AUSTRALIAN PRODUCT INFORMATION

CEPROTIN® (Protein C, human)

1 NAME OF THE MEDICINE

Protein C, human

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

CEPROTIN is available in the following strengths: 500IU and 1000IU.

Table 1

CEPROTIN	**500 IU**	**1000 IU**
Active ingredient:		
Human Protein C	500 IU	1000 IU
Total Protein	42.5 mg	85.0 mg
thereof:		
Human albumin	40.0 mg	80.0 mg

CEPROTIN is a freeze-dried, sterile high-purity Protein C preparation, intended for intravenous application.

The active ingredient, human plasma derived Protein C, is purified by column chromatography packed with monoclonal antibody against Protein C. It contains human albumin as stabilizer and the inactive ingredients, sodium chloride and sodium citrate, to assure isotonicity and stability of the reconstituted preparation.

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Protein C, powder for injection vial with diluent vial.

CEPROTIN is presented as a white to cream colour lyophilised powder in a single dose vial of neutral glass of either hydrolytic type I (500 IU) or hydrolytic type II (1000 IU).

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

CEPROTIN is indicated in purpura fulminans and coumarin-induced skin necrosis in patients with severe congenital protein C deficiency.

Since safety and efficacy data are not available in conditions other than severe congenital deficiency, use should be limited to these conditions.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Dosage
The dosage should be adjusted on the basis of laboratory assessment for each individual case.

Initially the activity of protein C at a level of 100% should be achieved and the activity should be maintained above 25% for the duration of the treatment. An initial dose of 60 to 80 IU/kg for determination of recovery and half-life is recommended. The determination of protein C activity using protein C specific chromogenic substrates is recommended for the assay of the patient's protein C plasma level before and during the treatment with CEPROTIN.

The dosage should be determined on the basis of laboratory determination of the protein C activity. This should be performed every 6 hours until the patient is stabilised, thereafter twice a day and always immediately before the next injection. It should be kept in mind that the half-life of protein C may be severely shortened in certain clinical conditions such as acute thrombosis with purpura fulminans and skin necrosis.

Patients treated during the acute phase of their disease may display much lower increases in protein C activity. The wide variation in individual responses implies that the effects of CEPROTIN on coagulation parameters should be regularly checked.

If the patient is switched to permanent prophylaxis with oral anticoagulants, protein C replacement is to be discontinued only when stable anticoagulation has been achieved. Furthermore, during the initiation of oral anticoagulant therapy, it is advisable to start with a low dose and adjust this incrementally, rather than use a standard loading dose.

In patients with combined severe congenital protein C deficiency and activated protein C (APC) resistance, there are limited clinical data to support the safety and efficacy of CEPROTIN.

No experience in the treatment of patients with renal and/or hepatic impairment is available and therefore it is recommended that such patients to be monitored more closely.

Method of administration

CEPROTIN is administered by intravenous injection after the lyophilised powder form is reconstituted with sterilised Water for Injection.

CEPROTIN should be administered at a maximum injection rate of 2 mL/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.

As with any intravenous protein product, allergic type hypersensitivity reactions may occur. The administration should be made within reach of life-supporting facilities, as the events of allergic symptoms may show up which are of an acute and life-threatening nature.

Instructions for use, handling and disposal

Reconstitute the lyophilised CEPROTIN powder with the supplied Water for Injection using sterile needle. Gently rotate the vial until all the powder has been dissolved. After reconstitution, the solution is drawn through the sterile filter needle into a sterile disposable syringe. A separate sterile filter needle must be used to withdraw the reconstituted CEPROTIN from each vial. The solution should be discarded if particulate matter is visible.

The reconstituted solution should be administered immediately by intravenous route injection.

All unused solution, empty vials and used needles and syringes must be discarded appropriately.

4.3 CONTRAINDICATIONS

Hypersensitivity to any of the components, to mouse protein or to heparin, except for control of life-threatening thrombotic complications.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Administration of CEPROTIN may result in allergic reaction in some patients. As the risk of an allergic type hypersensitivity reaction cannot be excluded, patients should be informed of the early signs of hypersensitivity reactions including hives, generalized urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. If these symptoms occur, they should inform the physician. Immediate discontinuation of product use should be considered. Adequate medical treatment and provisions should be available for immediate use in the rare event of an anaphylactic reaction.

Transmission of infectious agents

When medicinal products prepared from human blood or plasma is administered, infectious diseases due to transmission of infective agents cannot be totally excluded. This applies also to pathogens of hitherto unknown nature. The risk of transmission of infective agents is however reduced by:

- selection of donors by a medical interview and screening of donations for the three major pathogenic viruses, HIV, HCV, HBV;
- testing plasma pools for the absence of HCV genomic material;
- removal/inactivation procedures included in the production process that have been validated using model viruses and are effective for HIV, HCV, HAV, and HBV.

The viral removal/inactivation procedure is of limited value against parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased red cell production (e.g. haemolytic anemia)

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

Sodium content

A quantity of sodium in the maximum daily dose may exceed 200 mg. This should be taken into consideration by patients on a controlled sodium diet.

Heparin induced Thrombocytopenia

CEPROTIN may contain trace amounts of heparin. Heparin induced allergic reactions which can be associated with a rapid decrease in the number of platelets can occur (Heparin-induced thrombocytopenia, HIT). In patients with HIT, symptoms such as arterial and venous thrombosis, disseminated intravascular coagulation (DIC), purpura, petechia, and gut bleeding (melena), can occur. If HIT is suspected, the platelet count should be determined immediately and if necessary therapy with CEPROTIN should be stopped. Identifying HIT is complicated by the fact that these symptoms may already be present in acute phase patients with severe congenital protein C deficiency. Patients with HIT should avoid the use of heparin containing drugs in the future.

Bleeding episodes

In the context of clinical experience several bleeding episodes have been observed. Concurrent anticoagulant medication (such as heparin) may have been responsible for these bleeding episodes. However, it cannot be completely ruled out that administration of CEPROTIN further contributed to these bleeding episodes.

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. Adequate medical treatment and provisions should be available for immediate use in the event of an anaphylactic reaction.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interactions with other medicinal products are currently known. In patients starting treatment with oral anticoagulants of the vitamin K antagonists class (e.g. warfarin), 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 is a vitamin K dependent plasma protein having a shorter half-life than most of the vitamin K dependent proteins (factors II, IX, X). Subsequently, in the initial phase of treatment, the activity of protein C is suppressed more rapidly than that of procoagulant factors. For this reason, if the patient is switched to oral anticoagulants, protein C replacement must be continued until stable anticoagulation is achieved. Although warfarin-induced skin necrosis can occur in any patient during the initiation of oral anticoagulant therapy, individuals with congenital protein C deficiency are particularly at risk.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effect of protein C on fertility has not been investigated in animal studies.

Use in pregnancy

Australian Pregnancy Categorisation (Category B2)

The safety of protein C during pregnancy has not been established. CEPROTIN should not be used during pregnancy unless the benefit outweighs the risk to the fetus.

See section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE for information on Parvovirus B19 infection.

Use in lactation

The safety of CEPROTIN in lactation has not been established.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Only few data are available. No prospective safety studies have been performed. Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection sites, chills, flushing, rash, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting wheezing) have been observed infrequently.

In the clinical trials performed, two mild allergic adverse experiences occurred. The occurrence of fever, arrhythmia, bleedings and thrombosis in the course of the treatment has been reported. Some of these adverse reactions, experienced during the retrospective data collection are shown in Table 2.

Table 2: Some of the Adverse Reactions experienced during the Retrospective data collection

Body System	Preferred Term	Total of Symptoms
Application Site Disorder	Injection. site, pain	1
Body as whole- General Disorder	Death	5
	Fever	4
	Chest pain	2
	Oedema of extremities	2
	Back pain	1
	Influenzas-like Symptoms	1
	Pain	1
	Pain legs	1
Cardiovascular Disorder, General	Hypotension	2
	Hypotension, aggravated	1
	Hypertension	1
	Tachycardia	2
Central, peripheral Nervous System disorder	Headache	5
	Convulsions	1
	Hemiparesis	1
	Seizures Cerebral	1
Gastro-Intestinal System and metabolic Disorders	Abdominal pain	1
	Diarrhoea	1

	Emesis	1
	GI tracts bleed	1
	Haematemesis	1
	Nausea	1
	Acidosis	2
Respiratory System disorder	Hypoxaemia	1
	Pleural effusion	1
	Pulmonary oedema	1
	Sinus congestion	1
Skin Disorder	Rash	3
	Hives	2
	Skin disorder	2
	Skin ulceration	2
	Skin inflammation	1
Urinary System disorder	Blood in urine	1
	Oliguria	1
	Renal function abnormality	1
Vascular (extracardiac) disorders	Cerebral Haemorrhage	1
	Peripheral ischaemia	1
	Peripheral gangrene	1
	Thrombosis vena Cava inferior	1
	Subcutaneous haematoma	1

If the preparation is used in patients with severe congenital protein C deficiency, antibodies inhibiting protein C may develop.

Adverse Reactions from Clinical Trials

Based on clinical studies involving patients with severe congenital and acquired protein C deficiency who received treatment with CEPROTIN, only 3 adverse reactions, occurring in one subject, were considered to be related to CEPROTIN. These were itching, rash and light-headedness.

Table 3: Clinical Trial Adverse Reactions Following CEPROTIN Treatment

System Organ Class (SOC)	Adverse Reaction	Preferred MedDRA Term	Frequency
NERVOUS SYSTEM DISORDERS	Dizziness	Dizziness	Common
IMMUNE SYSTEM DISORDERS	Hypersensitivity	Rash Pruritus	Common Common

Legend: ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000)

Post-marketing Adverse Reactions

The following adverse reactions have been reported in the post-marketing experience, listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity, where feasible.

PSYCHIATRIC DISORDERS: Restlessness

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Hyperhidrosis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS:
Injection site reaction

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre telephone: 131126 (Australia).

No symptoms of overdose with CEPROTIN have been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Circulating protein C is converted by thrombin-thrombomodulin complex on the endothelial surface to activated protein C which is a serine protease with anticoagulant activity, especially in the presence of cofactor protein S. Activated protein C exerts its effect by inhibition of the activated forms of factors V and VIII which results in a decrease in thrombin formation. It has also been shown to have profibrinolytic activity.

Clinical trials

Congenital protein C deficiency syndrome is a very rare disease (1 per 160,000 to 300, 000 births). Due to the rarity of the disease, prospective controlled clinical trials to assess the efficacy and safety of CEPROTIN could not be conducted.

Efficacy and the safety were assessed through data collected retrospectively from patients treated over a ten-year period (1989 – 1999). A total of 79 subjects with protein C deficiency were treated under two clinical trial protocols (n=34 and n=4) or under compassionate provisions (n=41). Patients were treated in the USA, Canada and Europe.

Ten patients with severe congenital protein C deficiency were treated for a total 16 episodes of purpura fulminans and another four patients were treated for 6 episodes of coumarin-induced skin necrosis. Clinical efficacy was assessed by the investigator in terms of improvement in skin lesions at the end of each treatment course. In all 22 episodes the outcome of treatment was assessed as “markedly improved or healed”.

5.2 PHARMACOKINETIC PROPERTIES

Thirteen asymptomatic subjects with homozygous or double heterozygous protein C deficiency were evaluated for pharmacokinetic data. The protein C plasma activity was measured by chromogenic assay. The individual half-lives varied from 4.4 to 15.8 hours using a compartmental model and from 4.9 to 14.7 hours using the non-compartmental method. The individual in-vivo recovery ranged from 20.4 to 83.2 %. The patients differed significantly in age, body weight and plasma volume. In patients with acute thrombosis, both the increase in protein C plasma levels as well as half-life may be considerably reduced.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Protein C, was not mutagenic in an in-vitro test for reverse mutation in *S. typhymurium* (Ames test)

Carcinogenicity
Long term carcinogenicity studies with protein C have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Table 4: Inactive ingredients in CEPROTIN 500IU and 1000IU

CEPROTIN	**500 IU**	**1000 IU**
Inactive ingredient		
Sodium Chloride	44.0 mg	88.0 mg
Sodium Citrate	22.0 mg	44.0 mg
Sterilised Water for Injection No preservative is added to the formulation.	5 mL	10 mL

For active ingredients, refer to Section 2 – QUALITATIVE AND QUANTITATIVE COMPOSITION.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

36 months.
Contains no antibacterial agent. Product is for single use in one patient only. Discard any residue. The expiry date is shown on the label and packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

CEPROTIN should be stored at 2 ºC to 8 ºC (in a refrigerator). Do not freeze.

6.5 NATURE AND CONTENTS OF CONTAINER

CEPROTIN is presented as a white to cream colour lyophilised powder in a single dose vial of neutral glass of either hydrolytic type I (500 IU) or hydrolytic type II (1000 IU). It is accompanied by sterilised Water for Injection (WFI) in vials of neutral glass of hydrolytic type I (5mL and 10mL), used as diluent for 500 IU and 1000 IU, respectively. The product and the solvent vials are closed with butyl rubber stoppers.

Each pack also contains:
- one transfer needle
- one filter needle.

Pack size

1 vial and 1 vial of WFI (solvent)

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Name

Blood-coagulation factor XIV (MI).

Chemical Structure

Protein C is synthesized in the liver as a vitamin-K dependent plasma protein. It is a two-chain molecule consisting of a heavy and a light chain linked by a disulfide bridge. The apparent molecular weight of protein C is 62,000, which includes four N-linked carbohydrate side chains. The molecule contains several distinct domains of structural and functional significance. The 155-amino acid light chain consists of the N-terminal gamma-carboxyglutamic acid domain (with 9 gamma-carboxyglutamic acid residues) followed by two domains with homology to epidermal growth factor. The 252-amino acid heavy chain contains the 12-amino acids activation peptide and the serine protease domain. Upon activation of Protein C by thrombin-thrombomodulin complex, the 12 amino acids activation peptides are cleaved off, yielding activated Protein C.

CAS number
60202-16-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription only Medicine (S4).

8 SPONSOR

Shire Australia Pty Limited
Level 39
225 George Street
Sydney, NSW 2000
Australia
Telephone: 1800 012 612
www.shireaustralia.com.au

9 DATE OF FIRST APPROVAL

30 June 2005.

10 DATE OF REVISION

20 June 2018.

Summary table of changes

Section Changed	Summary of new information
All	Australian PI updated to new SPC format and insertion of table numbers to all tables
2	Minor editorial change: Table split into actives and excipients moved to section 6.2; not-required subheadings removed. Duplicate text removed.
4.7, 4.8 &4.9, 6.2, 6.6	Minor editorial change: New text in line with the new PI form added.
4.8	Safety update: Addition of hypersensitivity as a Clinical Trial Adverse reaction, amendment to ADR frequencies.
5.3	Minor editorial change: Text relocated from 4.6
6.7	Minor editorial change: Section moved from 2 to 6.7 and included CAS number.
8	Minor editorial change: Change in sponsor contact details.