Part VI: Summary of the risk management plan.

Summary of risk management plan for Prothromplex Total (human prothrombin complex).

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

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

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

I. The medicine and what it is used for:

Prothromplex Total is authorised for treatment of bleeding and perioperative prophylaxis of bleeding in acquired deficiency of prothrombin complex coagulation factors, such as a deficiency caused by treatment with vitamin K antagonists or in case of overdose with vitamin K antagonists, when rapid correction of the deficiency is required; and treatment and perioperative prophylaxis of haemorrhages in congenital deficiency of vitamin K-dependent coagulation factors, when purified specific coagulation factor concentrate is not available (see SmPC for the full indication). It contains human prothrombin complex as the active substance, and it is given by intravenous route of administration.

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

Important risks of Prothromplex Total, together with measures to minimise such risks and the proposed studies for learning more about Prothromplex Total 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 PSUR assessment 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 Prothromplex Total is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information.

Important risks of Prothromplex Total 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 Prothromplex Total. 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).

Table 26. List of important risks and missing information.

Important identified risks	Hypersensitivity reactions, including anaphylactic reactions.
	Thrombosis and Disseminated intravascular coagulation (DIC).
Important potential risks	Viral transmission.
	Inhibitor formation.
Missing information	Clinical data on safety in pregnant and breast-feeding women.

II.B Summary of important risks.

Table 27. Important identified risk: Hypersensitivity reactions, including anaphylactic reactions.

Evidence for linking the risk to the medicine	SmPC Heparin-associated allergic reactions have been reported in the literature to both unfractionated (UF) and low molecular weight heparins, but these reactions are quite rare. The spectrum of hypersensitivity reactions to heparin includes heparin-induced immune thrombocytopenia, delayed-type skin reactions, and allergic vasculitis. Heparin-induced thrombocytopenia occurs in about 1-4% of patients treated with UF heparin.
Risk factors and risk groups	Patients with previous hypersensitivity to active substance, heparin, excipients or any components.
Risk minimisation measures	**Routine risk minimisation measures** Section 4.3 *Contraindications,* of the SmPC. Section 4.4 *Special warnings and precautions for use*, of the SmPC. **Additional risk minimisation measures:** No additional risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Table 28. Important identified risk: Thrombosis and DIC

Evidence for linking the risk to the medicine	SmPC There have been reports of possible thrombosis after Prothrombin complex concentrate (PCC) therapy in the literature. It should be noted that in all of these cases, the patients receiving PCCs had increased risk of thrombosis due to medical history or current illness. As this reflects the usual context of PCC administration, a small number of complications may be expected. Thus, the possibility that PCC administration has some influence over the risk

Table 28. Important identified risk: Thrombosis and DIC

	cannot be excluded. However, in most recent cases in the literature, it seems unlikely that PCC alone was the cause of the thrombotic events.
Risk factors and risk groups	Therapy factors: • Use of high doses • Rapid infusion • Repetitive doses Predisposing clinical factors: • Liver disease • Antithrombin deficiency • Acquired disorders of hemostasis (large muscle hematomas, immobilization, surgery) • Congenital coagulation factor deficiency (isolated factor VII deficiency) • Quality of the PCC used
Risk minimisation measures	**Routine risk minimisation measures:** Section 4.4 *Special warnings and precautions for use*, of the SmPC. Section 4.9 *Overdose*, of the SmPC. **Additional risk minimisation measures:** No additional risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Table 29 Important potential risk: Viral transmission

Evidence for linking the risk to the medicine	SmPC As PCCs are produced from human plasma, they must undergo at least one viral reduction or elimination step (namely solvent/ detergent treatment, nanofiltration and/or pasteurization) to minimise the risk of virus transmission. These steps are effective for the inactivation and reduction of viruses including HIV, Hepatitis B and Hepatitis C. Thus, the risk of virus transmission with any PCC is considered minimal. In a recent systematic review conducted to evaluate the safety of PCCs, the risk of viral transmission appeared to be low.
Risk factors and risk groups	Patients with increased exposure to blood or plasma-derived products have an increased risk of viral transmission.

Table 29 Important potential risk: Viral transmission

Risk minimisation measures	**Routine risk minimisation measures** Section 4.4 *Special warnings and precautions for use,* of the SmPC. **Additional risk minimisation measures:** No additional risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Table 30 Important potential risk: Inhibitor formation

Evidence for linking the risk to the medicine	Since there have been no reports of inhibitor formation associated with Prothromplex Total, the information presented here was based on drugs of the same class (Advate and Recombinate). The exact rate of Factor IX inhibitor formation in individuals with prothrombin complex deficiency is unknown. However, in persons with hemophilia (PWH) B, approximately 30-45% have the severe form of the disease, and the development of inhibitory antibodies (which result in the neutralization of coagulation factor activity following infusion of Factor IX) is seen in about 1-3% of those with severe hemophilia B. In a recent retrospective study, inhibitor formation was observed in 3.89% of hemophilia B subjects receiving a Factor IX product.
Risk factors and risk groups	Severity of prothrombin complex deficiency, race, ethnicity, family history of inhibitors, and age (age at first factor replacement therapy) are all risk factors for the development of inhibitors.
Risk minimisation measures	**Routine risk minimisation measures:** Section 4.8 *Undesirable effects,* of the SmPC. **Additional risk minimisation measures:** No additional risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None.

Table 31 Missing information: Clinical data on safety in pregnant and breast-feeding women.

Risk minimisation measures	**Routine risk minimisation measures:** Section 4.6 *Fertility, pregnancy and lactation,* of the SmPC.

Table 31 Missing information: Clinical data on safety in pregnant and breast-feeding women.

	Additional risk minimisation measures: No additional risk minimisation activities.
Additional pharmacovigilance activities	**Additional pharmacovigilance 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 Prothromplex Total.

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

There are no studies required for Prothromplex Total.