PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for FEIBA (Human Plasma Fraction with FVIII Inhibitor Bypassing Activity

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

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

This summary of the RMP for FEIBA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for

FEIBA is authorised for control and prevention of bleeding in patients with haemophilia A (congenital and acquired) and haemophilia B (see the SmPC for the full indication). It contains Factor VIII Inhibitor Bypassing Activity as the active substance and it is given intravenously.

Further information about the evaluation of FEIBA’s benefits can be found in FEIBA SmPC.

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

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

II.A List of important risks and missing information

Important risks of FEIBA 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 FEIBA. 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 27. Summary of Safety Concerns

Important identified risks	Allergic type hypersensitivity reactions
	Thrombotic and thromboembolic events (including disseminated intravascular coagulation (DIC), myocardial infarction, venous thrombosis, pulmonary embolism, and stroke)
	Insufficient response to bypassing agents
	Passive transfer of hepatitis B surface antibodies
Important potential risks	Transmission of Infectious Agents
	Improper self-administration
	Inadvertent administration of the incorrect dose or concentration of FEIBA
	Thrombotic microangiopathy (TMA) with concomitant emicizumab use
Missing information	Insufficient data in children under 6 years of age
	Prophylactic use in haemophilia B patients with inhibitors
	Insufficient clinical data on use in pregnancy and lactation
	Insufficient clinical data on use in geriatric patients

II.B Summary of important risks

Table 28. Important Identified Risk: Allergic-type hypersensitivity reactions

Evidence for linking the risk to the medicine	As with any intravenous protein product allergic type hypersensitivity reactions are possible. Allergic type hypersensitivity reactions have been reported with FEIBA in the post-market setting.
Risk factors and risk groups	Patients with previous history of hypersensitivity to administration of medicinal products containing proteins, in particular intravenous administration.
Risk minimisation measures	**Routine risk minimisation measures:** 4.3 Contraindications 4.4 Special warnings and the precautions for use 4, 8 Undesirable effects **Additional risk minimisation measures:** None

Table 29. Important Identified Risk Thrombotic and thromboembolic events (including disseminated intravascular coagulation (DIC), myocardial infarction, venous thrombosis, pulmonary embolism, and stroke)

Evidence for linking the risk to the medicine	Thrombotic and thromboembolic events are a known complication with FEIBA and have been seen in the post-marketing setting. The risk

Table 29. Important Identified Risk Thrombotic and thromboembolic events (including disseminated intravascular coagulation (DIC), myocardial infarction, venous thrombosis, pulmonary embolism, and stroke)

	increases with high doses of FEIBA.
Risk factors and risk groups	Patients with one or more co-suspect medication (e.g., rFVIIa, tranexamic acid, other blood derived products or drugs with thrombogenic potential). Inhibitor development in patients with acquired haemophilia is thought to result from underlying medical conditions. Some of the medical conditions associated with the development of inhibitors are known to be associated with an increased risk of thrombosis. Sequential or combined treatment of bleeds in acquired haemophilia as well as in congenital haemophilia where inhibitors appears to increase the risk of thrombotic complications. Pre disposing co-morbidities and risk factors, for example, advanced age, severe injury, hypertension, diabetes, and immobility. DIC, myocardial infarction, stroke, venous thrombosis, pulmonary embolism, and myocardial infarction were also found to occur after receipt of a dose exceeding the recommended maximum daily dose and/or prolonged administration.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections: 4.3 Contraindications 4.4 Special warnings and the precautions for use 4, 8 Undesirable effects 4.9 Overdose **Additional risk minimisation measures:** None

Table 30. Important Identified Risk Insufficient response to bypassing agents

Evidence for linking the risk to the medicine	Response to treatment with FEIBA can vary with each patient.
Risk factors and risk groups	Response to treatment may depend on factors that are specific to each bleed and each patient, such as the location or severity of the bleed, patient's age, and the presence of a target joint.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections: 4.4 Special warnings and the precautions for use 4, 8 Undesirable effects **Additional risk minimisation measures:** None

Table 31. Important Identified Risk Passive transfer of Hepatitis B surface antibodies

Evidence for linking the risk to the medicine	When patients receive high doses of FEIBA this may lead to a rise of passively transferred Hepatitis B surface antibodies (HBsAb) , which may result in misleading interpretation of positive results in serological testing.
Risk factors and risk groups	All patients who receive high doses of FEIBA are potentially at risk for a measurable passive transfer of hepatitis B surface antibodies.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections: 4.4 Special warnings and the precautions for use 4, 8 Undesirable effects **Additional risk minimisation measures:** None

Table 32. Important Potential Risk Transmission of infectious agents

Evidence for linking the risk to the medicine	Multiple agents (viral, bacterial, etc.) can be potentially transmitted through blood and plasma based products. Techniques for careful screening and inactivation of organisms decrease the potential for transmission of infectious agents with the administration of FEIBA.
Risk factors and risk groups	Patients not receiving regular medical attention, or those not adhering to therapeutic regimen.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections: 4.4 Special warnings and the precautions for use **Additional risk minimisation measures:** None

Table 33. Important Potential Risk Improper self-administration

Evidence for linking the risk to the medicine	Patients and caregivers may make mistakes in the administration of medication. Examples include incorrect dosage, forgetting, mixing up medications, failing to recall indications, and taking out of date/inappropriately stored medication.
Risk factors and risk groups	Patients not receiving regular medical attention, or those not adhering to therapeutic regimen.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections: 4.2 Posology and method of administration 6.6 Special precautions for disposal and other handling

Table 33. Important Potential Risk Improper self-administration

	Additional risk minimisation measures: None

Table 34. Important Potential Risk Inadvertent administration of the incorrect dose or concentration of FEIBA

Evidence for linking the risk to the medicine	Patients and caregivers may make mistakes in the administration of medication. Examples include incorrect dosage, forgetting, mixing up medications, failing to recall indications, and taking out of date/inappropriately stored medication.
Risk factors and risk groups	Patients not receiving regular medical attention, or those not adhering to therapeutic regimen.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC Sections: 4.2 Posology and method of administration 6.5 Nature and contents of container 6.6 Special precautions for disposal and other handling **Additional risk minimisation measures:** None

Table 35. Important Potential Risk Thrombotic microangiopathy (TMA) with concomitant emicizumab use

Evidence for linking the risk to the medicine	TMA has not been reported in Company sponsored studies with FEIBA TMA was reported in one emicizumab trial Oldenburg et al 2017) where FEIBA was part of a treatment regimen for breakthrough bleeding.
Risk factors and risk groups	With concomitant use of emicizumab.
Risk minimisation measures	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None

Table 36. Missing Information Insufficient data in children under 6 years of age

Risk minimisation measures	**Routine risk minimisation measures:** 4.2 Posology and method of administration 4.4 Special warnings and the precautions for use **Additional risk minimisation measures:**

Table 36. Missing Information Insufficient data in children under 6 years of age

	None

Table 37. Missing Information Prophylactic use in haemophilia B patients with inhibitors

Risk minimisation measures	**Routine risk minimisation measures:** 4.1 Therapeutic indications 4.2 Posology and method of administration 4.4 Special warnings and the precautions for use **Additional risk minimisation measures:** None

Table 38. Missing Information> – Insufficient clinical data on use in pregnancy and lactation

Risk minimisation measures	**Routine risk minimisation measures:** 4.6 Fertility, pregnancy and lactation **Additional risk minimisation measures:** None

Table 39. Missing Information> – Insufficient clinical data on use in geriatric patients

Risk minimisation measures	**Routine risk minimisation measures:** 4.4 Special warnings and the precautions for use **Additional risk minimisation measures:** None

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of FEIBA.

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

There are no studies required for FEIBA.