VI.1 Elements for Summary Tables in the European Public Assessment Report (EPAR)

VI.1.1 Summary Table of Safety Concerns

Summary of Safety Concerns	
Important identified risks	• Use of Prothromplex Total in patients with hypersensitivity to active substance or heparin • Thrombosis and disseminated intravascular coagulation • Lack of effect
Important potential risks	• Risk of viral transmission • Inhibitor formation • Off-label use, in terms of a broader use, such as perioperative bleeding in patients without anticoagulant therapy
Important missing information	• Lack of clinical data in pregnancy or lactation • Lack of clinical data in pediatric patients

VI.1.2 Table of On-Going and Planned Additional Phv Studies/Activities in the Pharmacovigilance Plan

There are currently no on-going or planned additional PV studies or activities in the pharmacovigilance plan; routine pharmacovigilance and risk minimization measures are considered sufficient at this time.

VI.1.3 Summary of Post-Authorization Efficacy Development Plan

There are no post-authorization efficacy studies planned or ongoing.

VI.1.4 Summary Table of Risk Minimization Measures

Safety Concern	**Routine Risk Minimization Activities**	**Additional Risk Minimization Activities**
Use of Prothromplex Total in patients with hypersensitivity to active substance or heparin	Contraindications Section 4.3 of SmPC: • Hypersensitivity to the active substance or to any of the excipients. • Known allergy to heparin or anamnestically known heparin-induced thrombocytopenia. Special warnings and precautions for use Section 4.4 of SmPC: Allergic-type hypersensitivity reactions including anaphylactic reactions and anaphylactic shock have been reported with Prothromplex Total. If allergic or anaphylactic-type reactions	None proposed

	occur, the injection/ infusion should be stopped immediately. In the case of shock standard medical treatment for shock should be implemented	
Thrombosis and disseminated intravascular coagulation	Special warnings and precautions for use Section 4.4 of the SmPC: There is a risk of thrombosis and disseminated intravascular coagulation (DIC) when patients, with either congenital or acquired deficiency, are treated with human prothrombin complex concentrates, including Prothromplex Total, particularly with repeated dosing. Arterial and venous thromboembolic events including myocardial infarction, cerebrovascular accident (e.g. stroke), pulmonary embolism as well as DIC have been reported with Prothromplex Total. The risk may be higher in treatment of isolated FVII deficiency, since the other vitamin K-dependent coagulation factors, with longer half lives, may accumulate to levels considerably higher than normal. Patients given human prothrombin complex concentrates should be observed closely for signs and symptoms of intravascular coagulation or thrombosis. Because of the risk of thromboembolic complications, particularly close monitoring should be exercised when administering prothrombin complex concentrates to • patients with a history of coronary heart disease • patients with liver disease • pre or post-operative patients • neonates • other patients at risk of thromboembolic events or disseminated intravascular coagulation In each of these situations, the potential benefit of treatment should be weighed against the risk of these complications. Overdose Section 4.9 of the SmPC states: The use of high doses of human plasma prothrombin complex products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. Therefore in case of overdose, the risk of development of	None proposed

	thromboembolic complications or disseminated intravascular coagulation is enhanced.	
Lack of effect	Lack of effect may be associated with drug potency or inhibitor development. Undesirable effects Section 4.8 of the SmPC: Replacement therapy with human prothrombin complex concentrates, including therapy with Prothromplex Total, may result in the formation of circulating antibodies inhibiting one or more of the human prothrombin complex factors. If such inhibitors occur, the condition will manifest itself as a poor clinical response.	None proposed
Risk of viral transmission	Special warnings and precautions for use Section 4.4 of SmPC states: Standard measures to prevent infections which can be transmitted by medicinal products made from human blood or plasma include donor selection, testing of individual donations and plasma pools for specific infection markers and the execution of effective manufacturing steps to inactivate / remove viruses. Nevertheless, when medicinal products prepared from human blood or plasma are administered, infectious diseases due to transmission of infective agents – also of a hitherto unknown nature – cannot be completely ruled out. These measures are considered effective against enveloped viruses such as HIV, HBV and HCV as well as against the non-enveloped HAV virus. 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 (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia). When a medicinal product prepared from human blood or plasma is administered regularly / repeatedly, appropriate vaccinations (hepatitis A and B) must be considered. In the patient's interests, it is strongly recommended that each administration of Prothromplex Total is documented with the enclosed self-adhesive label in the medical	None proposed

	record.	
Inhibitor formation	Undesirable effects Section 4.8 of the SmPC: Replacement therapy with human prothrombin complex concentrates, including therapy with Prothromplex Total, may result in the formation of circulating antibodies inhibiting one or more of the human prothrombin complex factors. If such inhibitors occur, the condition will manifest itself as a poor clinical response.	None proposed
Off-label use, in terms of a broader use, such as perioperative bleeding in patients without anticoagulant therapy		None proposed
Lack of clinical data in pregnancy or lactation	Fertility, pregnancy and lactation Section 4.6 of the SmPC: There is no information on the effects of Prothromplex Total on fertility. There are no adequate data from the use of Prothromplex Total in pregnant or lactating women. Healthcare providers should carefully consider the potential risks and benefits for each specific patient before Prothomplex Total is used. Animal studies are not suitable to assess the safety with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Therefore Prothromplex Total should be used during pregnancy and lactation only if clearly indicated.	None proposed
Lack of clinical data in pediatric patients	Posology and method of administration Section 4.2 of the SmPC: <u>Pediatric population</u> The safety and efficacy of the use of Prothromplex Total in paediatric patients have not been established in Baxter clinical trials.	None proposed

VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

A combined deficiency of vitamin K-dependent clotting factors II, VII, IX, and X (and proteins C, S, and Z) is usually caused by liver disease, malabsorption, or warfarin overdose.

The number of individuals who receive long-term oral anticoagulant therapy (e.g., coumarin, warfarin), for the treatment and prevention of blood clot diseases has increased dramatically in recent years. Approximately 1-2% of the general population is treated with oral anticoagulants. Oral anticoagulants provide antithrombotic benefits but also increase the risk of severe and potentially fatal bleeding. Each year, approximately 3% to 7% of vitamin K-antagonist treated patients require rapid reversion of the anticoagulant effect in cases of overdose, active bleeding episodes, or for urgent surgery.

The medical need for urgent reversal or urgent warfarin reversal is confirmed by large scale epidemiological studies which show that in patients receiving oral anticoagulant therapy, the yearly occurance of major bleeding complications ranged from 1.1% to 1.5%, stomach and intestines and brain being the most frequently involved (30-60% and 17-30%, respectively). Factors related to an increased risk of bleeding include anticoagulation intensity, variability, and duration, age, patient co-morbidity and concomitant treatments.

VI.2.2 Summary of Treatment Benefits

Prothromplex Total 600 IU is a preparation made from human plasma (the liquid part of the blood). It contains the coagulation factors II, VII, IX, and X (prothrombin complex coagulation factors). These coagulation factors are vitamin K-dependent and they play an important role in blood coagulation. In the event of a deficiency of one or more of these factors, blood does not coagulate as rapidly as usually, which leads to an increased bleeding tendency.

Prothromplex Total 600 IU is used for:

Acquired deficiency of the prothrombin complex coagulation factors

- For the treatment of bleeding
- For the prevention of bleeding immediately before or after surgery. A deficiency of the vitamin K-dependent coagulation factors may be caused, for example, by a treatment with or an overdosage of medicinal products which reduce the effect of vitamin K (so-called vitamin K antagonists).

Congenital deficiency of the coagulation factors II, VII, IX and X

- For the treatment of bleeding
- For the prevention of bleeding immediately before or after surgery, provided that the appropriate individual factor concentrates is not available.

Minor bleeding caused by overdose with oral anticoagulants or by interactions of oral anticoagulants with other drugs can be treated with prothrombin complex concentrate (PCC), such as Prothromplex Total. PCC should also be given to prevent disease infections prior to surgery in patients undergoing oral anticoagulation. PCC is the treatment of choice since these preparations can raise prothrombin complex factor levels more rapidly and more extensively than fresh frozen plasma (FFP).

Lack of primary vitamin K is not common in healthy persons. The reasons for the lack in the vitamin K-dependent coagulation factors are mainly secondary to diseases or drug therapy (Olson 1987), for example bleeding in the newborn, dietary inadequacy, total parenteral nutrition, biliary obstruction, malabsorption syndromes, or drug therapy (broad-spectrum antibiotics including cephalosporins, megadoses of vitamins A and E). The administration of vitamin K in most cases is adequate for the treatment of the coagulation disorders. However, in acute life-threatening situations, replacement therapy with PCC is indicated (Ansell et al, 1977).

Severe liver insufficiency results in reduced levels of the vitamin K-dependent coagulation factors. Severe bleeding and prophylactic treatment before surgery are therefore considered indications for the administration of PCC in patients with liver diseases.

A congenital deficiency in factors II, VII, IX, and X may be diagnosed either for one factor or for a combination of more than one factors. Congenital factor VII and IX deficiencies are the most common.

Lack of factor II (prothrombin) is a rare autosomal recessive disorder that occurs in approximately 1 in 2 million people (Meeks et al, 2008). The prevention of bleeding activity of prothrombin is thought to be between 20% and 40%. Low prothrombin activity typically prolongs both the activated partial thromboplastin time (aPTT) and prothrombin time (PT). Diagnosis is confirmed by plasma prothrombin level assay. Both FFP and PCC contain prothrombin and may be used for treatment.

Congenital factor VII deficiency is rare, accounting for one symptomatic individual per 500,000 people. Clinical manifestations are heterogeneous, ranging from severe life-threatening hemorrhages, such as cerebral, gastrointestinal, and joint hemorrhages, to minor bleeding. Alternative therapeutic options are available, including highly purified plasma-derived FVII concentrate or recombinant activated factor VII, which are considered the treatments of choice.

Congenital factor IX deficiency (hemophilia B) is the most common congenital prothrombin complex factor deficiency. PCC such as Prothromplex Total, which contain factor IX, have been used for more than 30 years to treat hemophilia B. Nowadays, preference is given to purer factor IX concentrates and recombinant factor IX (Keeling et al, 2008), which are considered the treatments of choice.

Isolated, congenital factor X deficiency seems to occur more frequently than factor II deficiency, but nonetheless constitutes an extremely rare coagulation disorder (1 in every 1 000 000 people) (Menegatti et al, 2009). The clinical presentation of factor X deficiency places it among the most severe of the rare coagulation defects, typically including hemarthroses, hematomas, and umbilical cord, gastrointestinal, and central nervous system bleeding. Diagnosis is based on the concomitant prolongation of the PT and aPTT, and plasma factor X level assay. There is no specific factor X concentrate available, and current treatment includes the administration of FFP or PCC (Menegatti et al, 2009).

VI.2.3 Unknowns Relating to Treatment Benefits

The safety of human prothrombin complex concentrates for use in human pregnancy and during lactation has not been established. Therefore, human prothrombin complex should be used during pregnancy and lactation only if clearly indicated.

There is no restriction in the Prothromplex Total label in regards to pediatric use. However, there have been no well-controlled studies to assess the safety of human prothrombin complex concentrates for use in the pediatric population.

VI.2.4 Summary of Safety Concerns

Important Identified Risks

Risk	What is Known	Preventability
Severe sudden allergic reaction (Use of Prothromplex Total in patients with hypersensitivity to active substance or heparin)	There is a rare possibility of developing a severe sudden allergic reaction (anaphylactic reaction) to Prothromplex Total.	Monitoring for early symptoms of allergic reaction such as: - erythema (reddening of the skin) - skin rash - appearance of hives on the skin (nettle rash/urticaria) - itching anywhere on the body - swelling of lips and tongue - breathing difficulties/dyspnoea

Risk	What is Known	Preventability
		- tightness of the chest - general indisposition - dizziness - drop in blood pressure
Blood clots (Thrombosis and disseminated intravascular coagulation)	Blood clots (thromboses) may develop and be washed into the blood stream (embolisms). This may lead to complications such as heart attack, an increased consumption of blood platelets and blood coagulation factors with pronounced blood clot formation in the blood vessels (consumption coagulopathy), occlusion of the veins through blood clots (venous thrombosis) and occlusion of a lung vessel through a blood clot (pulmonary infarction).	The use of antithrombin and heparin
The drug is not working as it should (Lack of effect)	May be associated with drug strength or inhibitor development. The development of inhibitors may display as a lack of a clinical response.	Monitor cases of drug ineffectiveness evaluating the potency of Prothromplex Total and possibility of inhibitor development.

Important Potential Risks

Risk	What is known
Develop a resistance (inhibitors) to one or several of the coagulation factors (Inhibitor formation)	Patients may develop a resistance (inhibitors) to one or several of the coagulation factors, with subsequent inactivation of the blood coagulation factors.
Risk of viral transmission	Prothromplex Total is prepared from human plasma (the liquid component of blood). 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 and 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 unknown or emerging

Risk	What is known
	viruses or other types of infections.
Off-label use, in terms of a broader use, such as perioperative bleeding in patients without anticoagulant therapy	There may be a potential for broader use of prothrombin complexes, such as perioperative bleeding in patients without anticoagulant therapy. This is not encouraged.

Important Missing Information

Risk	What is known
Lack of clinical data in pregnancy or lactation	The safety of human prothrombin complex concentrates for use in human pregnancy and during lactation has not been established. Therefore, human prothrombin complex should be used during pregnancy and lactation only if clearly indicated.
Lack of clinical data in pediatric patients	There is no restriction in the Prothromplex label in regards to pediatric use. However, there have been no well-controlled studies to assess the safety of human prothrombin complex concentrates for use in the pediatric population.

VI.2.5 Summary of Additional Risk Minimization Measures by Safety Concern

There are no additional risk minimization measures in place for Prothromplex Total.

VI.2.6. Planned Post-Authorization Development Plan

There are no post-authorization studies planned for Prothromplex Total.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan Over Time			
Version	**Date**	**Safety Concerns**	**Comment**
1.0	24 November 2009	Important Identified Risks: • Use of Prothromplex Total in patients with hypersensitivity to active substance or heparin • Thrombosis/Disseminated intravascular coagulation • Inhibitor formation • Lack of Effect Important Potential Risk: • Risk of viral transmission	

		Important Missing Information: • Use of Prothromplex Total during pregnancy and lactation • Use of Prothromplex Total in pediatric patients	
2.0	02 August 2010	Important Identified Risks: • Use of Prothromplex Total in patients with hypersensitivity to active substance or heparin • Thrombosis/Disseminated intravascular coagulation • Inhibitor formation • Lack of Effect	A new safety concern, off-label use, in terms of a broader use, such as perioperative bleeding in patients without anticoagulant therapy, was identified and added. This addition was requested by the Austrian authorities (AGES) in its role as the RMS.
		Important Potential Risk: • Risk of viral transmission • Off-label use, in terms of broader use, such as perioperative bleeding in patients without anticoagulant therapy	
		Important Missing Information: • Use of Prothromplex Total during pregnancy and lactation • Use of Prothromplex Total in pediatric patients	
3.0	27 August 2010	Important Identified Risks: • Use of Prothromplex Total in patients with hypersensitivity to active substance or heparin • Thrombosis/Disseminated intravascular coagulation • Inhibitor formation • Lack of Effect	The RMP was updated to version 3.0 (issued 27Aug2010) because of a new SmPC with updated pediatric wording, which was requested by the Austrian authority. The sentence “however, the use of Prothromplex Total 600 IU in the pediatric population is referenced in the medical literature” was deleted from the SmPC and RMP.
		Important Potential Risk: • Risk of viral transmission • Off-label use, in terms of broader use, such as perioperative bleeding in patients without anticoagulant therapy	

		Important Missing Information: • Use of Prothromplex Total during pregnancy and lactation • Use of Prothromplex Total in pediatric patients	
4.0	20 March 2013	Important Identified Risks: • Use of Prothromplex Total in patients with hypersensitivity to active substance or heparin • Thrombosis and disseminated intravascular coagulation • Lack of Effect	At the request of AGES, was the change in classification of inhibitor formation from identified to important potential risk.
		Important Potential Risk: • Inhibitor formation • Risk of viral transmission • Off-label use, in terms of broader use, such as perioperative bleeding in patients without anticoagulant therapy	
		Important Missing Information: • Lack of clinical data in pregnancy or lactation • Lack of clinical data in pediatric patients	