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 (also called 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.[13, 15, 17, 19, 34, 36]

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.[13] Bleeding in body parts other than the head leads to death in 10 to 15 out of 100 people. [22, 27, 38] The parts of the body where serious bleeding usually happens when people are treated with VKAs are the stomach, the intestines, and the bladder.[15] Older patients are more likely to get blood clots and they need VKA treatment more often than younger patients. The average age of patients who need treatment to stop bleeding due to VKAs is 75 to 78 years. Also, more men than women need treatment to stop bleeding due to VKAs.[6, 8, 15, 23, 24]

Studies on ethnicity of patients with bleeding associated with VKA are not available.

The risk of bleeding due to VKA treatment increases if patients are older, have other diseases such as heart, kidney or liver problems, or use certain types of medicines such as heparin, anti-platelet agents, some painkillers, and possibly some cholesterol-lowering drugs.

The main treatments used to stop bleeding caused by treatment with VKAs are vitamin K with prothrombin complex concentrate (called PCC). PCCs are made from the plasma of blood and contain the blood clotting factors that are low in people treated with VKAs. If PCCs are not available, another treatment that can be used is fresh frozen plasma (called FFP).

Beriplex is a PCC. In many countries, Beriplex is a common treatment for serious bleeding caused by VKAs. Beriplex is also used to prevent bleeding during surgery.

VI.2.2 Summary of treatment benefits

A total of 431 people participated in 3 main studies, 3001, 3002, and 3003, to test how well Beriplex works.

Study 3001 was the main EU study. It tested how Beriplex works in 43 people with serious bleeding due to VKA treatment or in preventing bleeding during surgery. The study mainly looked at how well Beriplex can undo the effect of VKA to prevent or stop blood clotting. This was done by measuring something called 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). Study 3002 was the main US study to test how Beriplex works in 212 people with serious bleeding due to VKA treatment. Study 3003 was the main US study to test 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 plasma. The studies showed that Beriplex was at least as good, or better, than plasma. More people treated with Beriplex stopped bleeding than people treated with plasma. In Study 3002 bleeding stopped in 72 out of 100 people when treated with Beriplex compared to 65 out of 100 people treated with plasma. In Study 3003, bleeding was prevented in 90 out of 100 people treated with Beriplex compared to 75 out of 100 people treated with plasma. In addition, the INR values went down within 30 minutes in as many as 62 out of 100 people treated with Beriplex compared with 10 out of 100 people treated with plasma.

VI.2.3 Unknowns relating to treatment benefits

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

VI.2.4 Summary of safety concerns

Table 28: 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, by avoiding use in people with known allergies to plasma factors 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.	Yes, 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 29: 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 you with Beriplex and on the recommended dose. Errors in dosing Beriplex do not happen often.

Table 30: Missing information

Risk	What is known
Limited information on how well Beriplex works and its safety during pregnancy and in breast feeding 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 breast feeding 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 minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists, and other health care professionals with details on how to use the medicine, the risks, and recommendations for minimising 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 minimisation measures*".

The Beriplex European SmPC can be found in Annex A2.3 and the European package leaflet can be found in Annex A2.4.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post-authorisation development plan

The studies planned as part of the post-authorisation development plan are those listed in Table 27.

Studies which are a condition of the marketing authorisation

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

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

This is version 1.3 of the Beriplex RMP. Annex 2 – Replacement of Annex 2 - Consolidated EU-SPC (Rev. 07-NOV-2014) , EU-PIL (Rev. 07-NOV-2014), CCDS (Rev. 01-APR-2014) and CCPIs (Rev. 01-APR-2014) due to CCSI Update and Optimization of virus filtration.