

1. NAME OF THE MEDICINAL PRODUCT

CEPROTIN 500 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Protein C from human plasma purified by mouse monoclonal antibodies. CEPROTIN 500 IU* is prepared as a powder containing nominally 500 IU human protein C per container. The product reconstituted with 5 ml of Sterilised Water for Injections contains approximately 100 IU/ml human protein C.

The potency (IU) is determined using a chromogenic substrate method against the World Health Organisation (WHO) International standard.

*One International Unit (IU) of protein C corresponds to the amidolytically measured activity of protein C in 1 ml of normal plasma.

Excipients with known effect:

This medicinal product contains 22.5 mg sodium per vial.
For the full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Human protein C, powder and solvent for solution for injection.

Lyophilised white or cream coloured powder or friable solid. After reconstitution the solution has a pH of between 6.7 and 7.3 and an osmolality of not lower than 240 mosmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CEPROTIN is indicated for prophylaxis and treatment of purpura fulminans coumarin-induced skin necrosis and venous thrombotic events in patients with severe congenital protein C deficiency.

4.2 Posology and method of administration

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

Posology

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

Treatment of acute episodes and short-term prophylaxis (including invasive procedures)

A protein C activity of 100 % (1 IU/ml) should be achieved initially 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 advised.
The measurement of protein C activity using chromogenic substrates is recommended for the

determination of the patient's plasma level for protein C before and during treatment with CEPROTIN.

The dosage should be determined on the basis of laboratory measurements of the protein C activity. In the case of an acute thrombotic event these 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.

If the response to CEPROTIN injection is satisfactory (measured by chromogenic assays), dosing may be gradually reduced to 12 hourly dosing ensuring trough protein C activity >25% (>0.25 IU/ml).

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 checked regularly.

In patients receiving prophylactic administration of protein C, higher trough levels may be warranted in situations of an increased risk of thrombosis (such as infection, trauma, or surgical intervention).

Long-term prophylaxis

For the long-term prophylactic treatment, a dose of 45 to 60 IU/kg every 12 hours is recommended. Measurement of the protein C activity should be performed to ensure trough levels of 25% or more. Dose or frequency of infusions should be adjusted accordingly.

In rare and exceptional cases, subcutaneous infusion of 250-350 IU/kg was able to produce therapeutic protein C plasma levels in patients with no intravenous access.

Combination treatment

If the patient is switched to permanent prophylaxis with oral anticoagulants, protein C replacement is to be discontinued only when stable anticoagulation is obtained (see section 4.5). 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.

At start of a combination treatment of anticoagulants (especially Vitamin K antagonists) with Protein C, stable activity levels of Protein C above 0.25 IU/ml (chromogenic) should be maintained before starting the anticoagulation. Careful monitoring of the international normalized ratio (INR) is recommended. In the combination of Protein C Concentrate and -anticoagulants, a protein C trough level of about 10% or more is recommended to be maintained.

Special populations

Paediatric population

Based on the limited clinical experience in children from reports and studies covering 83 patients, dosing guidelines for adult subjects are considered valid for neonatal and paediatric patient population (see section 5.1).

Activated Protein C (APC) resistance

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

Renal and/or hepatic impairment

Safety and efficacy of CEPROTIN in patients with renal and/or hepatic impairment have not been established. Patients with any of these conditions should be monitored more closely.

Method of administration

CEPROTIN is administered by intravenous injection after reconstitution of the powder for solution for injection with Sterilised Water for Injections.

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/min.

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. For the events that allergic symptoms arise which are of an acute and life-threatening nature, administration should be made within reach of life-supporting facilities.

For instructions on reconstitution of the medicinal product before administration, see section.6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 or to mouse protein or heparin, except for control of life-threatening thrombotic complications.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity

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 is advised.

In case of shock, the current medical standards for shock treatment are to be observed.

Renal and/or hepatic impairment

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

Inhibitors

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

Transmissible agents

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection, and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped

viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

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

Heparin induced thrombocytopenia (HIT)

CEPROTIN may contain trace amounts of heparin. Heparin induced allergic reactions, which can be associated with a rapid decrease of the number of thrombocytes, may be observed (HIT). In patients with HIT, symptoms such as arterial and venous thrombosis, disseminated intravascular coagulation (DIC), purpura, petechiae and gastrointestinal bleeding (melena), may occur. If HIT is suspected, the number of thrombocytes 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.

Concurrent anticoagulant medication

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 the administration of CEPROTIN further contributed to these bleeding events.

Sodium

This medicinal product contains 22.5 mg sodium per vial, equivalent to 1.1% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions with other medicinal products are currently known.

Interaction with Vitamin K antagonists

In patients starting treatment with oral anticoagulants belonging to the class of vitamin K antagonists (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, itself a vitamin K dependent plasma protein, has a shorter half-life than most of the vitamin K dependent proteins (i.e. II, IX and X). Subsequently, in the initial phase of treatment, the activity of protein C is more rapidly suppressed than that of the procoagulant factors. For this reason, if the patient is switched to oral anticoagulants, protein C replacement must be continued until stable anticoagulation is obtained. Although Warfarin-induced skin necrosis can occur in any patient during the initiation of oral anticoagulant therapy, individuals with congenital protein C deficiency are particularly at risk. (See section 4.2).

4.6 Fertility, pregnancy and lactation

Although CEPROTIN has been used safely in the treatment of pregnant protein C-deficient women, its safety for use in human pregnancy has not been established in controlled clinical trials. Furthermore, no information on excretion of protein C in the milk is available. Therefore, the benefit of using CEPROTIN during pregnancy or lactation must be judged against the risk for the mother and baby and should be used only if clearly needed.

For information on parvovirus B19 infection, see section 4.4.

4.7 Effects on ability to drive and use machines

CEPROTIN has no influence or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

As with any intravenous product allergic type hypersensitivity reactions are possible. Patients should be informed of the early signs of hypersensitivity reactions, which may include angioedema, burning and stinging at the injection site, chills, flushing, rash, pruritus, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, and wheezing. Patients should be advised to immediately contact their physician if these symptoms occur (see section 4.4).

Tabulated list of adverse reactions

During clinical studies with CEPROTIN, a total of 3 adverse drug reactions (ADRs) were reported in 1 of 67 patients enrolled (rash and pruritus (grouped as hypersensitivity), and dizziness). In total 6375 administrations of CEPROTIN have been given. The distribution of the related ADRs is as follows:

Frequencies have been evaluated according to the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$); not known (cannot be estimated from the available data).

System Organ Class	Adverse Reaction	Preferred Term	Frequency Category by infusions
Immune System Disorders	Hypersensitivity	Rash	Rare
		Pruritus	Rare
Nervous System Disorders	Dizziness	Dizziness	Rare

Post-marketing experience

The following ADRs have been reported in the post-marketing experience and the frequency of these ADRs is not known:

Psychiatric disorders: restlessness

Skin and subcutaneous tissue disorders: hyperhidrosis

General disorders and administration site conditions: injection site reaction

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

No symptoms of overdose with CEPROTIN have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: group antithrombotic; ATC Code: B01AD12

Mechanism of action

Protein C is a vitamin K-dependent anticoagulant glycoprotein which is synthesised in the liver. It is converted by thrombin/thrombomodulin-complex on the endothelial surface to 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 intravenous administration of CEPROTIN provides for an immediate but temporary increase in plasma levels of protein C. Replacement of protein C in protein C deficient patients is expected to control or - if given prophylactically - prevent thrombotic complications.

Clinical efficacy

One prospective, multicenter, open-label, non-randomized, 3-part, phase 2/3 clinical study in subjects with severe congenital Protein C deficiency to evaluate the efficacy and safety of Protein C Concentrate was completed (pivotal study 400101). This study enrolled 18 subjects with severe congenital Protein C deficiency defined as protein C activity level <20% and with median age 5.8 years (range 0 to 26 years). In the long-term prophylaxis group the median age was 2.8 years (range 0 to 22 years). A total of 24 episodes of purpura fulminans (PF), coumarin-induced skin necrosis (CISN) and other vascular thromboembolic events were treated with CEPROTIN in 11 subjects. Seven courses of short-term prophylaxis prior to surgery or initiation of anticoagulation therapy and 8 courses of long-term prophylaxis were analysed. The results of this study demonstrate that CEPROTIN is efficacious for the treatment of acute thrombotic episodes and support the use of CEPROTIN for both short-term and long-term thrombotic prophylactic treatment.

Other experience with CEPROTIN covers case reports and a clinical study in overall 69 paediatric patients with acquired protein C deficiency. The study is a randomized, double-blind, placebo-controlled dose-finding study, in the indication of acquired protein C deficiency due to meningococcal sepsis (IMAG 112). The reports suggest that CEPROTIN is well tolerated in children and small infants.

Dosages of the above studies, covering 87 patients, indicate that dosing guidelines for adult subjects are also valid for neonatal and paediatric patient population.

5.2 Pharmacokinetic properties

21 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 using the non-compartmental method. The individual incremental recovery ranged from 0.50 to 1.76 [(IU/dL)/(IU/kg)]. The patients differed significantly in age, body weight and plasma volume.

In patients with acute thrombotic disease, both the incremental increase in protein C plasma levels as well as half-life may be considerably reduced.

5.3 Preclinical safety data

Protein C contained in CEPROTIN is a normal constituent of human plasma and acts like endogenous protein C. Therefore, experimental studies on tumorigenic or mutagenic effects - particularly in heterologous species - are not considered necessary.

Single dose toxicity testing showed that even doses of several times the recommended human dosage per kilogram body weight (10-fold) did not result in toxic effects on rodents.

CEPROTIN proved to have no mutagenic potential in the Ames test performed.

Repeated toxicity studies were not conducted because prior experience with coagulation preparations had shown them to be of limited value. Difference between the recipient species and human protein C will inevitably result in an immune response with antibody formation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Human albumin
Trisodium citrate dihydrate
Sodium chloride

Solvent

Sterilised Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years
The reconstituted solution should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C).
Do not freeze. Keep the vial in the outer carton in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

500 IU and 1,000 IU: CEPROTIN powder comes in vials of neutral glass of either hydrolytic type I (500 IU) or hydrolytic type II (1,000 IU).
The solvent comes in vials of neutral glass of hydrolytic type I. The product and the solvent vials are closed with butyl rubber stoppers.

Each pack also contains:

- one transfer needle
- one filter needle

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitute lyophilised CEPROTIN powder for solution for injection, with the supplied solvent (Sterilised Water for Injections) using the sterile transfer needle. Gently rotate the vial until all powder is dissolved. After reconstitution the solution is colourless to slightly yellowish and clear to slightly opalescent and essentially free from visible particles.

The solution is drawn through the sterile filter needle into a sterile disposable syringe. A separate unused filter needle must be used to withdraw each vial of reconstituted CEPROTIN. The solution should be discarded if particulate matter is visible.

The reconstituted solution should be administered immediately by intravenous injection.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
Industriestrasse 67
1221 Vienna
Austria

8. MARKETING AUTHORISATION NUMBER

EU/1/01/190/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 July 2001

Date of last renewal: 16 July 2006

10. DATE OF REVISION OF THE TEXT

16 December 2022

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.