Summary of risk management plan for CEPROTIN (Human Protein C)

This is a summary of the risk management plan (RMP) for CEPROTIN. The RMP details important risks of CEPROTIN, how these risks can be minimised, and how more information will be obtained about CEPROTIN's risks and uncertainties (missing information).

CEPROTIN's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how CEPROTIN should be used.

This summary of the RMP for CEPROTIN should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of CEPROTIN's RMP.

I. The medicine and what it is used for

CEPROTIN is currently indicated in purpura fulminans (PF) and coumarin-induced skin necrosis (CISN) in patients with Severe Congenital Protein C Deficiency (SCPCD). Furthermore, CEPROTIN is indicated for short-term prophylaxis in patients with SCPCD if one or more of the following conditions are met (1) surgery or invasive therapy is imminent, (2) while initiating coumarin therapy, (3) when coumarin therapy alone is not sufficient; and (4) when coumarin therapy is not feasible (see SmPC for the full indication). It contains human protein C as the active substance, and it is given by intravenous route. An initial dose of 60 to 80 International Unit/Kilogram for determination of recovery and half-life is advised. The dose should be adjusted on the basis of laboratory assessment for each individual case.

Further information about the evaluation of CEPROTIN's benefits can be found in CEPROTIN's EPAR, including in its plain-language summary, available on the European Medicine Agency (EMA) website, under the medicine's webpage: *https://www.ema.europa.eu/en/medicines/human/EPAR/ceprotin*.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of CEPROTIN, together with measures to minimise such risks and the proposed studies for learning more about CEPROTIN's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment - include PSUR statement only if product has PSUR requirements so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of CEPROTIN is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of CEPROTIN are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of CEPROTIN. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs

further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Hypersensitivity to the active substance or to any of the excipients or to mouse protein or heparin.
Important potential risks	• Bleeding episodes • Transmission of infectious agents • Inhibitor development • Heparin induced thrombocytopenia
Missing information	• The effects of CEPROTIN on fertility, pregnancy, and lactation have not been established in clinical trials Use in patients with moderate or severe hepatic impairment • No clinical data on use of CEPROTIN in patients with renal and/or hepatic impairment • No clinical data on use of CEPROTIN in patients aged ≥ 65 years

II.B Summary of important risks

Hypersensitivity to the active substance or to any of the excipients or to mouse protein or heparin	
Evidence for linking the risk to the medicine	SmPC, PSUR, medical literature.
Risk factors and risk groups	Patients with previous history of hypersensitivity to CEPROTIN or any other constituents of the product. 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 (Heparin-induced thrombocytopenia).
Risk minimisation measures	**Routine risk minimisation measures** 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, and tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, they should inform the physician. Immediate discontinuation of product use is advised. **Additional risk minimisation measures** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Hypersensitivity to the active substance or to any of the excipients or to mouse protein or heparin

Bleeding episodes	
Evidence for linking the risk to the medicine	SmPC, medical literature.
Risk factors and risk groups	Patients taking anti-coagulation medication in addition to CEPROTIN may be at an increased risk for bleeding episodes.
Risk minimisation measures	**Routine risk minimisation measures** 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. **Additional risk minimisation measures** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Transmission of infectious agents	
Evidence for linking the risk to the medicine	SmPC, medical literature.
Risk factors and risk groups	Patients with increased exposure to human blood or plasma- derived products have an increased risk of viral transmission.
Risk minimisation measures	**Routine risk minimisation measures** 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 infectious 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 Human immunodeficiency virus, Hepatitis B virus and Hepatitis C virus and for the non-enveloped virus Hepatitis A virus. The measures taken may be of limited value against nonenveloped viruses such as Parovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

Hypersensitivity to the active substance or to any of the excipients or to mouse protein or heparin	
	Appropriate vaccination (hepatitis A and B) should be considered for patients in regular / repeated receipt of human plasma-derived Protein C products. It is strongly recommended that every time that CEPROTIN is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product. **Additional risk minimisation measures** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Inhibitor development	
Evidence for linking the risk to the medicine	SmPC, medical literature.
Risk factors and risk groups	Patients receiving protein C replacement therapy.
Risk minimisation measures	**Routine risk minimisation measures** None. **Additional risk minimisation measures** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** None.

Heparin induced thrombocytopenia (HIT)	
Evidence for linking the risk to the medicine	SmPC, medical literature.
Risk factors and risk groups	Patients administered heparin concurrently with CEPROTIN.
Risk minimisation measures	**Routine risk minimisation measures** 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 (heparin induced thrombocytopenia [HIT]). In patients with HIT, symptoms such as arterial and venous thrombosis, Disseminated intravascular coagulation, purpura, petechial 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

Inhibitor development	
	complicated by the fact that these symptoms may already be present in acute phase patients with SCPCD. Patients with HIT should avoid the use of heparin containing drugs in the future. **Additional risk minimisation measures** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities** None.

Missing information: The effects of CEPROTIN on fertility, pregnancy, and lactation have not been established in clinical trials	
Risk minimisation measures	**Routine risk minimisation measures** None. **Additional risk minimisation measures** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: None.

Missing information: No clinical data on use of CEPROTIN in patients with renal and/or hepatic impairment	
Risk minimisation measures	**Routine risk minimisation measures** 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. **Additional risk minimisation measures** None.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Missing information: No clinical data on use of CEPROTIN in patients aged ≥ 65 years	
Risk minimisation measures	**Routine risk minimisation measures** None. **Additional risk minimisation measures** None.
Additional pharmacovigilance	**Additional pharmacovigilance activities:**

Missing information: No clinical data on use of CEPROTIN in patients aged ≥ 65 years	
activities	None.

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

There are no studies, which are conditions of the marketing authorisation or specific obligation of human protein C.

II.C.2. Other studies in post-authorisation development plan

There are no studies required for human protein C