Confidex®

(Human Prothrombinex Complex Concentrate)

Public Summary of Risk Management Plan

(Extract from the EU Risk Management Plan Version 2.0; 17-Mar-2017)

VI.2 Elements for a Public Summary

VI.2.1 Overview of Disease Epidemiology

People who have a risk of getting dangerous blood clots are sometimes treated with medicines called vitamin K antagonists (VKAs). Because they prevent the blood from clotting, VKAs can cause serious bleeding that will not stop. Serious bleeding caused by VKA treatment happens in 1 to 7 out of 100 people per year.

The bleeding caused by VKAs can be harmless, but can also be deadly. For example, bleeding inside the head leads to death or disability in 76 out of 100 people that it happens to. Bleeding in body parts other than the head leads to death in 10 to 15 out of 100 people that it happens to.

The main treatments used to stop bleeding caused by treatment with VKAs are vitamin K with prothrombin complex concentrate. Beriplex is a prothrombin complex concentrate. In many countries, Beriplex is a common treatment for serious bleeding caused by VKAs. Beriplex is also used to prevent bleeding during surgery in patients on VKAs.

VI.2.2 Summary of Treatment Benefits

A total of 442 people participated in 4 main studies to test how well Beriplex works.

The main European Union study tested how Beriplex works to stop or prevent blood clotting in 43 people with serious bleeding due to VKA treatment or in preventing bleeding during surgery. This was done by measuring the international normalized ratio (INR), which tells us how quickly the blood clots. The study looked to see if INR values went down after treatment with Beriplex. The study showed that bleeding was sufficiently reduced in all patients.

There were 2 studies in the United States (US). One study tested how Beriplex works in 212 people with serious bleeding due to VKA treatment and the other tested how Beriplex works to prevent bleeding when given before urgent surgery. Both studies compared how well and how fast Beriplex stopped bleeding or prevented bleeding due to VKA treatment compared to treatment with fresh frozen plasma (FFP). The studies showed that Beriplex was as good, or better, than FFP. More people treated with Beriplex stopped bleeding than people treated with FFP.

One study was conducted to evaluate Beriplex in Japanese patients. The effect of Beriplex was rated based on its ability to reduce the INR and to control bleeding. This study showed that Beriplex works in Japanese patients just as well as in the rest of the world where it has been studied.

VI.2.3 Unknowns Relating to Treatment Benefits

In the Beriplex studies, patients were aged between 18 and 96-years-old, with most patients aged over 60 years, and nearly all patients were White. There was no evidence to suggest that Beriplex would have any different effects in younger or non-White patients.

Summary of Safety Concerns

Table 34: Important identified risks

Risk	What is known	Preventability
Allergic reactions (hypersensitivity)	These are unwanted effects that may occur during injection. They range from mild (burning or stinging at the injection site, chills, flushing, or rashes) to severe (shock that leads to death). If an allergic reaction occurs, the treatment has to be stopped immediately and the person has to be treated appropriately according to the kind and severity of the unwanted effect.	Partially preventable, by avoiding use in people with known allergies to plasma products or to any of the other components in Beriplex.
Blood clots that can block blood vessels (thrombosis)	These are not common and may affect the arteries or veins. When blood clots occur in the veins it may lead to a painful swelling of the legs (deep vein thrombosis) and occasionally, life threatening or fatal clots in the lungs. Clots in the arteries may lead to a heart attack or stroke – particularly in people who already have problems with their arteries. People who are being treated with VKAs are usually older and are already at higher risk of blood clots so it is difficult to assess what extra risk is caused by Beriplex.	Preventable, by using Beriplex according to the directions in the package insert on when Beriplex should be used and how much to use.

VKA = vitamin K antagonist.

Table 35: Important potential risks

Risk	What is known (including reason why it is considered a potential risk)
The medicine could have a virus or other infectious agents in it	Beriplex is made from human plasma. When medicines are made from human blood or plasma, several steps are taken to prevent infections from being passed on to people treated with the medicine. These steps include: • Careful selection of blood and plasma donors to make sure donations are not taken from anyone who may have an infection, • Testing of each donation for signs of viruses, and • Treating the blood and plasma during the manufacturing process to inactivate or remove any viruses that might be present. Despite all these steps, when people are treated with medicines prepared from human blood or plasma, the possibility of passing on infection cannot be totally excluded. However, no confirmed cases of viral infection have ever been reported with Beriplex.
Medication/dosing errors	When a person is treated with Beriplex, it is probably because they are bleeding very badly and need to be treated quickly to stop the bleeding. In this emergency situation, it is possible that the doctors or nurses could accidentally give too much or too little medicine, or give the medicine the wrong way. If a person gets too much Beriplex, some of the important risks mentioned above could be more likely to happen, in particular unwanted blood clots. If a person gets too little Beriplex, their bleeding may be difficult to stop. Doctors and nurses have instructions available to them on the correct way to treat patients with Beriplex and on the recommended dose. Errors in dosing with Beriplex do not happen often.

Table 36: Missing information

Risk	What is known
Limited information on how well Beriplex works and its safety during pregnancy and in breastfeeding mothers	Pregnant women are not supposed to be treated with VKAs so it is unlikely that there would be a need to stop the effect of VKAs using Beriplex. For this reason, how well Beriplex works and how safe it is for use in pregnancy has not been determined. Beriplex should only be used during pregnancy or in breastfeeding mothers if clearly needed.
Limited information on how well Beriplex works and its safety in children	Children are very rarely treated with VKAs so there is little need to stop the effect of VKAs using Beriplex. For this reason, studies on how well Beriplex works and how safe it is in children have not been conducted. Beriplex should only be used in children if clearly needed.

VKA = vitamin K antagonist.

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

All medicines have a Summary of Product Characteristics which provides physicians, pharmacists, and other health care professionals with details on how to use the medicine, the risks, and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as "*routine risk minimization measures*".

The Beriplex European Summary of Product Characteristics can be found in Annex A2.3 and the European package leaflet can be found in Annex A2.4.

Beriplex has no additional risk minimization measures.

VI.2.6 Planned Post-authorization Development Plan

The studies planned as part of the post-authorization development plan are those listed in Table 32.

Studies which are a Condition of the Marketing Authorization

Study 4002 is a condition of the marketing authorization in the US.

VI.2.7 Summary of Changes to the Risk Management Plan Over Time

Table 37: Major changes to the RMP over time

Version	Date	Safety concerns	Comment
1.0	30 October 2013	**Important identified risks** Hypersensitivity reactions Thrombosis **Important potential risks** Transmission of infectious agents Medication/dosing errors **Missing information** Efficacy and safety during pregnancy Efficacy and safety in lactating mothers Efficacy and safety in the pediatric population	None.
1.1	14 April 2014	No additional identified or potential risks were added.	None.
1.2	22 April 2014	No additional identified or potential risks were added	None.
1.3	25 March 2015	No additional identified or potential risks were added	None.
2.0	17 March 2017	No additional identified or potential risks were added.	Of note, 'thrombosis' was changed to 'thromboembolic events' to align with the Company Core Safety Information.