Confidex®(Beriplex®)

(Human Prothrombin Complex Concentrate)

Public Summary of Risk Management Plan

(Extract from the EU Risk Management Plan Version 3.0; 29-Oct-2020)

Part VI: Summary of the risk management plan

Summary of Risk Management Plan for Beriplex P/N (Human Prothrombin Complex Concentrate)

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

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

I. The medicine and what it is used for

Beriplex is authorized for treatment and perioperative prophylaxis of bleeding in acquired deficiency of the prothrombin complex coagulation factors and in some countries congenital deficiency of any of the vitamin K-dependent coagulation factors (see SmPC for the full indication). It contains Prothrombin Complex Concentrate (Human) as the active substance and it is given by injection.

II. Risks associated with the medicine and activities to minimize or further characterize the risks

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

- Measures to minimize 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 authorized 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 minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Safety Update Report (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 if Beriplex is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Beriplex are risks that need special risk management activities to further investigate or minimize 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 Beriplex. 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 (eg, on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Thromboembolic events
Important potential risks	• Transmission of infectious agents
Missing information	• Not applicable

II.B Summary of important risks

Important identified risk: Thromboembolic events	
Evidence for linking the risk to the medicine	Thromboembolic events (TEEs) are a known class effect for plasma derived coagulation factor products. It is established that reversal of anticoagulant therapy with Prothrombin Complex Concentrates (or any other therapy) may be associated with TEEs as patients have a pre-existing risk for TEEs; however, it is difficult to differentiate the risk of the therapy used for anticoagulant reversal from the underlying risk of thrombosis, which initially required anticoagulation. Cases reporting TEEs have been received from multiple sources including clinical trials, post-marketing data, and published literature. There have been reported cases with Beriplex which provided evidence of a causal association.
Risk factors and risk groups	Lack of anticoagulation in patients with existing thromboembolic risks is considered a major risk factor contributing to TEEs. Cardiovascular risk factors (coronary heart disease, myocardial infarction (MI), cardiac valve disease, artificial cardiac valves and atrial fibrillation).

	Risk factors for thrombosis include smoking, age, immobility, postoperative status, and liver disease. Risk factors due to serious medical situations of bleeding conditions.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • SmPC Section 4.8 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • FDA post-marketing requirement study, BE1116-4001

Important potential risk: Transmission of infectious agents	
Evidence for linking the risk to the medicine	The potential for transmitting infectious agents is a known class effect of all blood/plasma-driven products. Cases of suspected viral transmission have been reported for Beriplex from multiple sources including post-marketing data and published literature, however none are confirmed cases of virus transmission. For this reason, the potential for transmission of infectious agents is considered an important potential risk for Beriplex.
Risk factors and risk groups	Hepatitis B and C are increased with exposure to other blood products and increased in intravenous drug users and homosexuals. Parvovirus B19 is a common infectious pathogen in humans and is acquired during childhood.
Risk minimization measures	Routing risk minimization measures: • SmPC Section 4.4 Additional risk minimization measures: None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: None

II.C Post-authorization development plan

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

There are no studies which are conditions of the EU marketing authorization or specific obligation of Beriplex.

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

US FDA post-marketing requirement study: BE1116_4001

An observational cohort study of the risk of TEEs among adult patients treated with Kcentra compared with plasma for urgent reversal of VKA therapy in the setting of acute major bleeding.
Purpose of the study: To assess the safety of Beriplex based on TEE and mortality.