ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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.

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 non-serious 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.

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

The distribution of the related ADRs is as follows:

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 the national reporting system listed in Appendix V.

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

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

1. NAME OF THE MEDICINAL PRODUCT

CEPROTIN 1,000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Protein C from human plasma purified by mouse monoclonal antibodies. CEPROTIN 1,000 IU* is prepared as a powder containing nominally 1,000 IU human protein C per container. The product reconstituted with 10 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 44.9 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 ours 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.

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 44.9 mg sodium per vial, equivalent to 2.2% 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 non-serious 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 (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 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 the national reporting system listed in Appendix V.

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

21asymptomatic 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/1/01/190/002

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

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

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Takeda Manufacturing Austria AG
Benatzkygasse 2-6
1221 Vienna
Austria

Name and address of the manufacturer(s) responsible for batch release

Takeda Manufacturing Austria AG
Industriestrasse 67
1221 Vienna
Austria

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The marketing authorisation holder (MAH) shall submit PSURs for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of an RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

CEPROTIN 500 IU
Powder and solvent for solution for injection
human protein C

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial provides 100 IU per ml of human protein C when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Human albumin, trisodium citrate dihydrate and sodium chloride

4. PHARMACEUTICAL FORM AND CONTENTS

Contents:
Powder and solvent for solution for injection
One transfer needle and one filter needle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/190/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ceprotin 500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CEPROTIN 500 IU
Powder for solution for injection
human protein C
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

One vial provides 100 IU per ml of human protein C when reconstituted as recommended.

6. OTHER

WATER FOR INJECTIONS

5 ml Sterilised Water for Injections

EXPIRY DATE

EXP

BATCH NUMBER

Lot

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

CEPROTIN 1,000 IU
Powder and solvent for solution for injection
human protein C

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial provides 100 IU per ml of human protein C when reconstituted as recommended.

3. LIST OF EXCIPIENTS

Human albumin, trisodium citrate dihydrate and sodium chloride

4. PHARMACEUTICAL FORM AND CONTENTS

Contents:
Powder and solvent for solution for injection
One transfer needle and one filter needle

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNINGS, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Takeda Manufacturing Austria AG
1221 Vienna,
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/190/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ceprotin 1,000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

CEPROTIN 1,000 IU
Powder for solution for injection
human protein C
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

One vial provides 100 IU per ml of human protein C when reconstituted as recommended.

6. OTHER

WATER FOR INJECTIONS

10 ml Sterilised Water for Injections

EXPIRY DATE

EXP

BATCH NUMBER

Lot

B. PACKAGE LEAFLET

Package leaflet: Information for the user

CEPROTIN 500 IU powder and solvent for solution for injection
human protein C

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What CEPROTIN is and what it is used for

CEPROTIN belongs to a class of medicines called antithrombotics. This medicine contains Protein C, a natural protein that is made in the liver and is present in your blood. Protein C plays a major role in prevention of excessive clot formation thus, prevent and/or treat intravascular thrombosis.

CEPROTIN is used in the treatment and prevention of thrombotic and haemorrhagic skin lesions (named purpura fulminans) in patients with severe congenital protein C deficiency. CEPROTIN may also be used in the treatment and prevention of a rare complication of a blood thinner medicine (anticoagulant medicine named coumarin) which may result in severe skin lesion (necrosis). Additionally, CEPROTIN may be used in the treatment of blood clot (venous thrombotic) events.

2. What you need to know before you use CEPROTIN

Do not use CEPROTIN

- if you are allergic to human protein C or any of the other ingredients of this medicine (listed in section 6) including mouse protein or heparin.

However, in the case of life-threatening thrombotic complications your doctor may still decide to continue treatment with CEPROTIN.

Warnings and precautions

Talk to your doctor or pharmacist before using CEPROTIN. Take special care with CEPROTIN if symptoms of allergy occur. Symptoms of allergy include rash, hives, breathing difficulties, low blood pressure, tightness of chest, and shock. If such symptoms occur during the administration of CEPROTIN, injection should be stopped. Such symptoms may constitute an allergic reaction to any of the components, to mouse protein or heparin. The preparation may contain traces of heparin and/or mouse protein as a result of the manufacturing process. If such a reaction occurs, your doctor will decide on the most appropriate treatment.

If the preparation is used in patients with severe congenital protein C deficiency, antibodies inhibiting protein C may develop that can inhibit protein C and therefore diminish the effect of the preparation. However, this has not been observed in the clinical studies to date.

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A virus. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B 19 infection may be serious for pregnant women (foetal infection) and for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or haemolytic anaemia).

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived Protein C products.

Other medicines and CEPROTIN

No interactions with other medicinal products are currently known.
Nevertheless, please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

If you change to treatment with oral anticoagulants, treatment with CEPROTIN must continue until the blood level of the oral anticoagulation is adequate and stable.

CEPROTIN with food and drink

Not applicable.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
Your doctor will decide if CEPROTIN may be used during pregnancy and lactation.

Driving and using machines

CEPROTIN has no influence on your ability to drive or to operate machines.

CEPROTIN contains Sodium

This medicine contains 22.5 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 1.1% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use CEPROTIN

CEPROTIN is intended for intravenous administration (infusion into a vein). It is given to you under close supervision of your doctor who is experienced in substitution therapy of coagulation

factors/inhibitors and where monitoring of protein C activity is possible. Dosage will vary depending on your condition and your body weight.

Dosage

The dose, administration frequency and duration of treatment depend on the severity of the protein C deficiency as well as on your clinical condition and on your plasma level of protein C. They should be adjusted accordingly on the basis of clinical effectiveness and laboratory assessment.

Treatment of acute episodes and short-term prophylaxis
A protein C activity of 100 % (1 IU/ml) should be achieved initially and the activity should be intained above 25 % for the duration of the treatment.

An initial dose of 60 to 80 IU/kg should be administered. Your physician will take several blood drawings over time to determine how long protein C is remaining in your body.

The measurement of protein C activity using chromogenic substrates is recommended for the determination of your 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 your condition 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, dosing may be gradually reduced to 12 hourly dosing ensuring trough protein C activity >25%.

If you receive 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. In rare cases, subcutaneous infusion of 250 - 350 IU/kg has produced therapeutic plasma protein C levels in patients with no intravenous access.

If you have kidney and/or liver disease, please inform your doctor, because he may have to adjust your treatment accordingly.

Combination treatment
If you are switched to permanent prophylaxis with oral anticoagulants, protein C replacement is to be discontinued only when stable anticoagulation is obtained (see “Important information about some of the ingredients of CEPROTIN”).

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 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.

If you have APC resistance which is a thromboembolic risk factor present in up to 5 % of the population in Europe your doctor may need to adjust your treatment accordingly.

Administration

CEPROTIN will be administered to you by intravenous injection after reconstitution of the powder for solution for injection with Sterilised Water for Injections. It is strongly recommended that every time you receive a dose of CEPROTIN the name and batch number of the product are recorded in order to maintain a record of the batches used.

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 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.

CEPROTIN should be administered at a maximum injection rate of 2 ml per minute. In children with a body weight of less than 10 kg, the injection rate should not exceed a rate of 0.2 ml/kg/min.

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

Frequency and duration of treatment depend on the severity of your protein C deficiency, on the results of determination of protein C levels in your plasma as well as on the location and extent of thrombosis.

In case of acute thrombosis CEPROTIN may be administered to you every 6 hours. As the tendency for thrombus formation decreases, the frequency may be reduced.

If you use more CEPROTIN than you should

It is recommended that you adhere to the dose level and frequency of administration as recommended by your doctor. In case you administered more CEPROTIN than recommended, please inform your doctor as soon as possible.

If you forget to use CEPROTIN

Not applicable.

If you stop using CEPROTIN

Do not stop using CEPROTIN without consulting your doctor.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You may notice any of the following side effects after administration of CEPROTIN:

- As with any product administered by infusion into a vein allergic reactions including severe and potentially life-threatening reactions (anaphylaxis) are possible.
  You should be aware of the early signs of allergic reactions such as burning and stinging at the injection site, chills, flushing, rash, hives, breathing difficulty, nausea, headache, lethargy, low blood pressure, and tightness of the chest.
- The following side effects were rarely observed during clinical studies (less than 1 case in 1,000 administrations given to patients): itching (pruritus), rash and dizziness.
- In the postmarketing experience there have been reports of restlessness, excessive sweating, and pain and redness at the injection site.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store CEPROTIN

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.
Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

The reconstituted solution should be used immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What CEPROTIN contains

Powder:
- The active substance is human protein C
- The other ingredients are human albumin, trisodium citrate dihydrate and sodium chloride. As solvent Sterilised Water for Injections is used.

What CEPROTIN looks like and contents of the pack

CEPROTIN is presented as powder and solvent for solution for injection and is a white or cream coloured powder or friable solid. After reconstitution the solution is colourless to slightly yellowish and clear to slightly opalescent and essentially free from visible particles.

Each pack also contains one transfer needle and one filter needle.

Marketing Authorisation Holder and Manufacturer

Takeda Manufacturing Austria AG
Industriestrasse 67
1221 Vienna
Austria

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Takeda Belgium NV
Tel/Tél: +32 2 464 06 11
medinfoEMEA@takeda.com

България
Такеда България ЕООД
Тел.: +359 2 958 27 36
medinfoEMEA@takeda.com

Česká republika
Takeda Pharmaceuticals Czech Republic s.r.o.
Tel: +420 234 722 722
medinfoEMEA@takeda.com

Danmark
Takeda Pharma A/S
Tlf: +45 46 77 10 10
medinfoEMEA@takeda.com

Deutschland
Takeda GmbH
Tel: +49 (0)800 825 3325
medinfoEMEA@takeda.com

Eesti
Takeda Pharma AS
Tel: +372 6177 669
medinfoEMEA@takeda.com

Ελλάδα
Takeda ΕΛΛΑΣ ΑΕ
Τηλ: +30 210 6387800
medinfoEMEA@takeda.com

España
Takeda Farmacéutica España S.A
Tel: +34 917 90 42 22
medinfoEMEA@takeda.com

France
Takeda France SAS
Tel. + 33 1 40 67 33 00
medinfoEMEA@takeda.com

Hrvatska
Takeda Pharmaceuticals Croatia d.o.o.
Tel: +385 1 377 88 96
medinfoEMEA@takeda.com

Ireland
Takeda Products Ireland Ltd
Tel: 1800 937 970
medinfoEMEA@takeda.com

Lietuva
Takeda, UAB
Tel: +370 521 09 070
medinfoEMEA@takeda.com

Luxembourg/Luxemburg
Takeda Belgium NV
Tel/Tél: +32 2 464 06 11
medinfoEMEA@takeda.com

Magyarország
Takeda Pharma Kft.
Tel: +36 1 270 7030
medinfoEMEA@takeda.com

Malta
Takeda HELLAS SA
Tel: +30 2106387800
medinfoEMEA@takeda.com

Nederland
Takeda Nederland B.V.
Tel: +31 20 203 5492
medinfoEMEA@takeda.com

Norge
Takeda AS
Tlf: +47 800 800 30
medinfoEMEA@takeda.com

Österreich
Takeda Pharma Ges.m.b.H.
Tel: +43 (0) 800-20 80 50
medinfoEMEA@takeda.com

Polska
Takeda Pharma Sp. z o.o.
Tel: +48223062447
medinfoEMEA@takeda.com

Portugal
Takeda Farmacêuticos Portugal, Lda.
Tel: + 351 21 120 1457
medinfoEMEA@takeda.com

România
Takeda Pharmaceuticals SRL
Tel: +40 21 335 03 91
medinfoEMEA@takeda.com

Slovenija
Takeda Pharmaceuticals farmacevtska družba d.o.o.
Tel: + 386 (0) 59 082 480
medinfoEMEA@takeda.com

Ísland
Vistor hf.
Sími: +354 535 7000
medinfoEMEA@takeda.com

Italia
Takeda Italia S.p.A.
Tel: +39 06 502601
medinfoEMEA@takeda.com

Κύπρος
Takeda ΕΛΛΑΣ ΑΕ
Τηλ.: +30 2106387800
medinfoEMEA@takeda.com

Latvija
Takeda Latvia SIA
Tel: +371 67840082
medinfoEMEA@takeda.com

Slovenská republika
Takeda Pharmaceuticals Slovakia s.r.o.
Tel: +421 (2) 20 602 600
medinfoEMEA@takeda.com

Suomi/Finland
Takeda Oy
Puh/Tel: 0800 774 051
medinfoEMEA@takeda.com

Sverige
Takeda Pharma AB
Tel: 020 795 079
medinfoEMEA@takeda.com

United Kingdom (Northern Ireland)
Takeda UK Ltd
Tel: +44 (0) 2830 640 902
medinfoEMEA@takeda.com

This leaflet was last approved in.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

Package leaflet: Information for the user

CEPROTIN 1,000 IU powder and solvent for solution for injection
human protein C

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any the side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What CEPROTIN is and what it is used for

CEPROTIN belongs to a class of medicines called antithrombotics. This medicine contains Protein C, a natural protein that is made in the liver and is present in your blood. Protein C plays a major role in prevention of excessive clot formation thus, prevent and/or treat intravascular thrombosis.

CEPROTIN is used in the treatment and prevention of thrombotic and haemorrhagic skin lesions (named purpura fulminans) in patients with severe congenital protein C deficiency. CEPROTIN may also be used in the treatment and prevention of a rare complication of a blood thinner medicine (anticoagulant medicine named coumarin) which may result in severe skin lesion (necrosis). Additionally, CEPROTIN may be used in the treatment of blood clot (venous thrombotic) events.

2. What you need to know before you use CEPROTIN

Do not use CEPROTIN

- if you are allergic to human protein C or any of the other ingredients of this medicine (listed in section 6) including mouse protein or heparin.

However, in the case of life-threatening thrombotic complications your doctor may still decide to continue treatment with CEPROTIN.

Warnings and precautions

Talk to your doctor or pharmacist before using CEPROTIN. Take special care with CEPROTIN if symptoms of allergy occur. Symptoms of allergy include rash, hives, breathing difficulties, low blood pressure, tightness of chest, and shock. If such symptoms occur during the administration of CEPROTIN, injection should be stopped. Such symptoms may constitute an allergic reaction to any of the components, to mouse protein or heparin. The preparation may contain traces of heparin and/or

mouse protein as a result of the manufacturing process. If such a reaction occurs, your doctor will decide on the most appropriate treatment.

If the preparation is used in patients with severe congenital protein C deficiency, antibodies inhibiting protein C may develop that can inhibit protein C and therefore diminish the effect of the preparation. However, this has not been observed in the clinical studies to date.

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of virus/infections. Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus and hepatitis C virus, and for the non-enveloped hepatitis A virus. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B 19 infection may be serious for pregnant women (foetal infection) and for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or haemolytic anaemia).

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived Protein C products.

Other medicines and CEPROTIN

No interactions with other medicinal products are currently known.
Nevertheless, please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

If you change to treatment with oral anticoagulants, treatment with CEPROTIN must continue until the blood level of the oral anticoagulation is adequate and stable.

CEPROTIN with food and drink

Not applicable.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
Your doctor will decide if CEPROTIN may be used during pregnancy and lactation.

Driving and using machines

CEPROTIN has no influence on your ability to drive or to operate machines.

CEPROTIN contains Sodium

This medicine contains 44.9 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 2.2% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use CEPROTIN

CEPROTIN is intended for intravenous administration (infusion into a vein). It is given to you under close supervision of your doctor who is experienced in substitution therapy of coagulation factors/inhibitors and where monitoring of protein C activity is possible. Dosage will vary depending on your condition and your body weight.

Dosage

The dose, administration frequency and duration of treatment depend on the severity of the protein C deficiency as well as on your clinical condition and on your plasma level of protein C. They should be adjusted accordingly on the basis of clinical effectiveness and laboratory assessment.

Treatment of acute episodes and short-term prophylaxis
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 should be administered. Your physician will take several blood drawings over time to determine how long protein C is remaining in your body.

The measurement of protein C activity using chromogenic substrates is recommended for the determination of your 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 your condition 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, dosing may be gradually reduced to 12 hourly dosing ensuring trough protein C activity >25%.

If you receive 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.

In rare cases, subcutaneous infusion of 250 - 350 IU/kg has produced therapeutic plasma protein C levels in patients with no intravenous access.

If you have kidney and/or liver disease, please inform your doctor, because he may have to adjust your treatment accordingly.

Combination treatment
If you are switched to permanent prophylaxis with oral anticoagulants, protein C replacement is to be discontinued only when stable anticoagulation is obtained (see “Important information about some of the ingredients of CEPROTIN”).

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 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, the Protein C trough level of about 10% or more is recommended to be maintained.

If you have APC resistance which is a thromboembolic risk factor present in up to 5 % of the population in Europe your doctor may need to adjust your treatment accordingly.

Administration

CEPROTIN will be administered to you by intravenous injection after reconstitution of the powder for solution for injection with Sterilised Water for Injections. It is strongly recommended that every time you receive a dose of CEPROTIN the name and batch number of the product are recorded in order to maintain a record of the batches used.

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 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.

CEPROTIN should be administered at a maximum injection rate of 2 ml per minute. In children with a body weight of less than 10 kg, the injection rate should not exceed a rate of 0.2 ml/kg/min.

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

Frequency and duration of treatment depend on the severity of your protein C deficiency, on the results of determination of protein C levels in your plasma as well as on the location and extent of thrombosis.

In case of acute thrombosis CEPROTIN may be administered to you every 6 hours. As the tendency for thrombus formation decreases, the frequency may be reduced.

If you use more CEPROTIN than you should

It is recommended that you adhere to the dose level and frequency of administration as recommended by your doctor. In case you administered more CEPROTIN than recommended, please inform your doctor as soon as possible.

If you forget to use CEPROTIN

Not applicable.

If you stop using CEPROTIN

Do not stop using CEPROTIN without consulting your doctor.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

You may notice any of the following side effects after administration of CEPROTIN:

- As with any product administered by infusion into a vein allergic reactions including severe and potentially life-threatening reactions (anaphylaxis) are possible.
  You should be aware of the early signs of allergic reactions such as burning and stinging at the injection site, chills, flushing, rash, hives, breathing difficulty, nausea, headache, lethargy, low blood pressure, and tightness of the chest.
- The following side effects were rarely observed during clinical studies (less than 1 case in 1,000 administrations given to patients): itching (pruritus), rash and dizziness.
- In the postmarketing experience there have been reports of restlessness, excessive sweating, and pain and redness at the injection site.

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store CEPROTIN

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.
Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.

The reconstituted solution should be used immediately.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What CEPROTIN contains

Powder:
- The active substance is human protein C
- The other ingredients are human albumin, trisodium citrate dihydrate and sodium chloride. As solvent Sterilised Water for Injections is used.

What CEPROTIN looks like and contents of the pack

CEPROTIN is presented as powder and solvent for solution for injection and is a white or cream coloured powder or friable solid. After reconstitution the solution is colourless to slightly yellowish and clear to slightly opalescent and essentially free from visible particles.

Each pack also contains one transfer needle and one filter needle.

Marketing Authorisation Holder and Manufacturer

Takeda Manufacturing Austria AG
Industriestrasse 67
1221 Vienna
Austria

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Takeda Belgium NV
Tel/Tél: +32 2 464 06 11
medinfoEMEA@takeda.com

България
Такеда България ЕООД
Тел.: +359 2 958 27 36
medinfoEMEA@takeda.com

Česká republika
Takeda Pharmaceuticals Czech Republic s.r.o.
Tel: +420 234 722 722
medinfoEMEA@takeda.com

Danmark
Takeda Pharma A/S
Tlf: +45 46 77 10 10
medinfoEMEA@takeda.com

Deutschland
Takeda GmbH
Tel: +49 (0)800 825 3325
medinfoEMEA@takeda.com

Eesti
Takeda Pharma AS
Tel: +372 6177 669
medinfoEMEA@takeda.com

Ελλάδα
Takeda ΕΛΛΑΣ ΑΕ
Τηλ: +30 210 6387800
medinfoEMEA@takeda.com

España
Takeda Farmacéutica España S.A
Tel: +34 917 90 42 22
medinfoEMEA@takeda.com

France
Takeda France SAS
Tel. + 33 1 40 67 33 00
medinfoEMEA@takeda.com

Hrvatska
Takeda Pharmaceuticals Croatia d.o.o.
Tel: +385 1 377 88 96
medinfoEMEA@takeda.com

Ireland
Takeda Products Ireland Ltd
Tel: 1800 937 970
medinfoEMEA@takeda.com

Lietuva
Takeda, UAB
Tel: +370 521 09 070
medinfoEMEA@takeda.com

Luxembourg/Luxemburg
Takeda Belgium NV
Tel/Tél: +32 2 464 06 11
medinfoEMEA@takeda.com

Magyarország
Takeda Pharma Kft.
Tel: +36 1 270 7030
medinfoEMEA@takeda.com

Malta
Takeda HELLAS SA
Tel: +30 2106387800
medinfoEMEA@takeda.com

Nederland
Takeda Nederland B.V.
Tel: +31 20 203 5492
medinfoEMEA@takeda.com

Norge
Takeda AS
Tlf: +47 800 800 30
medinfoEMEA@takeda.com

Österreich
Takeda Pharma Ges.m.b.H.
Tel: +43 (0) 800-20 80 50
medinfoEMEA@takeda.com

Polska
Takeda Pharma Sp. z o.o.
Tel: +48223062447
medinfoEMEA@takeda.com

Portugal
Takeda Farmacêuticos Portugal, Lda.
Tel: + 351 21 120 1457
medinfoEMEA@takeda.com

România
Takeda Pharmaceuticals SRL
Tel: +40 21 335 03 91
medinfoEMEA@takeda.com

Slovenija
Takeda Pharmaceuticals farmacevtska družba d.o.o.
Tel: + 386 (0) 59 082 480
medinfoEMEA@takeda.com

Ísland
Vistor hf.
Sími: +354 535 7000
medinfoEMEA@takeda.com

Italia
Takeda Italia S.p.A.
Tel: +39 06 502601
medinfoEMEA@takeda.com

Κύπρος
Takeda ΕΛΛΑΣ ΑΕ
Τηλ.: +30 2106387800
medinfoEMEA@takeda.com

Latvija
Takeda Latvia SIA
Tel: +371 67840082
medinfoEMEA@takeda.com

Slovenská republika
Takeda Pharmaceuticals Slovakia s.r.o.
Tel: +421 (2) 20 602 600
medinfoEMEA@takeda.com

Suomi/Finland
Takeda Oy
Puh/Tel: 0800 774 051
medinfoEMEA@takeda.com

Sverige
Takeda Pharma AB
Tel: 020 795 079
medinfoEMEA@takeda.com

United Kingdom (Northern Ireland)
Takeda UK Ltd
Tel: +44 (0) 2830 640 902
medinfoEMEA@takeda.com

This leaflet was last approved in.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.