PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for BeneFIX (Nonacog alfa)

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

BeneFIX's SmPC and its package leaflet give essential information to healthcare professionals and patients on how BeneFIX should be used.

This summary of the RMP for BeneFIX 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 BeneFIX's RMP.

I. The Medicine and What It Is Used For

BeneFIX is authorised for treatment and prophylaxis of bleeding in patients with haemophilia B (congenital FIX deficiency) (see SmPC for the full indication). It contains nonacog alfa as the active substance and it is given by intravenous infusion.

Further information about the evaluation of BeneFIX's benefits can be found in BeneFIX's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/benefix.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of BeneFIX, together with measures to minimise such risks and the proposed studies for learning more about BeneFIX'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 events is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of BeneFIX 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 BeneFIX. 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 1. List of important risks and missing information

Important identified risks	Inhibitor development Allergic reactions Thrombogenicity
Important potential risks	Medication errors/product confusion
Missing information	None

II.B. Summary of Important Risks

Table 2. Important Identified Risk: Inhibitor Development

Evidence for linking the risk to the medicine	Inhibitor development has been reported in BeneFIX clinical trials and has also been reported in the postmarketing setting.
Risk factors and risk groups	Several risk factors predispose a patient to inhibitor development. Two (2) such factors are the presence of severe disease (FIX activity of <1 IU/dL), and specific gene mutations such as major derangements of the F9 gene due to large deletions, stop codons, and frame shift mutations. Other possible risk factors to be considered include the role of concomitant immune system challenges, and the type of factor concentrate used in treatment.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> SmPC Sections 4.4 and 4.8 PL Sections 2 and 4 <u>Additional risk minimisation measures:</u> None

Table 3. Important Identified Risk: Allergic Reactions

Evidence for linking the risk to the medicine	Allergic reactions have been reported in BeneFIX clinical trials and have also been reported in the postmarketing setting.
Risk factors and risk groups	Allergic reactions have occurred in close temporal association with development of FIX inhibitor. One (1) contributing factor is the nature of the gene mutation. Patients with large gene deletions are more susceptible to inhibitor development. Complete gene deletions confer the highest risk for anaphylaxis. PUPs with severe haemophilia B treated with any FIX replacement therapy may be more susceptible to develop an allergic reaction compared to PTPs.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 4.3, 4.4, and 4.8 PL Sections 2 and 4 Additional risk minimisation measures: None

Table 4. Important Identified Risk: Thrombogenicity

Evidence for linking the risk to the medicine	Thrombogenic events have been reported in BeneFIX clinical trials and has also been reported in the postmarketing setting. Literature data.
Risk factors and risk groups	The use of FIX concentrates has historically been associated with the development of thromboembolic complications. When administering this product to patients with liver disease, to patients post-operatively, to neonates, or to patients at risk of thrombotic phenomena or DIC, the benefit of treatment with BeneFIX should be weighed against the risk of these complications.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.4 and 4.8 PL Section 4 Additional risk minimisation measures: None

Table 5. Important Potential Risk: Medication Errors/Product Confusion

Evidence for linking the risk to the medicine	Medication errors have been reported for BeneFIX primarily in the postmarketing setting.
Risk factors and risk groups	No clinically important sub-population differences in risk were identified.

Table 5. Important Potential Risk: Medication Errors/Product Confusion

Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.2, 6.2, 6.3, 6.4, 6.5, and 6.6 PL Sections 3, 5, and 6 Package designs: Color-coding is utilised on the carton and protein vial. Additional risk minimisation measures: None

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

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

II.C.2. Other Studies in Post-Authorisation Development Plan

There are no studies required for BeneFIX.