Summary of risk management plan for Refixia (nonacog beta pegol)

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

Refixia's Summary of Product Characteristics (SmPC), and its package leaflet give essential information to healthcare professionals and patients on how Refixia should be used.

This summary of the RMP for Refixia 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 EPAR.

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

I. The medicine and what it is used for

Refixia is authorised for treatment and prophylaxis of bleeding in adolescent and adult patients (≥12 years of age) with haemophilia B (congenital factor IX deficiency; see SmPC for the full indication). It contains nonacog beta pegol as the active substance and is given by intravenous injection.

Further information about the evaluation of Refixia's benefits can be found in Refixia's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: *EPAR link*.

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

Important risks of Refixia together with measures to minimise such risks and the proposed studies for learning more about Refixia'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 public (e.g., with or without prescription) can help to minimises 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.

If important information that may affect the safe use of Refixia is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Refixia 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 Refixia. 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).

List of important risks and missing information	
Important identified risks	• Allergic/hypersensitivity reactions • FIX inhibitors
Important potential risks	• Thromboembolic events • Nephrotic syndrome following ITI • Inadequate treatment due to assay overestimation of FIX activity • Accumulation of PEG in the brain (choroid plexus) and in other tissues/organs after long-term treatment
Missing information	• Females, including pregnant or breastfeeding women

Abbreviations: FIX = factor IX; ITI = immune tolerance induction; PEG = polyethylene glycol.

II.B Summary of important risks

An overview of important identified risks, important potential risks and missing information for Refixia is provided in the tables below.

Important identified risks	
Allergic/hypersensitivity reactions	
Evidence for linking the risk to the medicine	This is an important class risk for all FIX products and a risk associated with all protein-based medicinal products. Allergic reactions have been observed in the clinical trials with nonacog beta pegol as the IMP and are described in the literature in patients treated with FIX products. The percentage of patients that have experienced serious hypersensitivity/allergic reactions in the clinical trials is in line with the results in observational studies of patients with haemophilia B treated with recombinant and plasma-derived FIX products. Taken together, the strength of evidence for the risk of hypersensitivity/allergic reactions in patients treated with nonacog beta pegol is moderate.
Risk factors and risk groups	There is an established correlation between the occurrence of a FIX inhibitor and allergic reactions, and patients with FIX inhibitors are at an increased risk of anaphylaxis with subsequent exposure to FIX. Furthermore, anaphylactic type reactions have been reported following immune tolerance induction with FIX. Patients with a history of allergic reactions or with known hypersensitivity to the active substance (rFIX or PEG), to Chinese hamster proteins or to excipients are at higher risk. The risk of allergic/hypersensitivity reactions is expected to be higher with the initial administrations compared to subsequent administrations.

Risk minimisation measures	*Routine risk minimisation measures:* Routine risk communication: The identified risk of allergic/hypersensitivity reactions is addressed in the labelling: Section 4.8 of the SmPC and Section 4 of the PL. Hypersensitivity to the active substance or excipients and known allergy to hamster protein are listed as contraindication in Section 4.3 of the SmPC and Section 2 of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: Information on how to detect early signs of allergic/hypersensitivity reactions is included in Section 4.4 of the SmPC and Section 2 of the PL. Other routine risk minimisation measures beyond the Product Information: None *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	PASS (NN7999-4031) Clinical trials (NN7999-3774 and NN7999-3895) PASS registry study (NN7999-4413) See Section II.C of this summary for an overview of the post-authorisation development plan.
FIX inhibitors	
Evidence for linking the risk to the medicine	This is an important class risk for all FIX products. Development of neutralising anti-FIX antibodies (FIX inhibitors) has been observed in the ongoing clinical trial with nonacog beta pegol in PUPs with haemophilia B, a population at high risk of inhibitor development. Inhibitor development associated with the treatment with recombinant and plasma-derived FIX products is well-known and described in the literature. The frequency of inhibitor development in clinical trials with nonacog beta pegol is in line with the results of observational studies of patients with haemophilia B treated with recombinant and plasma derived FIX products. Taken together, the strength of evidence for the risk is high.
Risk factors and risk groups	The risk of inhibitor development is highest in PUPs with severe haemophilia B.

	Several patient-related factors have been associated with the risk of developing inhibitors, such as FIX gene mutation, family history of inhibitors and ethnicity. Non-genetic risk factors include surgery and intensive treatment.
Risk minimisation measures	*Routine risk minimisation measures* Routine risk communication: The identified risk of FIX inhibitors is addressed in the labelling: Section 4.8 of the SmPC and Section 4 of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendation for careful monitoring by appropriate clinical observations and laboratory tests included in SmPC Section 4.4 and PL Section 2. Other routine risk minimisation measures beyond the Product Information: None *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	PASS (NN7999-4031) Clinical trials (NN7999-3774 and NN7999-3895) PASS registry study (NN7999-4413) See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: FIX = factor IX; IMP = investigational medicinal product; PUP = previously untreated patient; PASS = post-authorisation safety study; PEG = polyethylene glycol; PL = package leaflet; rFIX = recombinant factor IX; SmPC = Summary of Product Characteristics.

Important potential risks	
Thromboembolic events	
Evidence for linking the risk to the medicine	This is a class risk for FIX products. No thromboembolic events have been reported in patients treated with nonacog beta pegol in clinical trials or in the post-marketing setting. Thrombotic events in relation to coagulation factor concentrates have been reported in patients with haemophilia B in the literature. The strength of evidence for the risk of thromboembolic events in patients treated with nonacog beta pegol is considered low.
Risk factors and risk groups	Possible general risk factors (not specific for patients with haemophilia B only) include thromboembolic diseases, disseminated intravascular coagulation, liver disease, advanced atherosclerotic disease, arrhythmias, hypertension, crush injury, cancer, diabetes, hypercholesterolemia, obesity, post-surgical status, septicaemia, immobilisation, smoking, old age, new-born infants and use of central venous access devices.
Risk minimisation measures	*Routine risk minimisation measures* Routine risk communication: The potential risk of thromboembolic events is addressed in the labelling: Section 4.8 of the SmPC and Section 2 of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: A recommendation is included in Section 4.4 of the SmPC to monitor for early signs of thrombotic and consumptive coagulopathy by appropriate clinical observations and appropriate biological testing in patients with liver disease, in patients post-operatively, in new-born infants or in patients at risk of thrombotic phenomena or DIC. Other risk minimisation measures beyond the Product Information: None *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	PASS (NN7999-4031) Clinical trials (NN7999-3774 and NN7999-3895) PASS registry study (NN7999-4413) See Section II.C of this summary for an overview of the post-authorisation development plan.

Nephrotic syndrome following ITI	
Evidence for linking the risk to the medicine	Evidence from the literature supports the high risk of developing nephrotic syndrome following ITI in patients with haemophilia B. Nephrotic syndrome following ITI has not been reported in clinical trials with nonacog beta pegol because ITI is not being used. No cases concerning patients treated with nonacog beta pegol have been reported from post-marketing sources. The strength of evidence for this potential risk is low.
Risk factors and risk groups	Patients with haemophilia B with inhibitors receiving ITI, particularly in those patients who have experienced anaphylactic reactions to FIX concentrate. Nonacog beta pegol is not indicated for ITI but might be used for ITI although this is not an indication in the labelling, as common clinical practice is to use the factor product that was used at the time of inhibitor development for the ITI regimen. No marketed FIX products have an indication for ITI.
Risk minimisation measures	*Routine risk minimisation measures* Routine risk communication: The potential risk of nephrotic syndrome following ITI is addressed in the labelling: Section 4.8 of the SmPC and Section 2 of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the Product Information: None *Additional risk minimisation measures* None
Additional pharmacovigilance activities	None See Section II.C of this summary for an overview of the post-authorisation development plan.

Inadequate treatment due to assay overestimation of FIX activity	
Evidence for linking the risk to the medicine	This risk is based on theoretical concerns related to nonacog beta pegol assay validation. The strength of evidence for the risk is low since no cases have been reported in the post-marketing setting.
Risk factors and risk groups	Patients treated at centres where only one-stage clotting assay is available for monitoring of factor IX activity. Patients in whom monitoring of factor IX activity is important for decision to treat or not and for selection of dose. This is particularly relevant in situations where the physician decides to monitor the patients' factor IX levels (e.g., if experiencing a severe bleed, if treated in connection with major surgery or multi-trauma or in situations of inhibitor development/suspicion of inhibitor development).
Risk minimisation measures	*Routine risk minimisation measures* Routine risk communication: Section 4.2 of the SmPC includes information about the risk of FIX activity overestimation by use of a specific assay. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the Product Information: None *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	None. See Section II.C of this summary for an overview of the post-authorisation development plan.

Accumulation of PEG in the brain (choroid plexus) and in other tissues/organs after long-term treatment	
Evidence for linking the risk to the medicine	The risk is based on nonclinical safety studies showing the presence of PEG in epithelial cells of the choroid plexus of the brain. The strength of evidence for the risk in humans is very low as neither potential accumulation of PEG nor clinical consequences have been established.
Risk factors and risk groups	Children are theoretically considered more vulnerable to a potential impact of PEG due to neurodevelopment milestones being reached before the age of 12 years. Currently, there is no evidence for any deleterious consequences of the potential presence of PEG in the choroid plexus or any other tissues in patients after long-term treatment with nonacog beta pegol.
Risk minimisation measures	*Routine risk communication:* None *Routine risk minimisation activities recommending specific clinical measures to address the risk*: None *Other risk minimisation measures beyond the Product Information:* None
Additional pharmacovigilance activities	PASS (NN7999-4031) Clinical trial (NN7999-3774, NN7999-3895) PASS registry study (NN7999-4413) See Section II.C of this summary for an overview of the post-authorisation development plan.

Abbreviations: FIX = factor IX; ITI = immune tolerance induction; PASS = post-authorisation safety study; PEG = polyethylene glycol; PL = package leaflet; SmPC = Summary of Product Characteristics.

Missing information	
Females, including pregnant and lactating women	
Risk minimisation measures	*Routine risk minimisation measures:* Routine risk communication: Lack of experience in this population is mentioned in Section 4.6 of the SmPC. Routine risk minimisation activities recommending specific clinical measures to address the risk: None Other risk minimisation measures beyond the Product Information: None *Additional risk minimisation measures*: None
Additional pharmacovigilance activities	None

Abbreviations: SmPC = Summary of Product Characteristics.

II.C Post-authorisation development plan

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

The following study is a condition of the marketing authorisation:

NN7999-4031 PASS

Purpose of the study: Novo Nordisk has received an obligation from the CHMP to conduct a PASS to investigate the potential effects of PEG accumulation in the choroid plexus of the brain and other tissues/organs.

The primary objective of the study NN7999-4031 is to investigate safety of nonacog beta pegol in prophylaxis and during long-term routine use in patients with haemophilia B in the manner it is prescribed by physicians. This will include assessment of specific pharmacological risks for FIX replacement products (FIX inhibitors, allergic reactions and thromboembolic events).

Secondary objectives are to further evaluate the general safety and clinical effectiveness of nonacog beta pegol in prophylaxis and during long-term routine use in patients with haemophilia B in the manner it is prescribed by the physicians.

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

NN7999-4413 PASS

Purpose of the study: In alignment with the EMA initiative for patient registries, Novo Nordisk has established collaboration with two registries to obtain adverse event data for nonacog beta pegol to complement routine post-marketing pharmacovigilance activities and the data collection in PASS NN7999-4031.

The primary objective of this study is to investigate potential clinical effects of longer-term exposure to nonacog beta pegol in patients with haemophilia B and to assess specific pharmacological risks for FIX replacement products, including nonacog beta pegol (FIX inhibitors, allergic-type hypersensitivity reactions and thrombotic events).

Clinical trial NN7999-3774

Purpose of the study: The main purpose for performing this trial is to investigate safety, efficacy and pharmacokinetic properties of N9-GP in the treatment of haemophilia B patients ≤12 years. Based on clinical and nonclinical studies conducted, nonacog beta pegol is a promising drug candidate for prevention/prophylaxis and on-demand treatment of bleeding episodes in haemophilia B patients.

The primary objective is to evaluate immunogenicity of nonacog beta pegol in PTP ≤12 years of age. The secondary objectives are to investigate safety of nonacog beta pegol other than immunogenicity, efficacy in long-term prophylaxis treatment including pharmacokinetic properties of nonacog beta pegol, to monitor the FIX consumption for prophylaxis and breakthrough bleeding episodes and to evaluate patient reported outcomes and assess health economic impact of treatment with nonacog beta pegol.

Clinical trial NN7999-3895

Purpose of the study: The main purpose is to investigate safety and efficacy of nonacog beta pegol in the treatment of PUPs with haemophilia B, hereby supporting the marketing authorisation of nonacog beta pegol and line extension in the PUP population.

The EMA requires separate investigation of PUPs as part of the development programme initiated before market authorisation (MA) can be obtained. A final guideline on the clinical investigation of recombinant and human plasma-derived factor IX products from the CHMP describes the mandatory components for trials in PUP. In some countries outside the EU, PUP paediatric investigation is necessary to achieve labelled indication for all children.

Primary objective: To evaluate immunogenicity of nonacog beta pegol.

Secondary objectives: To investigate the following in patients <6 years of age previously untreated with a FIX product and with moderate to severe haemophilia B during the trial period:

- Safety of nonacog beta pegol
- Efficacy of nonacog beta pegol in long-term prophylaxis treatment
- Efficacy of nonacog beta pegol in the treatment of bleeding episodes through the surrogate marker, FIX activity
- Efficacy of nonacog beta pegol through monitoring of number of doses and consumption of nonacog beta pegol.