. ➢ No effect on arresting development of superficial skin lesions after 48h of treatment or arresting progression of tissue lesions after 24 h of treatment.	➢ Treatment discontinued due to a serious adverse event possibly or probably related to treatment with Protein C Concentrate. ➢ Occurrence of additional thromboembolic complication after 48 h following initiation of treatment with Protein C Concentrate.
Not Rated	➢ Initiation of thrombolytic treatment prior to assessment of lesion response to treatment with Protein C Concentrate.	➢ Treatment of a thrombotic episode with Protein C Concentrate terminated by the investigator for the utilization of a thrombolytic treatment within 5 Days following initiation of treatment with Protein C Concentrate.

[a] Definition of complete resolution of non-necrotic lesion: no infarcted skin, no indurations and pain.

[b] Oral anticoagulation did not have to be achieved if the subject is transitioning to Part 2 or Part 3.

[c] Definition of resolution of necrotic lesion: lesion completely covered by clean granulation tissue or tissue is successfully engrafted.

[d] If Day 4-5 imaging showed the extent of thrombus was > thrombus on Day 2-3, then imaging was to be repeated by Day 10 ± 2 to determine the extent of thrombus.

LICENSING REVIEW COMMITTEE

Timothy Lee, Ph.D. (Scientific Lead/CMC/Product)	Nisha Jain, M.D. (Clinical: Safety and Efficacy)
Susan Yu (CMC/Facility)	Paul Buehler, Ph.D. (Preclinical:Pharm/Tox)
Nancy Chamberlain (Labeling)	Michael Wiack (Regulatory Project Manager)