CEPROTIN- protein c concentrate human
Takeda Pharmaceuticals America, Inc.

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.

CEPROTIN® [Protein C Concentrate (Human)] Lyophilized Powder for Solution for Injection
Initial U.S. Approval: 2007

INDICATIONS AND USAGE

CEPROTIN, Protein C Concentrate (Human), is an anticoagulant indicated for neonates, pediatric and adult patients with severe congenital Protein C deficiency for the prevention and treatment of venous thrombosis and purpura fulminans. (1)

DOSAGE AND ADMINISTRATION

For intravenous administration only.

- Initiate treatment under the supervision of a physician experienced in using coagulation factors/inhibitors where monitoring of Protein C activity is feasible. (2.1)
- Table provides the CEPROTIN dosing schedule for acute episodes, short-term prophylaxis, and long-term prophylaxis*

	Initial Dose*	Subsequent 3 Doses*	Maintenance Dose*
Acute Episodes, 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 clinical trial of 15 patients.
* Adjust the dose according to the pharmacokinetic profile for each individual patient(2.1).
† Continue CEPROTIN until desired anticoagulation is achieved., NA = Not applicable; Q = every.

- Administer CEPROTIN at a maximum injection rate of 2 mL per minute except for children with a bodyweight of < 10 kg, where the injection rate should not exceed a rate of 0.2 mL/kg/minute.

DOSAGE FORMS AND STRENGTHS

BLUE BAR: Approximately 500 IU/vial (3)
GREEN BAR: Approximately 1000 IU/vial (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Discontinue administration of CEPROTIN if symptoms of hypersensitivity/allergic reactions occur. (2.1, 5.1, 6)
- Because CEPROTIN is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease agent. (5.2, 11)
- Simultaneous administration of CEPROTIN with tPA and/or anticoagulants may increase the risk of bleeding. (5.3)
- CEPROTIN contains heparin. If heparin-induced thrombocytopenia is suspected, check platelet counts immediately and discontinue administration. (5.4)
- CEPROTIN contains sodium >200 mg. Inform patients on a low sodium diet and/or patients with renal impairment. (5.5)

ADVERSE REACTIONS

Common adverse reactions observed in clinical trials were rash, itching, and lightheadedness. (5.1, 6)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals U.S.A., Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.
Revised: 9/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CEPROTIN®, Protein C Concentrate (Human), is an anticoagulant indicated for neonates,

pediatric and adult patients with severe congenital Protein C deficiency for the prevention and treatment of venous thrombosis and purpura fulminans.

2 DOSAGE AND ADMINISTRATION

For intravenous administration only.

2.1 Dose

- Initiate treatment with CEPROTIN 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.
- Adjust the dose regimen according to the pharmacokinetic profile for each individual patient. *[See DOSAGE AND ADMINISTRATION: Protein C Activity Monitoring]*.

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

Table 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

NA = Not applicable; Q = every.

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

† Adjust the dose according to the pharmacokinetic profile for each individual patient.

‡ Continue CEPROTIN until desired anticoagulation is achieved.

- Determine protein C recovery and half-life with an initial dose of 100-120 IU/kg in patients receiving treatment for acute episodes and short-term prophylaxis.
- Adjust the dose to maintain a target peak protein C activity of 100 %.
- Continue the patient on the same dose after resolution of the acute episode to maintain trough protein C activity level above 25% for the duration of treatment.
- Patients receiving prophylactic administration of CEPROTIN may warrant higher peak protein C activity levels in situations of an increased risk of thrombosis (such as infection, trauma, or surgical intervention). Therefore it is recommended to maintain trough protein C activity levels above 25%.
- 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)].*

Protein C Activity Monitoring

- Determine the patient's protein C plasma level before and during treatment with CEPROTIN by measuring protein C activity using a chromogenic assay.Certain clinical conditions, such as acute thrombosis, purpura fulminans, and skin necrosis, may shorten the half-life of CEPROTIN. See *CLINICAL PHARMACOLOGY: Pharmacokinetics (12.3).* In case of an acute thrombotic event, immediately measure protein C activity before the next injection until the patient is stable and monitor 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. In addition to protein C activity measurement, check the coagulation parameters also;however, data were insufficient to establish correlation between protein C activity levels and coagulation parameters in clinical trials.

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 because protein C, 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 protein C activity is more rapidly suppressed than that of the procoagulant factors. For this reason, if the patient switched to oral anticoagulants, they must continue protein C replacement 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.

2.2 Preparation

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 before use.
4. Remove protective covering from one end of the double-ended transfer needle and insert the 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 Takeda Pharmaceuticals Customer Service at 1-877-TAKEDA-7 (1-877-825-3327).
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.

2.3 Administration

Administration: Use Aseptic Technique

Visually inspect CEPROTIN for particulate matter and discoloration before administration.

After reconstitution, the solution should be colorless to slightly yellowish and clear to slightly opalescent, and free of visible particles. Do not use the solution if it does not meet these criteria. Administer CEPROTIN 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. Use filter needles 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.

Record the name and batch number of the product every time CEPROTIN is administered to a patient.

Administration by Infusion

Administer CEPROTIN at a maximum injection rate of 2 mL per minute except for children with a bodyweight 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

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 Transmissible Infectious Agents

Because CEPROTIN is made from human plasma, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) agent, and theoretically, the Creutzfeldt-Jakob disease agent.

All infections suspected by a physician to have been possibly transmitted by this product should be reported by the physician or other healthcare provider to Takeda Pharmaceuticals at 1-877-TAKEDA-7 (1-877-825-3327). Discuss the risks and benefits of this product with your patient.

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, which can be associated with a rapid decrease of the number of thrombocytes. Identifying HIT is complicated because these symptoms may already be present in acute phase patients with severe congenital protein C deficiency. Determine the platelet count immediately and consider discontinuation of CEPROTIN.

5.5 Low Sodium Diet/Renal Impairment

Inform patients on a low sodium diet that the quantity of sodium in the maximum daily dose of CEPROTIN exceeds 200 mg. Monitor patients with renal impairment closely for sodium overload.

6 ADVERSE REACTIONS

The common adverse reactions related to CEPROTIN treatment observed were the following hypersensitivity or allergic reactions: lightheadedness and itching and rash.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial 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.

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 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of CEPROTIN. 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.

Psychiatric Disorders: Restlessness

Skin and Subcutaneous Tissue Disorders: Hyperhydrosis

General Disorders and Administration Site Conditions: Injection Site Reaction

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: Dose (2.1) Initiation of Vitamin K Antagonists].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no data with CEPROTIN use in pregnant women to inform a drug-associated risk. 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 during labor and delivery.

In the U.S. general population, the estimated background risk of major birth defects and miscarriages in clinically recognized pregnancies is 2-4% and 15-20%, respectively, regardless of drug exposure.

8.2 Lactation

Risk Summary

There is no information regarding the presence of CEPROTIN in human milk, the effect on the breastfed infant, or the effects on milk production. CEPROTIN has not been studied for use in nursing mothers.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CEPROTIN and any potential adverse effects on the breastfed child from CEPROTIN or from the underlying maternal condition.

8.4 Pediatric Use

Neonatal and pediatric subjects were enrolled during the prospective and retrospective studies described in *CLINICAL STUDIES (14)*. Of the 18 subjects enrolled during the prospective study, 1 was newborn, 3 were between 28 days and 23 months, 9 were between 2 and 11 years, 1 was between 12 and 16 years, and 4 were older than 16 years. Of the 11 subjects enrolled and treated during the retrospective study, 9 were between 2 and 11 years, and 2 were older than 16 years *[see CLINICAL STUDIES (14)]*.

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.

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 AND PRECAUTIONS: Transmissible Infectious Agents (5.2)].*

The manufacturing process for CEPROTIN includes processing steps designed to reduce the risk of viral transmission. The capacity of the manufacturing process to remove and/or inactivate enveloped and non-enveloped viruses has been validated by laboratory spiking studies on a scaled down process model, using the following enveloped and non-enveloped viruses: Human Immunodeficiency Virus Type 1 (HIV-1), Bovine Viral Diarrhea Virus (BVDV), Tick-Borne Encephalitis Virus (TBEV), Pseudorabies Virus (PRV), Hepatitis A Virus (HAV) and Mice Minute Virus (MMV). Virus reduction steps consist of detergent treatment (Polysorbate 80, P80), heat inactivation (Vapor Heating) and immunoaffinity chromatography (IAX).

Virus clearance studies for CEPROTIN have demonstrated that the process provides for a robust overall virus clearance capacity. A summary of $\log_{10}$ virus reduction factors per virus and manufacturing step is presented in Table 2.

Table 2: Summary of Mean Log10 Virus Reduction Factors for the CEPROTIN Manufacturing Process

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	3.9	2.9	3.8	4.0	0.9	3.5
Vapor Heating	4.6	>5.9	n.d.	5.9	>4.2	1.2

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 [HCV]); 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.

* Coupled with IEX. I

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: Dose (2.1) Initiation of Vitamin K Antagonists]*. 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 APC. 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.

Table 3: 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 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. Consider this fact when a dosing regimen for children is determined. Doses should be individualized based upon protein C activity levels *[See DOSAGE AND ADMINISTRATION: Dose (2.1) Protein C Activity Monitoring]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, 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 Toxicology 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

In a multi-center, open-label, non-randomized study in 3 parts, the safety and efficacy of CEPROTIN was evaluated 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 study to the historical controls. Inadequate data is available for treatment of WISN.

Table 4: Comparison of Primary Efficacy Ratings of Episodes of Purpura Fulminans in the Protein C Concentrate (Human) Study of Historical Controls

		Protein C Concentrate (Human)		**Historical Controls**	
Episode Type	Primary Efficacy Rating	N	%	N	%
	Effective	17	94.4	11	52.4

Purpura Fulminans	Effective with Complication	1	5.6	7	33.3
	Not Effective	0	0.0	3	14.3
	Total	18	100	21	100

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.

Table 5: Summary of Secondary Treatment Ratings for Treatment of Skin Lesions and Other Thrombotic Episodes - Protein C Concentrate (Human) 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 (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.

Table 6: Number of Days to Complete Healing of Skin Lesions in the Protein C Concentrate (Human) 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 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.

Table 7: Summary of Complications During Short Term Prophylaxis in the Protein C Concentrate (Human) 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 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.

Table 8: 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) Study

Summary Statistic	Long-Term Prophylactic Treatment			While On-Demand*			Time to First Episode After Existing 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

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, Protein C Concentrate (Human), 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).

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

BLUE BAR: 500 IU per vial: (NDC: 0944-4177-05)
GREEN BAR: 1000 IU per vial: (NDC: 0944-4179-10)

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

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Inform patients of the following:

- Early signs of hypersensitivity reactions include hives, generalized urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. The risk of an allergic type hypersensitivity reaction cannot be excluded *[See WARNING AND PRECAUTIONS:*

Hypersensitivity (5.1)]. 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. Immediately discontinue the injection/infusion and inform their physician as soon as possible if symptoms of hypersensitivity/allergic reaction occur.

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Cambridge, MA 02142
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CEP367

PATIENT INFORMATION

CEPROTIN® [Protein C Concentrate (Human)]
Pronounced: see PRO ten

Please read this leaflet carefully before using CEPROTIN [Protein C Concentrate (Human)]. This leaflet is based on the information provided to your doctor and is a summary of the important information you need to know about your medicine for your severe congenital Protein C deficiency. This leaflet does not take the place of talking with your doctor and does not contain all of the information available about CEPROTIN.

Use this leaflet only after you have received instructions from your doctor. If you have any questions after reading this leaflet, ask your doctor or pharmacist.

1. What is CEPROTIN and what is it used for?

The name of your medicine is CEPROTIN, pronounced "see PRO ten".

CEPROTIN contains Protein C, a natural protein that is made in the liver and is present in your blood. Protein C is a part of human plasma that regulates the blood clotting (coagulation) system and prevents abnormal clot formation (thrombosis). Plasma is the liquid part of human blood.

CEPROTIN is used to treat patients with Severe Congenital Protein C Deficiency for the prevention and treatment of:

- venous thrombosis (blood clot in the vein), and
- purpura fulminans (blood spots, bruising, and discoloring to skin as a result of clotting of small blood vessels in the skin).

2. How does CEPROTIN work?

CEPROTIN temporarily raises the levels of Protein C in the body. Protein C plays a major role in preventing your body from forming too many blood clots. CEPROTIN is for those patients who either don't produce enough Protein C or whose Protein C doesn't work correctly. CEPROTIN allows your body's blood clotting process to function properly.

3. Who should not use CEPROTIN?

Do not use CEPROTIN unless your doctor confirms that you have severe congenital Protein C deficiency.

Tell your doctor about all your medical conditions.

Allergic to Mouse Protein or Heparin:

If you are known to have allergic-type reactions (rash, hives, itching, tightness of the chest, difficulty breathing, throat tightness, and low blood pressure) to mouse protein or heparin, talk to your doctor before using this product. CEPROTIN contains small amounts of heparin and/or mouse protein as a result of the manufacturing process.

Low Sodium Diet/Kidney Impairment:

Talk with your doctor before using CEPROTIN if you are on a low sodium diet or have problems with your kidney, as the amount of sodium in the maximum daily dose of CEPROTIN exceeds 200 mg.

Pregnancy or Breastfeeding:

Inform your doctor if you are pregnant or breastfeeding. Your doctor will decide if CEPROTIN may be used during pregnancy and/or breastfeeding.

Tell your doctor about all the medicines you are taking, including prescription and nonprescription medicines, vitamins, and herbal supplements. Tell your doctor if you are on a special diet.

4. What is the most important information I need to know about CEPROTIN?

You could have an allergic reaction to CEPROTIN. You should be aware of the early signs of allergic reactions. These include rash, hives, itching, tightness of the chest, difficulty breathing, throat tightness, and low blood pressure. The signs and symptoms of low blood pressure can include a weak pulse, feeling lightheaded or dizzy when you stand, and possibly shortness of breath. If you experience any of these symptoms while being treated with CEPROTIN, stop the treatment and contact your doctor. If you experience a severe allergic reaction, including difficulty breathing and (near) fainting, seek emergency treatment.

You could get an infectious disease since this drug product is made from human plasma. However, there are steps in collecting the plasma and in the making of CEPROTIN to lessen this possibility. For example, blood and plasma donors are screened for certain viral infections. There are also steps in the processing of the plasma that can inactivate or remove viruses.

5. What are the possible side effects of CEPROTIN?

Like all medicines, CEPROTIN can cause side effects, although not everyone gets them.

The common side effects to CEPROTIN observed in clinical trials were hypersensitivity or allergic reactions: lightheadedness itching, and rash.

There have also been individual reports, after the drug was marketed, of restlessness, increased sweating, and injection site reaction.

If you develop any side effects, including any not listed in this leaflet, please contact your doctor.

6. How do I use CEPROTIN?

CEPROTIN is given by intravenous administration (infusion into a vein). It is given to you under the close supervision of your doctor who is experienced in replacement therapy of coagulation factors/inhibitors and where monitoring of protein C activity is possible. Your dosage will vary depending upon your condition, your age, and your body weight. Your doctor may require that you have blood taken to help determine the dose of CEPROTIN that you should get. See the following **Instructions for Use**.

7. How do I store CEPROTIN?

Store CEPROTIN in powder form, without the diluent (Sterile Water for Injection) added. Store CEPROTIN in the refrigerator at 2°C to 8°C (36°F to 46°F). Store the vial in the original carton to protect it from light. Do not freeze to prevent damage to the diluent vial.

Do not use CEPROTIN beyond the expiration date printed on the CEPROTIN vial.

8. What are the ingredients in CEPROTIN?

Active ingredient: human Protein C

Other ingredients: human albumin, sodium chloride and trisodium citrate dihydrate

9. What does CEPROTIN look like?

CEPROTIN is a white or cream colored powder that is mixed with the water provided in the package (Sterile Water for Injection) before injection. After mixing with the Sterile Water for Injection, the solution is colorless to slightly yellowish and clear to slightly opalescent and free from visible particles.

10. What are the contents of the CEPROTIN package?

CEPROTIN comes in the following strengths:

BLUE BAR: Approximate dosage strength of 500 IU per vial.
GREEN BAR: Approximate dosage strength of 1000 IU per vial.

One package of CEPROTIN contains one vial of CEPROTIN powder, one vial of Sterile Water for Injection (diluent), one double-ended transfer needle, one filter needle, one full prescribing physician insert, and one patient package insert.

11. How can I contact Takeda for more product information?

Takeda Customer Service: 1-877-TAKEDA-7 (1-877-825-3327)
Product website: www.ceprotin.com

CEP367

Revised: 9/2024

INSTRUCTIONS FOR USE

CEPROTIN® [see-PRO-ten]
Protein C Concentrate (Human)
for intravenous use

This "Instructions for Use" contains information on how to inject CEPROTIN.

IMPORTANT: Contact your doctor if you experience any problems with this procedure.

These instructions are intended only as an aid for those patients who have been instructed by their doctor on the proper way to self-infuse the product. **Do not attempt to self-infuse unless you have been taught how by your doctor.**

1. Prepare a clean surface and gather all the materials you will need for the infusion. You will need to gather exam gloves (optional), alcohol swabs (or other suitable solution suggested by your doctor), a winged infusion set, and a tourniquet, as these are not provided with your package of CEPROTIN.
2. Check the expiration date on the CEPROTIN vial. Do not use CEPROTIN after the expiration date.
3. Let the vial of CEPROTIN and the vial of Sterile Water for Injection, USP (diluent) warm up to room temperature.
4. Wash your hands and put on clean exam gloves (optional).
5. Remove caps from the CEPROTIN and diluent vial to expose the centers of the rubber stoppers.
6. Cleanse the stoppers with an alcohol swab (or other suitable solution suggested by your doctor) by rubbing the stoppers firmly for several seconds and allow them to dry.
7. Remove the protective covering from one end of the double-ended transfer needle and insert the exposed needle through the center of the diluent vial stopper.
8. While keeping the needle in the diluent vial, remove the protective covering from the other end of the double-ended transfer needle.
9. Invert the diluent vial over the upright CEPROTIN vial. Then, 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 CEPROTIN vial, do not use the product. Contact Takeda Pharmaceuticals Customer Service.
10. Separate the two vials by removing the needle from the diluent vial stopper. Then, remove the transfer needle from the CEPROTIN vial. **Do not attempt to recap the needle and do not dispose it in ordinary household trash.** Place the needle in a hard-walled Sharps container for proper disposal.
11. Gently swirl the CEPROTIN vial until all the powder is completely dissolved. The solution should be colorless to slightly yellowish and free of visible particles. Do not use the solution if you see particles in it. Administer CEPROTIN at room temperature within 3 hours of mixing.
12. Attach the filter needle to a disposable syringe and draw back the plunger to allow air into the syringe. Insert the filter needle into the reconstituted CEPROTIN.
13. Inject air into the vial, and then withdraw the solution into the syringe.
14. Remove and discard the filter needle from the syringe. **Do not attempt to recap the needle and do not dispose it in ordinary household trash.** Place the needle in a hard-walled Sharps container for proper disposal.
15. Attach a winged infusion set, if available, or a suitable needle (not supplied) for the injection.
16. Point the needle up and remove any air bubbles by gently tapping the syringe with your finger and slowly and carefully pushing air out of the syringe.
17. Apply a tourniquet, and prepare the injection site by wiping the skin well with an alcohol swab (or other suitable solution suggested by your doctor).
18. Insert the needle into the vein, and remove the tourniquet. Infuse CEPROTIN. CEPROTIN should be administered at a maximum injection rate of 2 milliliters (mL) per minute except for children with a bodyweight of < 10 kg (22 pounds), where the injection rate should not exceed a rate of 0.2 mL per kilogram per minute.

19. Remove the needle from the vein and apply pressure with sterile gauze to the infusion site for several minutes. **Do not attempt to recap the needle after the infusion, and do not dispose it in ordinary household trash.** Place the needle with the used syringe in a hard-walled Sharps container for proper disposal.
20. Clean up any blood with a freshly prepared mixture of 1 part bleach and 9 parts water, soap, and water, or any household disinfecting solution.

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CEP367

Revised: 9/2024

Important: Contact your doctor if you have any questions or experience any adverse effects. These instructions are intended as an additional aid only for those patients who have been instructed by their doctor on the proper way to self-infuse CEPROTIN. If you have not been instructed to self-infuse by your doctor, do not attempt to self-infuse.

PRINCIPAL DISPLAY PANEL - Kit Carton - NDC 0944-4177-05

NDC 0944-4177-05

Protein C
Concentrate (Human)
CEPROTIN®

Single-dose Vial

Lyophilized Powder for Solution for Injection

For Intravenous Administration Only.

See enclosed package insert for dosage and directions for use. Store in refrigerator (2 – 8°C [36° – 46°F]). Avoid freezing to prevent damage to the diluent bottle. Protect from light.

During reconstitution, swirl vial gently until all material is dissolved.

Administer within 3 hours after reconstitution. Do not refrigerate after reconstitution.

Takeda

PRINCIPAL DISPLAY PANEL - Vial Label - NDC 0944-4176-01

NDC 0944-4176-01

Protein C Concentrate (Human)
CEPROTIN®

Single-dose Vial

Lyophilized Powder for Solution for Injection.
For Intravenous Administration Only.

See package insert. **Rx only**
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Takeda

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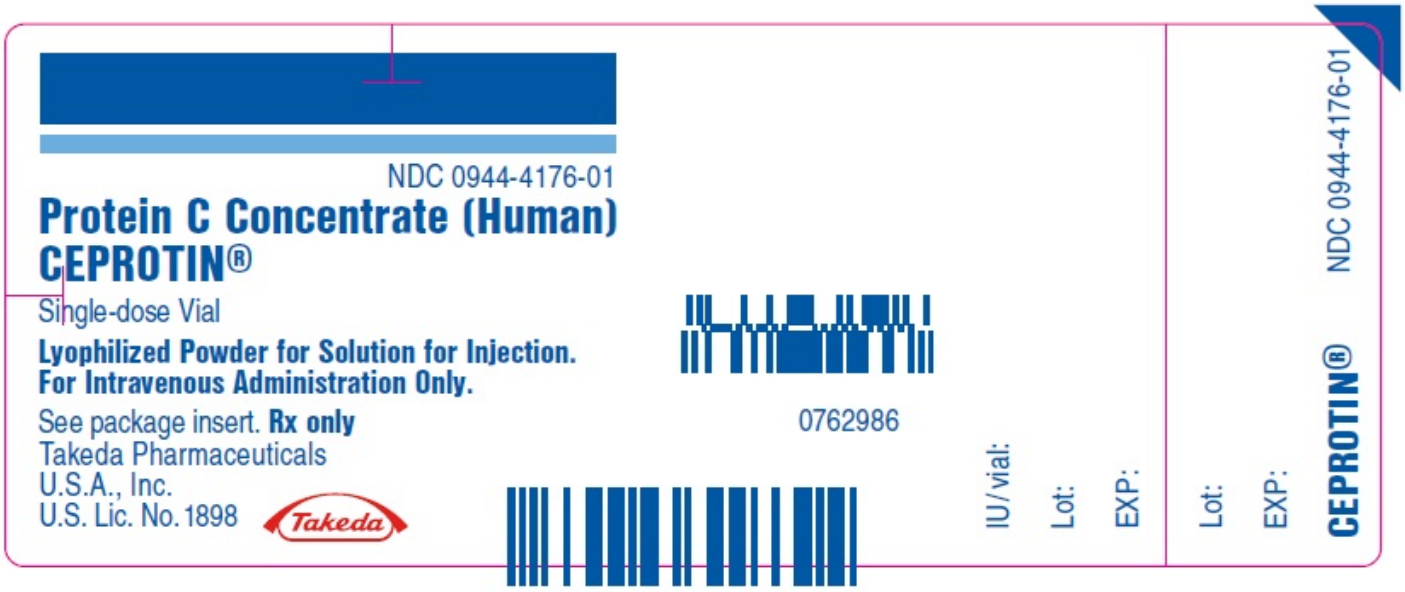


PRINCIPAL DISPLAY PANEL - Kit Carton - NDC 0944-4179-10

NDC 0944-4179-10

Protein C
Concentrate (Human)
CEPROTIN®

Single-dose Vial

Lyophilized Powder for Solution for Injection

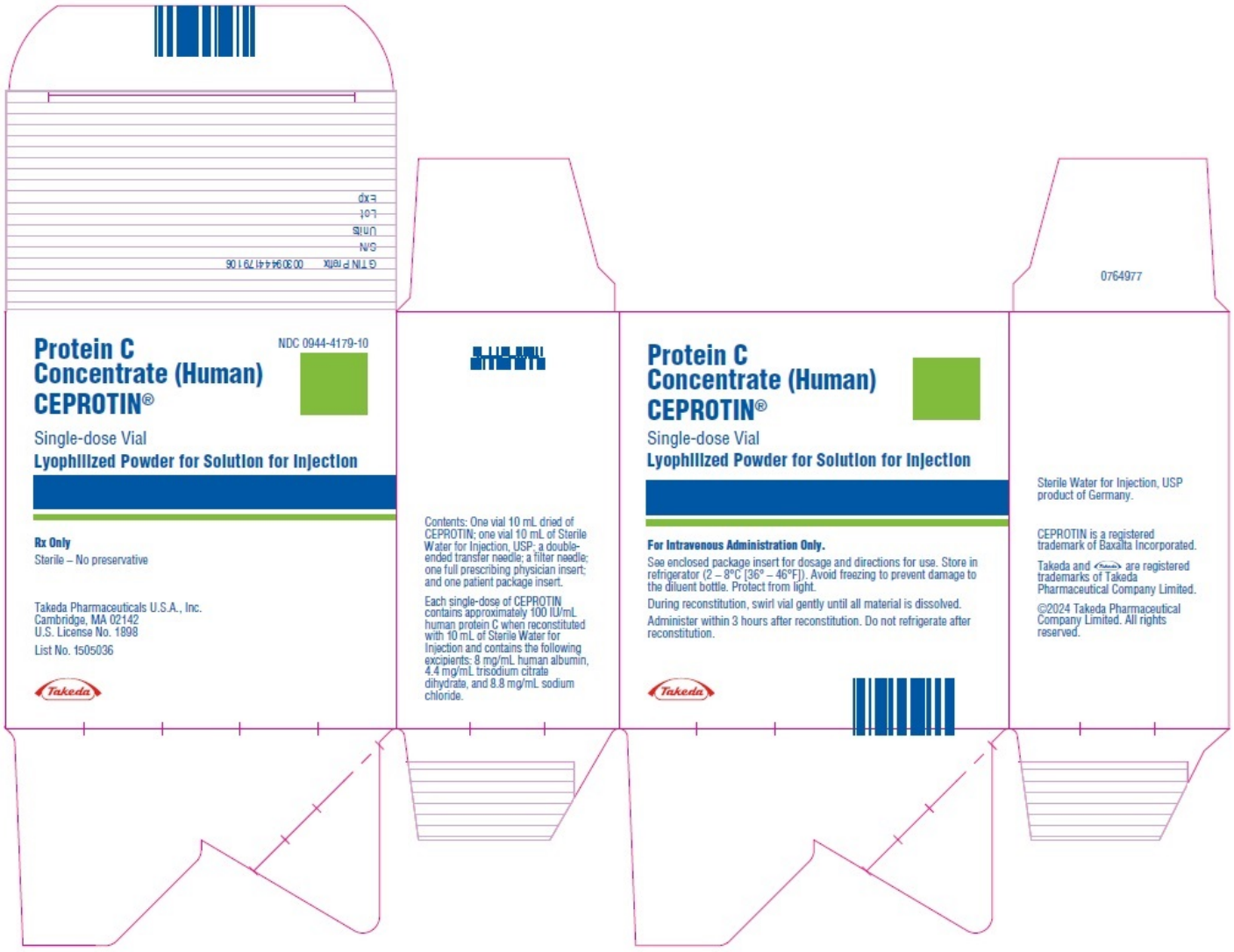
For Intravenous Administration Only.

See enclosed package insert for dosage and directions for use. Store in refrigerator (2 – 8°C [36° – 46°F]). Avoid freezing to prevent damage to the diluent bottle. Protect from light.

During reconstitution, swirl vial gently until all material is dissolved.

Administer within 3 hours after reconstitution. Do not refrigerate after reconstitution.

Takeda



PRINCIPAL DISPLAY PANEL - Vial Label - NDC 0944-4178-02

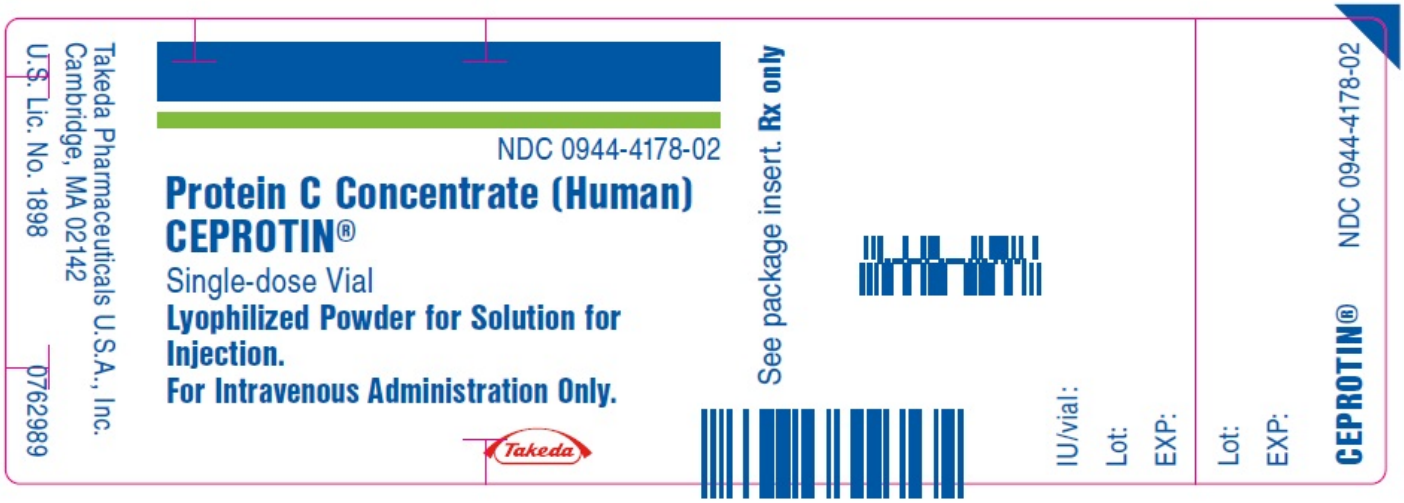
NDC 0944-4178-02

Protein C Concentrate (Human)
CEPROTIN®

Single-dose Vial

Lyophilized Powder for Solution for Injection.
For Intravenous Administration Only.

Takeda



CEPROTIN

protein c concentrate human kit

Product Information			
Product Type	PLASMA DERIVATIVE	**Item Code (Source)**	NDC:0944-4177

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0944-4177-05	1 in 1 CARTON		

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 VIAL, GLASS	5 mL
Part 2	1 VIAL, GLASS	5 mL

Part 1 of 2

CEPROTIN

protein c concentrate human injection, powder, lyophilized, for solution

Product Information	
Item Code (Source)	NDC:0944-4176
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**

PROTEIN C (UNII: 3Z6S89TXPW) (PROTEIN C - UNII:3Z6S89TXPW)	PROTEIN C	500 [iU] in 5 mL

Inactive Ingredients

Ingredient Name	Strength
ALBUMIN HUMAN (UNII: ZIF514RVZR)	
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0944-4176-01	5 mL in 1 VIAL, GLASS; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125234	08/09/2010	

Part 2 of 2

STERILE WATER

water liquid

Product Information

Item Code (Source)	NDC:64764-515
Route of Administration	INTRAVENOUS

Inactive Ingredients

Ingredient Name	Strength
WATER (UNII: 059QF0KO0R)	5 mL in 5 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:64764-515-50	5 mL in 1 VIAL, GLASS; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125234	08/09/2010	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125234	08/09/2010	

CEPROTIN

protein c concentrate human kit

Product Information

Product Type	PLASMA DERIVATIVE	**Item Code (Source)**	NDC:0944-4179

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:0944-4179-10	1 in 1 CARTON		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 VIAL, GLASS	10 mL
Part 2	1 VIAL, GLASS	10 mL

Part 1 of 2

CEPROTIN

protein c concentrate human injection, powder, lyophilized, for solution

Product Information

Item Code (Source)	NDC:0944-4178
Route of Administration	INTRAVENOUS

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
PROTEIN C (UNII: 3Z6S89TXPW) (PROTEIN C - UNII:3Z6S89TXPW)	PROTEIN C	1000 [iU] in 10 mL

Inactive Ingredients	
Ingredient Name	**Strength**
ALBUMIN HUMAN (UNII: ZIF514RVZR)	
TRISODIUM CITRATE DIHYDRATE (UNII: B22547B95K)	
SODIUM CHLORIDE (UNII: 451W47IQ8X)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:0944-4178-02	10 mL in 1 VIAL, GLASS; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125234	08/09/2010	

Part 2 of 2

STERILE WATER

water liquid

Product Information	
Item Code (Source)	NDC:64764-516
Route of Administration	INTRAVENOUS

Inactive Ingredients	
Ingredient Name	**Strength**
WATER (UNII: 059QF0KO0R)	10 mL in 10 mL

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:64764-516-10	10 mL in 1 VIAL, GLASS; Type 9: Other Type of Part 3 Combination Product (e.g., Drug/Device/Biological Product)		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date

BLA	BLA125234	08/09/2010	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA125234	08/09/2010	

Labeler - Takeda Pharmaceuticals America, Inc. (039997266)

Establishment

Name	Address	ID/FEI	Business Operations
Takeda Manufacturing Austria AG		300434670	MANUFACTURE(0944-4177, 0944-4179)

Establishment

Name	Address	ID/FEI	Business Operations
Siegfried Hameln GmbH		315869123	MANUFACTURE(64764-515, 64764-516)

Revised: 12/2025 Takeda Pharmaceuticals America, Inc.