Risk Management Plan

Nonacog beta pegol (Refixia®)

Active substance(s)	Nonacog beta pegol
RMP version number	Version 6.0
Data lock point for this RMP	31 Jul 2024
Date of final sign off	See signature page
Rationale for submitting an updated RMP	This RMP is submitted in connection with the submission of Type II variation application for updating completed clinical studies data which are RMP commitments.
Summary of significant changes in this RMP	• Since the last RMP update, two clinical studies NN7999-3895 and -3774 have been completed. Data pertaining to these studies has been updated in the RMP. • Additionally, data from clinical studies, post-marketing sources (including exposure) and epidemiological sources has been updated as of the data lock point (DLP). • Minor editorial changes are made across the RMP
Other RMP versions under evaluation	None
Details of the currently approved RMP	Version number: 5.2 Approved with procedure: EMEA/H/C/004178/II/0032 Date of approval (opinion date): 04 Aug 2023
QPPV	Wasim Anwar
QPPV signature	See signature page

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Abbreviations

ADR	adverse drug reaction
AR	adverse event
aPTT	activated partial thromboplastin time
BU	Bethesda unit
CD4	cluster of differentiation 4
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CNS	central nervous system
CTR	clinical trial report
DDD	defined daily dose
DLP	data lock point
EEA	European economic area
EMA	European Medicines Agency
EUHASS	European Haemophilia Safety Surveillance
FIX	coagulation factor IX
FPFV	first patient first visit
GVP	Good Pharmacovigilance Practices
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLT	high-level term
HLGT	high-level group term
IMP	investigational medicinal product
INN	international nonproprietary name
IU	international units
i.v.	intravenous
ITI	immune tolerance induction
LAR	Legally Acceptable Representative
LPLV	last patient last visit
MAH	marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
N9-GP	nonacog beta pegol
NEC	not elsewhere classified
PASS	post-authorisation safety study
PEG	polyethylene glycol
PYE	patient/participant-years of exposure
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PTP	previously treated patient
PUP	previously untreated patient
rFIX	recombinant human blood coagulation factor IX
RMP	risk management plan
RR	reporting rate

1 Product overview

Table 1-1 Product overview

Active substance(s) (INN or common name)	**Nonacog beta pegol**
Pharmacotherapeutic group(s) (ATC Code)	Antihaemorrhagics: blood coagulation factor IX (B02BD04)
Marketing authorisation holder	Novo Nordisk A/S DK-2880 Bagsværd Novo Allé Denmark
Medicinal products to which this RMP refers	Refixia® (Rebinyn® in the US and Canada)
Invented name(s) in the European Economic Area (EEA)	Refixia®
Marketing authorisation procedure	Centralised procedure
Brief description of the product	***Chemical class***: Nonacog beta pegol is a glycopegylated recombinant human factor IX (rFIX).
	Summary of mode of action: Nonacog beta pegol is a glycopegylated recombinant human factor IX (rFIX). Nonacog beta pegol replaces deficient or absent human FIX in patients with haemophilia B. It has a 40 kDa polyethylene glycol (PEG) selectively attached to the rFIX activation peptide that increases the plasma half-life and upon activation of rFIX, PEG is removed along with the activation peptide to leave the native FIX. The activated FIX, in combination with activated factor VIII, catalyses the activation of the coagulation blood factor X, thus initiating the thrombin burst and the formation of a stable haemostatic plug.
	Important information about its composition Nonacog beta pegol is expressed by a genetically engineered Chinese hamster ovary (CHO) cell line, which produces rFIX into the cell culture medium. The rFIX protein is purified by a series of chromatographic steps to selectively isolate rFIX from the cell culture medium, followed by conjugation of the PEG-group by an enzymatic reaction during purification. No additives of human or animal origin are used in the cell culture, purification, conjugation and formulation of nonacog beta pegol.
Hyperlink to the Product Information	**Refixia® SmPC**
Indication(s) in the EEA	**Current (if applicable):** Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). Refixia can be used for all age groups.
	Proposed (if applicable): Not applicable

Active substance(s) (INN or common name)	**Nonacog beta pegol**
Dosage in the EEA	**Current (if applicable)** Routine prophylaxis: 40 IU/kg body weight once weekly. Bleeding episodes: 40 IU/kg body weight (mild/moderate bleeding), 80 IU/kg body weight (severe bleeding). Additional doses of 40 IU/kg can be given. Minor surgery: 40 IU/kg body weight pre-operative dose and additional doses can be given if needed. Major surgery: 80 IU/kg body weight pre-operative dose. Two repeated doses of 40 IU/kg (in 1–3 days interval) should be considered within the first week after surgery. Due to the long half-life of nonacog beta pegol, the frequency of dosing in the post-surgical period may be extended to once weekly after the first week until the bleeding stops, and healing is achieved. Nonacog beta pegol is administered by intravenous bolus injection.
	Proposed (if applicable) Not applicable
Pharmaceutical form(s) and strengths	**Current (if applicable)** Powder and solvent for solution for injection. Each vial contains nominally 500 IU, 1,000 IU, 2,000 IU or 3000 IU nonacog beta pegol. One mL of the solution contains approximately 125 IU, 250 IU, 500 IU or 750 IU nonacog beta pegol, respectively, after reconstitution with 4 mL histidine solvent. The potency (IU) is determined using the European Pharmacopoeia one stage clotting assay. The specific activity is 144 IU/mg protein.
	Proposed (if applicable) Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: EEA = European Economic Area; PEG = polyethylene glycol; rFIX = recombinant human factor IX.

2 Safety specification

2.1 Module SI: Epidemiology of the indication(s) and target population

2.1.1 Haemophilia B

Haemophilia B is a rare congenital bleeding disorder inherited in an X-linked recessive manner. The condition is caused by mutations in the coagulation factor IX (FIX) gene. The gene defects may result in FIX insufficiency, lack of FIX or the production of a biochemically defective FIX protein, leading to impaired haemostasis, prolonged bleeding and rebleeding. Although congenital haemophilia B is a hereditary disorder, it also occurs by spontaneous mutations.

Haemophilia B severity is classified according to the residual endogenous plasma activity of FIX as ‘severe’ (<1% of the normal activity level), ‘moderate’ (1–5%) or ‘mild’ (>5–40%).

2.1.1.1 Incidence and prevalence

The incidence and prevalence of haemophilia B are as follows:

- **Incidence:** Iorio *et al*. estimated the prevalence at birth of haemophilia B to be 4.7 per 100,000 males based on patient registries in France, Canada and the United Kingdom.[1]

- **Prevalence:** According to the annual global survey by the World Federation of Hemophilia (WFH), approximately 42,203 patients have been diagnosed with haemophilia B globally.[2-3] The reported prevalence of haemophilia B varies considerably by country and across economic classes of a country. The prevalence of haemophilia B in European countries, the US, China and Japan is presented in Table 2-1. The worldwide prevalence is 0.58 per 100,000 inhabitants, and thus lower than the prevalence in most European countries because low and middle-income countries have relatively fewer adult patients with haemophilia B than high-income countries, and some cases might not be diagnosed in low-ranking economies. Hence, the actual worldwide prevalence of haemophilia B is expected to be higher.

Table 2-1 Prevalence of haemophilia B reported in selected European countries, the UK, the US, China and Japan

Country	Population size	Number of patients	Prevalence per 100,000
Austria	9,042,528	149	1.65
Belgium	11,669,446	265	2.27
Finland	5,556,880	34	0.61
France	67,935,660	1,909	2.81
Hungary	9,683,505	250	2.58
Ireland	5,086,988	233	4.58
Italy	58,856,847	707	1.20
Netherlands	17,703,090	243	1.37
United Kingdom	66,971,411	1,721	2.57
United States	333,287,557	4,373	1.31
China	1,412,175,000	4,799	0.34
Japan	125,124,989	1,294	1.03

Note: Numbers for all countries are from the WFH Annual Global Survey 2022.[2]

Abbreviation: WFH = World Federation of Hemophilia.

2.1.1.2 Demographics of the target population – Age, gender, racial and ethnic origin

The distribution of patients with haemophilia B by age group is presented in Table 2-2.

Table 2-2 Distribution of patients with haemophilia B by age group in selected European countries, the UK, the US and China

Country	Patients with haemophilia B	0–4 years	5–13 years	14–18 years	19–44 years	>45 years	Age not known
Austria	149	5.37%	14.77%	10.7%	39.6%	29.5%	0.0%
Belgium	265	0.75%	8.3%	7.17%	33.2%	50.2%	0.38%
Finland	34	NA	NA	NA	NA	NA	100%
France	1,909	5.19%	14.1%	10.5%	35.8%	34.42%	0.0%
Hungary	250	3.2%	7.2%	3.2%	38.4%	48.0%	0.0%
Ireland	233	3.86%	10.7%	9.2%	37.6%	32.8%	0.0%
Italy	707	NA	NA	NA	NA	NA	NA
Netherlands	243	3.7%	10.7%	7.4%	36.6%	41.6%	0.0%
United Kingdom	1,721	4.36%	17.18%	7.1%	36.66%	37.7%	0.0%
United States	4,373	9.97%	21.95%	10.9%	33.5%	23.7%	0.0%
China	4,799	4.06%	22.8%	11.6%	40.7%	17.3%	3.63%

Note: Numbers for all countries are from the WFH Annual Global Survey 2022.[2-4]
Abbreviation: WFH = World Federation of Hemophilia.

Haemophilia B is a congenital disease that almost exclusively affects men, as it is due to a gene defect inherited in an X-linked recessive manner. According to the global data from the WFH, ~89% of patients with haemophilia B are men, ~5.5% of the patients are women and the gender is unknown for ~4.5% of the patient population.[3]

The severity of the disease differs significantly between male and female patients (see Table 2-3). Although the definition of severity based on FIX activity levels may vary in some countries, haemophilia B is generally classified as severe, moderate and mild (see Section 2.1.1 for details). The distribution by severity is however difficult to estimate since this information is not always available and many of the mild cases remain undiagnosed.

Haemophilia B affects people from all racial and ethnic groups.

Table 2-3 Severity of haemophilia B by gender

Severity	Males	Females
Mild	23.4%	83.1%
Moderate	32.8%	5.4%
Severe	35.8%	3.1%
Unknown	8.0%	8.3%

Note: Percentages are from the 2022 WFH Annual Global Survey and reflect the distribution of severity of haemophilia B across all countries.[2-3] Distribution by severity includes data from patients where severity data were available.
Abbreviation: WFH = World Federation of Hemophilia.

2.1.1.3 Risk factors for the disease

Haemophilia B is a rare genetic bleeding disorder caused by mutations in the FIX gene located in the distal part on the long arm of the X chromosome.

Haemophilia B is caused by any of a variety of genetic anomalies distributed throughout the FIX gene, with almost every family manifesting its own unique pattern. The anomalies can be arbitrarily classified as deletions or nonsense mutations (i.e., genes incapable of producing FIX) or missense mutations, causing amino acid changes in the FIX molecule that result in a functionally defective protein. The gene defects are transferred from a heterozygotic mother (carrier) or are ascribable to new, spontaneous mutations.

Approximately 30% of all patients with haemophilia have no known family history of the disease and are called sporadic or isolated cases. It is possible that familial haemophilia is underestimated, given that some patients may be less well informed about the medical histories of their families.[4] No information is available that describes other risk factors for the disease apart from the genetics.

2.1.1.4 The main existing treatment options

The primary goals of haemophilia therapy are the prevention of bleeds, rapid and definitive treatment of bleeds and provision of adequate haemostasis during surgery and other major challenges to haemostasis.

The standard treatment for patients with haemophilia B in most middle and high-income countries is replacement therapy, including intravenous administration of plasma-derived or recombinant FIX (rFIX) products.

Development of FIX inhibitors significantly limits the treatment options.

For patients with severe phenotype haemophilia B, the WFH recommends regular long-term prophylaxis as the standard of care.

Replacement therapy with current commercially available FIX products can be provided either as:

- A prophylactic regimen to prevent bleeds (1−3 injections per week)
- An on-demand regimen with treatment of bleeds when they occur (1−3 injections per bleed dependent on the severity of the bleed)
- Procedural therapy to reduce risk of bleeding related to invasive procedures or specific situations with high risk of haemorrhage

Prophylactic therapy instituted early in life (prior to the onset of frequent bleeds or joint damage) is recommended as optimal therapy for patients with severe haemophilia B (FIX activity <1%) by the Medical and Scientific Advisory Council of the US National Haemophilia Foundation[5] and by national guidelines in other countries.

Prophylactic treatment of patients with haemophilia B with inhibitors includes bypassing agents, and if low responder inhibitors, FIX replacement.[6] Tissue factor pathway inhibitor (TFPI) is available for prophylaxis in patients with HB.

2.1.1.5 Natural history of the indicated condition including mortality and morbidity

Haemophilia B is a chronic disease requiring life-long treatment with replacement therapy. Individuals with severe haemophilia B are usually diagnosed around birth or within the first 1–2 years of life; those with moderate haemophilia B at 5–6 years of age and individuals with mild haemophilia B may not be diagnosed until later in life and even into adulthood.

The clinical manifestations of haemophilia B are bleeding episodes due to impaired haemostasis. The bleeds in patients with severe haemophilia B typically occur spontaneously or after mild trauma in joints, muscles and soft tissues. Bleeding episodes may occur in all parts of the body, including rare but life-threatening events such as bleeding in the central nervous system (CNS), throat, neck or retroperitoneum. The bleeds often occur in the muscles and joints of the elbows, knees and ankles, causing acute haemarthrosis. Recurrent bleeds may lead to synovitis, chronic arthropathy, muscular atrophy and deformities.

Inhibitor development is a known serious complication occurring mainly in patients with severe haemophilia following replacement therapy with coagulation FIX. Inhibitors of FIX are immunoglobulins, usually IgG, that partially or completely neutralise the clotting activity of FIX. It is estimated that 7–12% of previously untreated patients with haemophilia B develop inhibitors depending on the severity of the disease.[7-8] Inhibitor titre is usually measured in Bethesda units (BU) using the modified Nijmegen Bethesda assay.[9] FIX inhibitors can be divided into low titre (0.6 to <5 BU) and high titre (≥5 BU) inhibitors, where low titre inhibitors are considered less serious and high titre inhibitors have serious negative effect on treatment with FIX replacement products. Moreover, low titre FIX inhibitors are often of a transient nature, whereas high titre FIX inhibitors tend to be persistent. The presence of inhibitors in patients with haemophilia B significantly worsens the prognosis, especially in high-titre patients.

Very few research groups have investigated the mortality across specific types of haemophilia. The overall causes of death among patients with haemophilia are becoming more similar to the background population, when deaths attributable to human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are excluded. Coagulation factor products have been virally safe for HIV and HCV since 1985 and 1992, respectively.[10]

For patients with haemophilia not infected with HIV, the mortality rate has been found to be 1.4 times higher compared to the general population.[11] The mortality rate for severe haemophilia is 2.69 per 1,000 person-years, whereas the mortality rate for moderate/mild haemophilia is 1.19 per 1,000 person-years.

In Italian patients with haemophilia B between 1990 and 2007, the death rate was found to be 1.38, 6.84 and 12.85 per 1,000 person-years in people with mild, moderate and severe disease, respectively.[12] The overall death rate in patients with haemophilia was 7.1 per 1,000 person-years. The life expectancy increased in patients with haemophilia B from 40.3 years of age in 1990–1999 to 66.3 years of age in 2000–2007.

Darby *et al.* investigated mortality rates and life expectancy among patients with haemophilia in the UK.[11] The median life expectancy was 63 years in people with severe haemophilia, 75 years in moderate/mild haemophilia and 78 years in the general male population.

A Canadian study from 2022 using administrative health data from 2012 to 2019 reported a crude mortality of hemophilia B among male patients to be 4.3 per 1000 person-years. Standardized mortality ratios of hemophilia B compared to the general male population was 1.1 (95%CI 1.2;3.7)[13].

2.1.1.6 Important co-morbidities found in the target population

Co-morbidities considered important in the haemophilia B population are HIV, HCV and hepatitis B virus (HBV).

2.2 Module SII: Nonclinical safety findings

2.2.1 Important nonclinical safety findings and their relevance to human use

Table 2-4 Important nonclinical safety findings and their relevance to human use

Key safety findings (from nonclinical studies)	Relevance to human usage
Toxicity: Acute or repeat-dose toxicity: No histopathological findings in cynomolgus monkeys or Rowett nude rats indicating specific target organ or systemic toxicity of nonacog beta pegol. Nonacog beta pegol was well tolerated at doses up to 1,200 IU/kg every fifth day for 26 weeks in repeat dose toxicity studies in Rowett nude rats[14] and in cynomolgus monkeys at doses up to 1,300 IU/kg/week for 4 weeks. Special investigations, immunohistochemical (IHC) staining for PEG presence and electron microscopy (EM), were conducted to determine the localisation of PEG in brain tissue. PEG was shown to be distributed to connective tissue and epithelial cells of the choroid plexus in both rats and monkeys. Judged by EM (rat), PEG stored in lysosomes did not affect normal epithelial cell function, as evaluated from the overall cell ultrastructure, including rough endoplasmatic reticulum and polysomes. PEG was not detected in any other brain structures. The presence of PEG in the choroid plexus epithelial cells was not considered adverse as it did not result in histopathological changes or cellular dysfunction. **Juvenile toxicity:** A juvenile neurotoxicity study was conducted in male rats to evaluate effects on neurodevelopment, sexual maturation, and fertility following repeat-dosing of nonacog beta pegol. Male rats were dosed twice weekly from day 21 of age with nonacog beta pegol (120, 380 and 1200 IU/kg twice weekly) or vehicle for 10 weeks, followed by a dosing-free recovery period for 13 weeks. Overall, dosing nonacog beta pegol to juvenile rats did not result in any functional effects, as measured by neurobehavioural/neurocognitive tests, including motor activity, sensory function, learning and memory as well as growth, sexual maturation, and fertility. Test item-related histopathological changes commonly observed in relation to the administration of pegylated compounds were observed in the pituitary gland (vacuolated macrophages in Rathke's cleft).	In general, no safety concerns are expected for human use based on findings from repeat dose toxicity studies in relation to PEG presence; see below. Dosing of nonacog beta pegol to juvenile rats did not identify any adverse effects on growth, sexual maturation and fertility, clinical and histological pathology, or neurodevelopment related to PEG exposure and supports the prophylactic use of nonacog beta pegol in children.

Key safety findings (from nonclinical studies)	Relevance to human usage
Vacuolated macrophages were not considered as an adverse effect, but this vacuolization reflects the normal physiological function of the macrophages. No cellular inflammation or degeneration in relation to the vacuolated macrophages were observed. Plasma and choroid plexus PEG exposure increased with dose and consecutive doses, PEG exposure decreased but remained detectable in plasma in the high dose group and in all dose groups in choroid plexus after a 13-week recovery period. PEG was not detectable in cerebrospinal fluid. PEG was detected by IHC staining present in the extravascular space and in epithelial cells within the choroid plexus, in five circumventricular organs (CVOs: the pineal gland, median eminence, subfornical organ, vascular organ of lamina terminalis and area postrema), and motor neurons located in the brainstem (hypoglossal, ambiguous, oculomotorius, accessory abducens, trigeminus and facial motor nuclei). A diffuse stain for PEG was also observed in the nucleus tractus solitarius (NTS). The immunohistochemical stains in the CVO and cranial motor neurons increased dose dependently in the treatment period and there was a numerical reduction of PEG stain in the recovery period. No functional effects related to the PEG staining in the described areas have been observed.	
General safety pharmacology: Safety pharmacology endpoints (blood pressure, electrocardiography, respiratory rate, temperature, neurological/central nervous system endpoints and urinalysis) were included in the 4-week repeat dose toxicity study in cynomolgus monkey. No adverse effects on any of the safety pharmacology parameters were observed with nonacog beta pegol at up to 1,300 IU/kg. Mild and transient body tremors in the high dose group (3,750 IU/kg) were noted on a single or two occasions. Tremors were not seen beyond the third dose and only seen in the high dose group (3,750 IU/kg/week). The mechanism behind the tremors was not identified. Immunogenicity: Cross-reacting neutralising antibodies developed in monkeys resulting in acquired haemophilia and decreased exposure in monkeys. These results precluded the use of monkeys for chronic toxicity studies. No toxicity and no anti-drug antibodies developed in Rowett nude rats exposed to nonacog beta pegol through a 26-week dosing period.[14] Relative immunogenicity was compared in rats using the commercially available rFIX (BeneFIX®) and nonacog beta pegol. No difference in immunogenicity was seen between nonacog beta pegol and BeneFIX® at comparable weekly exposure for up to 8 weeks.	The dose (3,750 IU/kg) where tremors were seen in cynomolgus monkeys was 45–90 times higher than the recommended clinical dose (40-80 IU/kg) and it was considered unlikely to pose a safety risk to humans. No tremors were seen in any of the clinical studies. The predictability of animal models for human immunogenicity is generally considered to be low. There is no indication of an increased risk of immunogenicity with nonacog beta pegol compared to BeneFIX® in rats. Human immunogenicity has been addressed in the clinical development programme (see Section 2.7.3).

Key safety findings (from nonclinical studies)	Relevance to human usage
Other toxicity-related information or data: Distribution, metabolism and excretion of PEG: In distribution studies in mice and rats, nonacog beta pegol (radiolabelled in the PEG moiety) was distributed rapidly throughout the body, with the highest concentration in the highly perfused tissues. Low levels of radioactivity related to the PEG part were still detectable in the carcass 12 weeks after a single dose. The radioactivity was not confined to any particular organ. Terminal elimination half-life of the PEG moiety in plasma and tissues were estimated to 15–49 days depending on the organ. Metabolism and excretion studies showed that the protein part of nonacog beta pegol was degraded leaving 40 kDa PEG in circulation until excreted via urine (44–56%) and faeces (28–50%). Local tolerance: Local tolerance was assessed as part of the repeat dose toxicity studies in Rowett nude rats and monkeys and in a dedicated rabbit local tolerance study. Local reactions were primarily related to the injection procedure. Slightly more pronounced local reactions with nonacog beta pegol compared to vehicle control were seen in rabbits after intra-arterial administration but not after intravenous administration in Rowett nude rats or monkey.	The distribution and excretion studies show that PEG is cleared from organ/tissues over time (including choroid plexus). Based on these data, estimated elimination half-lives were calculated of all organs and used to create a model and to simulate plasma and tissue concentrations following repeated dosing in rats and in humans. The model was updated with data from the juvenile toxicity study. The results indicate that a maximum concentration (steady state) will be reached for most organs within 1 year and for choroid plexus within 4.5 years in humans.[a] Thus, in the clinical studies, steady state PEG levels are anticipated to have been reached; no unexpected safety findings have been seen. However, 'Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment' is considered an important potential risk (Section 2.7.3.6). The reactions were considered acceptable for clinical administration and are not considered an important safety concern for human. Injection site reactions are known to possibly occur when injecting a protein intravenously. It has been reported in the clinical studies and is included as an adverse drug reaction in the label.

[a]In clinical studies, 38 patients have been exposed to nonacog beta pegol for more than 4.5 years as of 31 Jul 2024.

Abbreviations: IHC = immunohistochemical; NTS= nucleus tractus solitarius; PEG = polyethylene glycol; rFIX = recombinant human blood coagulation factor IX; RMP = risk management plan.

2.2.2 Conclusions on nonclinical data

No safety concerns of nonacog beta pegol arising from nonclinical data have been confirmed by clinical data (Table 2-5).

The important potential risk 'Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment' is the only safety concern that is based on nonclinical data. A juvenile neurotoxicity study in male rats was performed to investigate the potential risk in juvenile animals. The findings were in line with the results of the repeat-dose toxicity studies in adult animals.

Table 2-5 Nonclinical summary of safety concerns

Safety concern	
Important identified risks (confirmed by clinical data)	• None
Important potential risks (not refuted by clinical data or which are of unknown significance)	• Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment
Missing information	• None

Abbreviation: PEG = polyethylene glycol.

2.3 Module SIII: Clinical study exposure

2.3.1 Brief overview of the clinical development programme

This risk management plan (RMP) is prepared for the indication of nonacog beta pegol in the European Economic Area (EEA) stated in Table 1-1.

The clinical study programme for nonacog beta pegol was initiated in 2009. An overview of clinical studies conducted with nonacog beta pegol is presented in Table 2-6. The DLP of the clinical study exposure presented in Sections 2.3.1 and 2.3.2 is 31 July 2024 (close to the DLP of the latest PSUR – 31 May 2024).

Nonacog beta pegol was investigated in paediatric, adolescent and adult male patients with severe and moderate haemophilia B with FIX activity ≤2%. The clinical study programme for nonacog beta pegol includes a first human dose study, a pharmacokinetic study and six phase 3 studies.

One phase 3 study is ongoing as of 31 Jul 2024 which is a study in Chinese PTPs with haemophilia B (NN7999-4670, aged 12-70 years) see Table 2-6.

Table 2-6 Overview of completed and ongoing clinical studies

Study ID/ Phase	Population	Description	Status
NN7999-3639 Phase 1	16 previously treated patients with haemophilia B aged 18-65 years	The first human dose study investigated the safety and pharmacokinetics of nonacog beta pegol in 3 ascending single i.v. doses.	Completed
NN7999-4260 Phase 1	15 adult patients (18–70 years) with haemophilia B	The randomised, two-sequence, two-period cross-over study compared the single-dose pharmacokinetics of nonacog beta pegol and ALPROLIX® in patients with haemophilia B (without inhibitors).	Completed
NN7999-3747 Phase 3a	74 previously treated patients with haemophilia B aged 13-70 years.	The randomised pivotal study investigated the safety, efficacy and pharmacokinetics of nonacog beta pegol. Patients on prophylaxis were exposed to nonacog beta pegol once weekly for 12 months and patients on on-demand for 6 months.	Completed
NN7999-3773 Phase 3a	13 previously treated patients with haemophilia B aged 13-70 years.	A surgery study investigating the safety and efficacy of nonacog beta pegol during surgical procedures.	Completed
NN7999-3775 Phase 3b	71 previously treated patients with haemophilia B, including patients from 3747 and 3773.	An extension study to the pivotal (NN7999-3747) and surgery studies (NN7999-3773) investigating the safety and efficacy following long-term exposure (up to 2 years) of nonacog beta pegol.	Completed
NN7999-3774 Phase 3a	25 previously treated patients with haemophilia B aged ≤12 years.	A paediatric study investigating the safety, efficacy and pharmacokinetics of nonacog beta pegol administered once weekly. The study consisted of a main phase of 52 weeks followed by an optional extension phase.	Completed
NN7999-3895 Phase 3a	54 previously untreated patients with haemophilia B aged <6 years. .	A study investigating the safety and efficacy of nonacog beta pegol. The study was completed when the patient had achieved 100 exposure days for up to 8 years (mean of 4.04 years).	Completed
NN7999-4670 Phase 3b	30 previously treated patients with haemophilia B aged 12 years–70 years.	A study evaluating efficacy, safety and pharmacokinetics of nonacog beta pegol when used for treatment and prophylaxis of bleeding episodes in Chinese patients with haemophilia B.	Ongoing

Note: All patients have moderate or severe haemophilia B (FIX activity ≤2%). A clinical study is considered completed when a final clinical study report is available. Any clinical study for which enrolment (FPFV) has begun but for which a final clinical study report is not available is considered ongoing.

Abbreviations: DLP = data lock point; FPFV= first patient first visit; i.v. = intravenous; RMP = risk management plan.

2.3.2 Clinical study exposure

No major differences in the safety profile of nonacog beta pegol have been observed between age groups or dose levels in the clinical studies. Therefore, exposure data from all completed and ongoing studies have been pooled to allow a more comprehensive assessment of the exposure and safety of nonacog beta pegol.

A total of 192 unique male patients (including 80 children [0–12 years of age]) have been exposed to nonacog beta pegol as investigational drug as of 31 July 2024 in 8 clinical studies. Of these, 130 previously treated male patients and 54 previously untreated male patients were exposed to nonacog beta pegol in the 7 completed clinical studies (NN7999-3639, NN7999-4260, NN7999-3747, NN7999-3773, NN7999-3775, NN7999-3774 and NN7999-3895) and 30 previously treated male patients have been exposed to nonacog beta pegol in the single ongoing study (N7999-4670). Most PTPs participated in more than one study/study phase; therefore, the sum of patients in the individual studies is higher than the total number of unique patients.

Exposure to nonacog beta pegol in all completed and ongoing studies as of 31 Jul 2024 is presented by duration (Table 2-7 and Figure 2-1) and type of treatment (Table 2-8). For exposure by age group and race/ethnicity, data from all completed and ongoing studies up to 31 Jul 2024 are provided in Table 2-9 and Table 2-10.

Table 2-7 Duration of exposure to nonacog beta pegol by type of treatment

Duration of exposure	Phase 1 Single dose N	Prophylaxis Multiple dose N	On-demand N	Surgery N
0 - <3 months	31	5	2	42
3 - <6 months	-	3	-	-
6 - <9 months	-	9	15	1
9 - <12 months	-	30	8	-
12 - <15 months	-	7	3	-
15 - <18 months	-	4	-	-
18 - <21 months	-	10	-	-
21 - <24 months	-	23	3	-
24 - <27 months	-	28	-	-
27 - <30 months	-	1	-	-
30 - <33 months	-	5	-	-
33 - <36 months	-	3	-	-
36 - <39 months	-	2	-	1
39 - <42 months	-	1	-	-
42 - <45 months	-	2	-	-
45 - <48 months	-	2	-	-
48 - <51 months	-	4	-	-
51 - <54 months	-	2	-	-
54 - <57 months	-	3	-	-
57 - <60 months	-	1	-	-
63 - <66 months	-	4	-	-
66 - <69 months	-	2	-	-
69 - <72 months	-	5	-	-
78 - <81 months	-	1	-	-
84 - <87 months	-	3	-	-
87 - <90 months	-	2	-	-
90 - <93 months	-	2	-	-
93 - <96 months	-	4	-	-
96 - <99 months	-	2	-	-
120 - <123 months	-	1	-	-
123 - <126 months	-	1	-	-
126 - <129 months	-	4	-	-
132 - <135 months	-	4	-	-

Duration of exposure to nonacog beta pegol by type of treatment

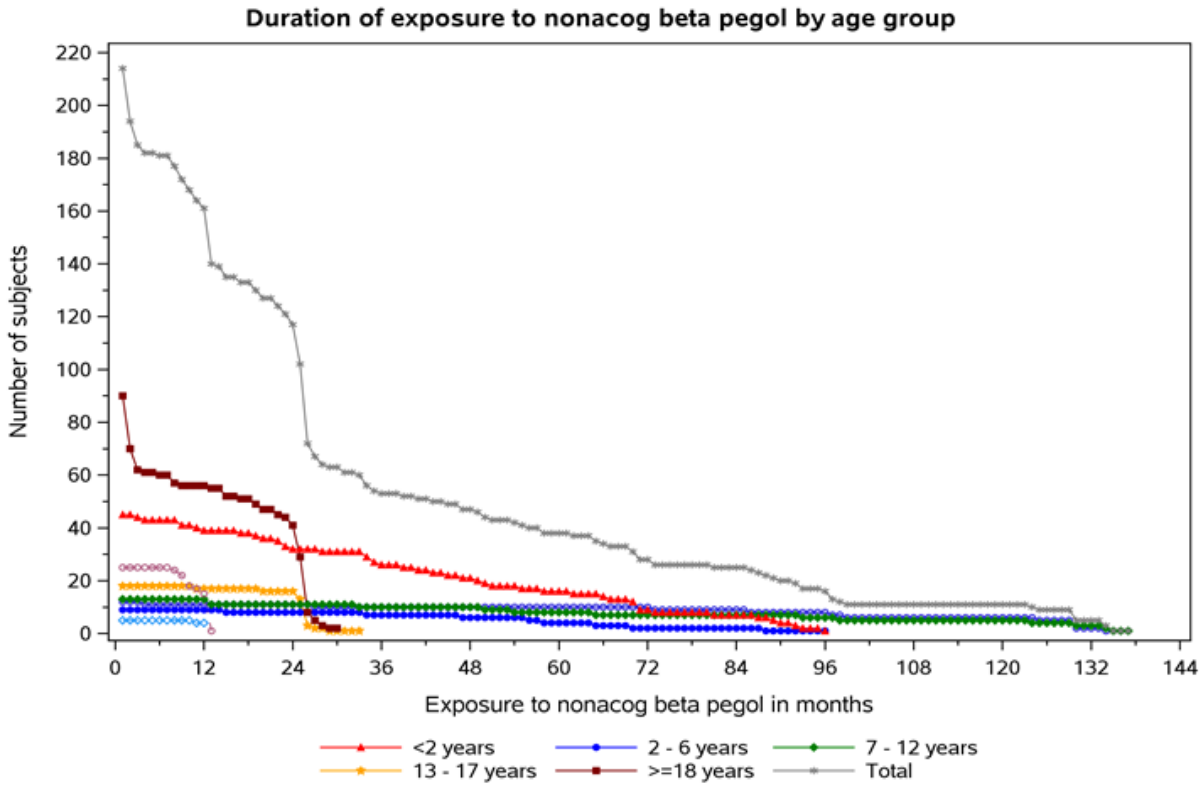
Duration of exposure	Phase 1 Single dose N	Prophylaxis Multiple dose N	On-demand N	Surgery N
135 - <138 months	-	1	-	-

Cumulative reporting period: start of the study - 31Jul2024.
Subjects may be counted in more than one type of treatment.
Surgery includes all major and minor surgeries across all trials.

nn7999/nn7999-filing/psurrmp_20241029_er
29OCT2024:09:28:43 - t_exp_dur.sas/t_0070_exp_dur.txt

Note: Exposure data up to 31 Jul 2024 are included from studies NN7999-3639, NN7999-3747, NN7999-3773, NN7999-3775, NN7999-4260, NN7999-3774, NN7999-3895 and NN7999-4670. Duration of exposure for patients on on-demand treatment represents total time on this treatment regimen.

Figure 2-1 Duration of exposure to nonacog beta pegol by age group



Note: Exposure data up to 31 Jul 2024 from studies NN7999-3639, NN7999-3747, NN7999-3773, NN7999-3775, NN7999-4260, NN7999-3774, NN7999-3895 and NN7999-4670.

Table 2-8 Total exposure by type of treatment

Type of treatment	Number of subjects	Exposure days	Subject years exposure
Phase 1 Single dose	31	31	1.83
Prophylaxis Multiple dose	181	28035	522.24
On-demand	31	529	13.34
Surgery	44	289	7.67
Total	214	28732	542.54

Cumulative reporting period: start of the study - 31Jul2024.
Subjects may be counted in more than one type of treatment, meaning the total reflects the number of unique subjects and not the sum of the rows above.
Surgery includes all major and minor surgeries across all trials.
There might be more than one type of treatment on the same exposure day.
nn7999/nn7999-filing/psurrmp_20241029_er
29OCT2024:09:28:41 - t_exp.sas/t_0080_exp_trt.txt

Note: Exposure data up to 31 Jul 2024 from studies NN7999-3639, NN7999-3747, NN7999-3773, NN7999-3775, NN7999-4260, NN7999-3774, NN7999-3895 and NN7999-4670.

Exposure by age group in all completed and ongoing clinical studies with nonacog beta pegol as investigational drug is presented in Table 2-9.

Table 2-9 Total exposure to nonacog beta pegol by age group

Age group	Number of subjects	Exposure days	Subject years exposure
Infants (<2 years)	55	11987	243.63
Children (2-6 years)	11	3626	69.28
Children (7-12 years)	14	4690	89.43
Adolescents (13-17 years)	23	1948	36.53
Adults (>=18 years)	92	6450	128.01
Total	192	28701	566.89

Cumulative reporting period: start of the study - 31Jul2024.
Subjects may be counted in more than one type of treatment, meaning the total reflects the number of unique subjects and not the sum of the rows above.
Surgery includes all major and minor surgeries across all trials.
There might be more than one type of treatment on the same exposure day.
nn7999/nn7999-filing/psurrmp_20241029_er
29OCT2024:09:28:42 - t_exp_age.sas/t_0085_exp_age.txt

Note: Exposure data up to 31 Jul 2024 from the clinical studies NN7999-3639, NN7999-4260, NN7999-3747, NN7999-3773, NN7999-3775, NN7999-3774, NN7999-3895 and NN7999-4670. All participants were male. Age is defined for each patient as age at baseline in the first study. No participants were above 65 years of age at baseline. An exposure day is a day where the patient received at least one dose of nonacog beta pegol.

Table 2-10 Total exposure to nonacog beta pegol by ethnic or racial origin

Ethnic / racial origin	Number of subjects	Exposure days	Subject years exposure
White	90	13528	262.23
Black Or African American	14	2007	43.01
Asian	77	10836	215.33
Other	11	2330	46.31
Total	192	28701	566.89

Cumulative reporting period: start of the study - 31Jul2024.
Subjects may be counted in more than one type of treatment, meaning the total reflects the number of unique subjects and not the sum of the rows above.
Surgery includes all major and minor surgeries across all trials.
There might be more than one type of treatment on the same exposure day.
nn7999/nn7999-filing/psurrmp_20241029_er
29OCT2024:09:28:44 - t_exp_race.sas/t_0086_exp_race.txt

Note: Exposure data up to 31 July 2024 from the clinical studies NN7999-3639, NN7999-4260, NN7999-3747, NN7999-3773, NN7999-3775, NN7999-3774, NN7999-3895 and NN7999-4670. An exposure day is a day where the patient received at least one dose of nonacog beta pegol. Two patients entered race as "Other" in NN7999-3747, but then entered race as White in NN7999-3775. The entries from NN7999-3747 are used here.

Exposure in special populations

No patients have been exposed to nonacog beta pegol in the clinical development programme within the special populations of pregnant or lactating women or patients with renal or hepatic impairment at the time of enrolment.

2.4 Module SIV: Populations not studied in clinical studies

2.4.1 Exclusion criteria in pivotal clinical studies within the development programme

Key exclusion criteria in the clinical development programme for nonacog beta pegol are presented in Table 2-11. The majority of the exclusion criteria are based on the guideline for the development of FIX products and were not introduced for safety reasons.[15]

Table 2-11 Key exclusion criteria in clinical studies within the development programme

Criteria	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Known or suspected hypersensitivity to active substance, any excipients or hamster proteins.	Allergic reactions may be potentially severe, life-threatening or fatal.	No. The product is not anticipated to be used in patients with known or suspected hypersensitivity. Due to the potential impact on the health of the target population, there is a contraindication for this patient population in the SmPC.
Previously untreated patients	In accordance with the regulatory guideline, all clinical studies in the development programme, except for NN7999-3895, only included previously treated patients with haemophilia B.	No. Safety information regarding this population is available in the safety database, as previously untreated patients have been monitored up to 8 years (mean of 4.04 years (0.17-7.97 years)) in the completed study NN7999-3895.

Criteria	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Patients >70 years	To avoid confounding by concomitant illness, elderly patients >70 years were excluded. Furthermore, the number of elderly patients with haemophilia B is limited.	No. Elderly patients >70 years were not excluded due to safety reasons. The safety profile of nonacog beta pegol is not expected to be different in elderly patients compared with patients in other age groups.
Patients with mild haemophilia B (FIX activity >5%) or moderate haemophilia B with FIX activity >2–5%	In accordance with regulatory guideline, only patients with severe and moderate haemophilia B with FIX activity ≤2% were included in the clinical studies.[15]	No. Patients with haemophilia B with FIX activity >2% were not excluded due to safety reasons. The safety profile of nonacog beta pegol is not expected to differ with severity of the disease. Replacement therapy with FIX follows the same basic principles regardless of severity of haemophilia B.
Females	Haemophilia is an X-linked disorder; females are carriers and are only rarely symptomatic.[16] Investigation in few female patients would not be representative for the female haemophilia B population.	Yes. Females, including breastfeeding and pregnant women, are included as missing information for nonacog beta pegol to monitor for adverse effects in this patient population. Fertility and use during pregnancy and lactation is addressed in the SmPC Section 4.6.
Patients with HIV with high viral load and low CD4 count	In accordance with the regulatory guideline,[14] patients enrolled in the clinical development programme should be HIV negative or if positive, should have a CD4 count >200/µL or and/or a viral load <400,000 copies/mL. High viral load is a sign of clinically relevant immunodeficiency, which might prevent the patients from developing inhibitors and thereby obstruct investigation of the primary objective.[17]	No. Patients with HIV with high viral load and low CD4 count were not excluded due to safety reasons. A high viral load of HIV in haemophilia B patients is not expected to affect the patients' medical need for replacement therapy with a FIX product.
Patients with a history of FIX inhibitors	FIX inhibitors might result in lack of efficacy in patients with haemophilia B treated with nonacog beta pegol. Patients with known history of FIX inhibitors were excluded as the intention of the studies was to investigate the immunogenicity and to demonstrate efficacy.	No. This population was not excluded due to safety reasons. The important identified risk of FIX inhibitor development is described in warning/precautions for use in the SmPC.
Patients with a history of thromboembolic events	Patients treated with FIX products have a potential risk for development of thromboembolic events. This risk is increased in patients with a history of thromboembolic events. To avoid confounding of the study endpoints, these patients have been excluded.	No. No patients developed thromboembolic events during participation in any of the nonacog beta pegol studies and the risk is expected to be low.

Criteria	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
		The risk of thrombotic complications is addressed in the SmPC (Warning/precautions for use). It is an important potential class risk for FIX products.
Platelet count <50,000 platelets/µL	Patients with low platelet counts have an increased bleeding tendency not related to insufficiency or lack of FIX. Low platelet count may therefore be a confounding factor.	No. Patients with low platelet counts were not excluded due to safety reasons. Replacement therapy with FIX must always be considered in the prevention and treatment of bleeds in patients with haemophilia B. Low platelet count in patients with haemophilia B will add to the bleeding tendency but the patients are not expected to respond differently to nonacog beta pegol.
Congenital or acquired coagulation disorders other than haemophilia B	Nonacog beta pegol is investigated for the treatment of patients with haemophilia B only. Patients with other coagulation disorders were excluded in order to avoid confounding by concomitant illness.	No. These patients were not excluded due to safety reasons. The safety profile of nonacog beta pegol is not expected to be different in patients with other coagulation disorders than haemophilia B. Nonacog beta pegol is indicated for the treatment of patients with haemophilia B only.

Abbreviations: CD4 = cluster of differentiation 4; FIX = factor IX; HIV = human immunodeficiency virus; SmPC = Summary of Product Characteristics.

2.4.2 Limitations of ADR detection common to clinical study development programmes

In the clinical development programme, patients were continuously exposed to nonacog beta pegol up to 10 years in the two completed clinical studies investigating safety and efficacy of nonacog beta pegol as replacement therapy (NN7999-3774 and NN7999-3895) as of 31 Jul 2024. A total of 89 patients have been exposed for more than 2 years (prophylactic treatment), where 39 patients were exposed for more than 4.5 years. However, due to the relatively low number of patients, the clinical study programme has a low likelihood of detecting uncommon or rare adverse reactions.

For the same reason, the clinical development programme is limited in its ability to detect adverse reactions caused by prolonged (long-term) exposure or cumulative exposure as well as adverse reactions with a long latency. However, the completed clinical studies that evaluated the long-term outcomes compensated for the relatively low number of patients exposed to nonacog beta pegol.

2.4.3 Limitations with respect to populations typically under-represented in clinical study development programmes

Table 2-12 Exposure by indication in special populations included or not in clinical study development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme. Haemophilia B is primarily a male condition; females are carriers and are only rarely symptomatic. No reproduction studies have been conducted with nonacog beta pegol. Nonacog beta pegol as well as the attached PEG molecule are large molecules unlikely to cross the placenta. The safety profile for nonacog beta pegol is not expected to be different in females compared with males. Therefore, based on the therapeutic need, the use of nonacog beta pegol may be considered.
Breastfeeding women	
Children below 12 years of age	In total, 79 children (0–12 years of age at the time of enrolment) have been exposed to nonacog beta pegol as of 31 Jul 2024 with 20,244 exposure days (401.38 patient-years of exposure).
Previously untreated patients	In total, 54 previously untreated patients (all children <6 years of age) have been exposed to nonacog beta pegol as of 31 Jul 2024 with 10,579 exposure days (216.94 patient-years of exposure).
Elderly patients	There is limited clinical experience with nonacog beta pegol in elderly patients (≥65 years). However, one 65-year-old elderly patient has been exposed to nonacog beta pegol in the clinical study NN7999-3747 and the same patient was recruited again in the study NN7999-3775 at the age of 66 years.
Patients with renal impairment	Not included in the clinical development programme (see Section 2.4.3.1).
Patients with hepatic impairment	Not included in the clinical development programme (see Section 2.4.3.2).
Patients with cardiovascular impairment	Not included in the clinical development programme.
Immunocompromised patients	Patients with HIV with high viral load and low CD4 T cell count were not included in the clinical development programme (see Table 2-11).
Patients with a history of FIX inhibitors	Not included in the clinical development programme (see Table 2-11).
Patients with a history of thromboembolic events	Not included in the clinical development programme (see Table 2-11).
Patients with relevant different ethnic origin	Nonacog beta pegol has primarily been investigated in White and Asian patients (Table 2-10). However, other races have also been included in the development programme. No difference in the therapeutic response to nonacog beta pegol is expected based on racial or ethnic origin.
Patients on ITI regimen	Not included in the clinical development programme.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme. Genetic polymorphism of hepatic cytochromes is not expected to have any influence on the metabolism of FIX. The PEG moiety in nonacog beta pegol is attached to the FIX activation peptide. Upon activation, the activation peptide, including the PEG moiety, is cleaved off leaving native FIX which then follows the same metabolic route as endogenous FIX.

Abbreviations: CD4 = cluster of differentiation 4; FIX = factor IX; ITI = immune tolerance induction; PEG = polyethylene glycol.

2.4.3.1 Patients with renal impairment

There is no clinical experience with nonacog beta pegol in patients with creatinine level ≥1.5 times above the upper limit of normal reference ranges. Based on nonclinical data, nonacog beta pegol and PEG are expected to be excreted via both the kidneys and the liver. High doses of nonacog beta pegol (1,200 IU/kg) have been administered nonclinically with no treatment-related macroscopic or histopathological changes, changes in biochemistry and haematology or clinical effects in the animals.

The safety profile of nonacog beta pegol is not expected to be different in patients with renal impairment compared to other patients. Patients with renal impairment were not excluded due to safety reasons; therefore, this population is not considered as missing information. Renal function will be monitored through routine pharmacovigilance in clinical studies and in the post-marketing setting.

2.4.3.2 Patients with hepatic impairment

There is limited clinical experience with nonacog beta pegol in patients with hepatic impairment, defined as alanine aminotransferase levels >3 times above normal levels. These patients were excluded from the clinical development programme in order to not confound the endpoints of the study. Among the patients with available data on HCV status, 48 patients (42%) were HCV positive. No children or adolescents were HCV positive.

The safety profile for nonacog beta pegol is not expected to be different in patients with hepatic impairment when compared to patients with normal liver function. During the clinical studies, some of the HCV positive patients had abnormal liver parameters, which is expected for this population; however, no trends in safety issues possibly related to nonacog beta pegol were identified. Hepatic function will be monitored through routine pharmacovigilance in clinical studies and in the post-marketing setting.

2.5 Module SV: Post-authorisation experience

2.5.1 Post-authorisation exposure

Novo Nordisk has released a total sales volume of 376,958,560 IU nonacog beta pegol cumulatively as of 31 Jul 2024. The number represents the total volume of product distributed from Novo Nordisk to external customers and does not reflect the actual use in patients. A crude estimate of the total post-authorisation patient exposure is approximately 3.011 patient-years of exposure (cut-off date: 31 Jul 2024).

2.5.1.1 Method used to calculate exposure

Estimation of the defined daily dose and calculation of estimated exposure

Nonacog beta pegol is indicated for both treatment and prophylaxis of bleeding in patients with haemophilia B of all age groups. The posology can be adjusted individually for each patient based on bleeding tendencies or severity of haemophilia B. Due to the numerous factors that influence the treatment regimen of each patient, an accurate calculation of patient exposure is not possible.

Considering that nonacog beta pegol is used for both treatment of bleeding and as prophylaxis, an estimated defined daily dose (DDD) for nonacog beta pegol could be calculated based on a once-weekly prophylactic dose of 40 IU/kg in a 60 kg patient (a suggested average patient weight, reflective of treatment in children and adults), equal to a DDD of 343 IU/day.

Based on these assumptions, the patient exposure for nonacog beta pegol is estimated as patient-years of exposure (PYE):

$$\text{PYE} = \frac{\text{Reported sales (IU)}}{\text{DDD } \left(\frac{\text{IU}}{\text{day}}\right) \text{x } 365 \left(\frac{\text{days}}{\text{years}}\right)}$$

A patient on a once-weekly prophylaxis dose regimen equates to approximately 52 exposure days (ED) per patient-year.

2.5.1.2 Exposure

The estimated patient exposure to nonacog beta pegol from post-marketing experience by operational region based on sales data is shown in Table 2-13. The exposure in Europe (the EEA, Switzerland and the UK) accounts for almost half of the total worldwide exposure cumulatively (48%), while the exposure in Japan and the US accounts for around 9% and 13% of the total exposure, respectively. The exposure in the 'Rest of the World' category accounts for 30% of the total exposure.

Table 2-13 Market exposure to nonacog beta pegol by operational region

	Patient-years of exposure[a]				
	Europe[b]	**Japan**	**US**	**Rest of the World**	**Total**
Cumulative period	1,448	267	393	903	**3,011**

Note: As the exposure is based on volume distributed to external customers and average daily usage rather than actual patient exposure, the numbers can be over- or underestimated. The EEA consists of the member states of the EU and three countries of the EFTA (Iceland, Liechtenstein and Norway).

[a]Patient-years of exposure (PYE) is calculated as reported sales (IU) / DDD (IU/day/365 [days/year]).

[b]Europe includes the EEA, Switzerland and the UK.

Abbreviations: DDD = daily drug dose; EEA = European Economic Area; PYE = patient-years of exposure.

Since the estimated exposure is based on sales figures and not on prescription information, it is not possible to provide estimated exposure by gender, age, dose or formulation.

2.5.2 Post-authorisation use and off-label use

Two non-interventional studies (NIS) designed to collect data on safety and effectiveness of nonacog beta pegol (prophylaxis treatment) in male patients with haemophilia B in real-life routine clinical practice are currently ongoing: one in Europe and Canada (NN7999-4031) and the other in Japan (NN7999-4404). Details on the post-authorisation safety study (PASS) NN7999-4031 are included in Section 3.2).

As of 31 Jul 2024, 65 patients have been exposed in the PASS in Europe and Canada (NN7999-4031) and 28 patients have been exposed in the NIS in Japan (NN7999-4404). No new safety concerns have been identified from these studies.

Off-label use

As of 31 Jul 2024, a total of 15 cases of off-label use have been reported cumulatively. Almost half of the cases (8 cases) concerned children who were treated with nonacog beta pegol in the EU. Due to the age limitation that restricts the use of nonacog beta pegol in children below the age of 12 years in the EU, this is considered outside the approved indication in the EU. The remaining cases concerned off-label dosing (4 cases), off-label use due to Incorrect schedule of administration (1 case), Intentional deviation from dosage regimen (1 case) and Off label use (1 case). Of the 15 cases, 4 cases had co-reported events which were non serious: an adverse event with the PT Pain, a medication error with the PT Product storage error, an AE with PT Heart rate increased and PT Epistaxis and an event with PT Injection site swelling. One serious case concerned a 33-year-old male who was treated with nonacog beta pegol for haemophilia A (off label use in unapproved indication) and reported the following PTs: Arthralgia, Blood pressure increased, COVID-19, Haemarthrosis, Poor venous access, Post procedural contusion and Vein disorder. While the outcome of COVID-19 was not recovered, the outcomes of the other PTs were unknown.

2.6 Module SVI: Additional EU requirements for the safety specification

2.6.1 Potential for misuse for illegal purposes

FIX products are not known to have stimulating, sedative or hallucinogenic effects on the central nervous system. Furthermore, the pharmacodynamic profile of the drug does not indicate a potential for misuse for illegal purposes.

As of 31 Jul 2024, 4 cases of misuse or abuse have been reported cumulatively with 2 cases each of PT Intentional product misuse and Intentional dose omission. The Intentional product misuse concerned 2 events of patients rarely delaying, postponing or missing a treatment on purpose. One case of Intentional dose omission concerned a 5-year-old whose treatment was sometimes delayed or postponed intentionally due to pain in the injection site and the other case of Intentional dose omission was the patient cancelling the infusion appointment due to anxiety. Reports of misuse for illegal purposes will be continuously monitored through routine pharmacovigilance.

2.7 Module SVII: Identified and potential risks

2.7.1 Identification of safety concerns in the initial RMP submission

Not applicable as the initial RMP was approved prior to revision 2 of the guideline on Good Pharmacovigilance Practices (GVP) Module V coming into effect on 31 Mar 2017.

2.7.2 New safety concerns and reclassification with a submission of an updated RMP

No new safety concerns have been identified and no currently endorsed safety concerns have been reclassified with the submission of this RMP.

2.7.3 Details of important identified risks, important potential risks, and missing information

2.7.3.1 Important identified risk: Allergic/hypersensitivity reactions

Potential mechanisms

Any intravenously administered exogenous protein such as FIX is associated with a potential risk for hypersensitivity/allergic reactions. The aetiology of the hypersensitivity reaction is not fully understood but could be mediated by antibody–drug complexes, by complement activation-related pseudo-allergy reactions or by IgE.

Evidence source and strength of evidence

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 studies with nonacog beta pegol as the IMP and are described in the literature in patients treated with FIX products.[18] The percentage of patients that have experienced serious hypersensitivity/allergic reactions in the clinical studies 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.

Characterisation of the risk

Frequency/Seriousness/Outcome

Clinical studies

Allergic reactions or hypersensitivity reactions assessed as possibly or probably related to nonacog beta pegol have been reported in approximately 19.6% of all patients exposed to nonacog beta pegol in all completed and ongoing Novo Nordisk-sponsored clinical studies (85 events in 42 participants).

Four (4) serious allergic/hypersensitivity reactions assessed as possibly related to nonacog beta pegol have been reported cumulatively in the clinical studies (one in a PTP and 3 in PUPs). Most (>95%) of the allergic/hypersensitivity reactions reported from clinical studies were non-serious and with an outcome reported as recovered or recovering. No fatal cases were reported.

Post-marketing data

Cumulatively, 7 serious allergic/hypersensitivity reactions have been reported, 6 of which were from spontaneous post-marketing sources. One (1) serious AR was reported with nonacog beta pegol as the suspected drug in a spontaneous case report based on a literature article that does not mention the specific rFIX product used.

Incidence and prevalence of allergic reactions

Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported for marketed FIX products. A retrospective study describing the incidence of allergic reactions to FIX treatment in patients with haemophilia B by reviewing medical charts from centres in North America and

Europe found that 3.9% of the patients had allergic reactions. Among those receiving rFIX, 2.45% of the participants had an allergic reaction and 3.41% of individuals taking pdFIX products developed an allergic reaction.[18]

Based on the reported number of allergic/acute reactions reported to the European Haemophilia Surveillance Survey and the number of people included by the end of each surveillance year, the incidence rate of allergic reactions has been estimated to be in the range of 1.7–2.8 events per 1,000 person-years.[19]

Although PEG has been found to be immunologically inert, some studies have reported that PEGylated therapeutics can activate the complement system after the first dose. Approximately 75% of acute allergic reactions are not initiated or mediated by IgE antibodies and are referred to as pseudoallergic reactions.[20] One case report concerning allergic reactions in connection with the administration of a PEGylated drug has been reported. It concerned a patient who experienced an anaphylactic shock caused by PEG and a positive skin prick test result for a PEGylated drug (PEGylated interferon-a2a).[21]

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.[15, 22]

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.[21]

Preventability

Nonacog beta pegol is contraindicated in patients with hypersensitivity to the active substance, excipients or to hamster protein.

Patients should be informed of the early signs of hypersensitivity reactions. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact a healthcare professional who should ensure appropriate treatment.

As patients with FIX inhibitors are at an increased risk of allergic reactions, patients should be monitored for inhibitor formation.

Impact on the benefit−risk balance of the product

The risk of allergic reactions/hypersensitivity reactions is a class risk for all protein-based medicinal products. Immune reactions can range from mild to severe and life-threatening. The impact on the benefit–risk balance of the product is assessed to be moderate, considering the severity of the reactions and the low incidence of severe and life-threatening reactions.

Public health impact

The impact on public health is negligible, as the haemophilia B population is relatively small and the predicted incidence of FIX inhibitor development in the target population is low.

2.7.3.2 Important identified risk: FIX inhibitors

Potential mechanisms

Intravenous administration of proteins can trigger the immune system, leading to the development of antibodies. In FIX-deficient patients, the immune system is more likely to recognise nonacog beta pegol as an antigen, compared to patients without FIX deficiency. Neutralising antibodies against FIX result in an inhibitory action, thus decreasing or preventing the haemostatic effect of nonacog beta pegol (lack of efficacy). Consequently, lack of drug effect may point to inhibitor development and such cases will be evaluated in connection with this risk.

Evidence source and strength of evidence

This is an important class risk for all FIX products. Development of neutralising anti-FIX antibodies (FIX inhibitors) has been observed in the completed clinical study with nonacog beta pegol in previously untreated patients 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.[8, 23-26] The frequency of inhibitor development in clinical studies 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.

Characterisation of the risk

Frequency/Seriousness/Outcome

Clinical study data

Five (5) out of 54 PUPs (9.3%; no PTPs) have been reported with confirmed FIX inhibitor development in the clinical studies with nonacog beta pegol as the investigational drug. Four out of the 5 confirmed cases were serious and were assessed as possibly/probably related to the study product, and the patients did not recover from the events.

Post-marketing data

Two serious ARs of ‘FIX inhibition’ and one serious AR of ‘Anti-FIX antibody increased’ have been received from spontaneous post-marketing sources. All ARs were reported with nonacog beta pegol as the suspected drug based on a literature article that does not mention the specific rFIX product used.

Incidence and prevalence of FIX inhibitor development

According to the World Federation of Hemophilia (WFH), 0.9% of the patients reported to have haemophilia B had inhibitors in 2022. According to Fischer *et al*., as part of the European Haemophilia Safety Surveillance, the cumulative incidence of inhibitor development in PUPs with

severe haemophilia B was 6.9%.[8] Van Den Berg *et al*. reported that 11.8% of PUPs with severe haemophilia B developed FIX inhibitors.[27]

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.[28]

Preventability

No clinically relevant methods are available for the prevention of inhibitor development in replacement therapy.

Impact on the benefit−risk balance of the product

FIX inhibitor development is a class risk for FIX products with the main clinical consequence of lack of efficacy. The consequences can be severe or life-threating depending on disease severity. Considering the frequency of events in PUPs observed in clinical studies, which is comparable to other FIX products, and the severity of the clinical consequences, the impact on the benefit–risk balance of the product is assessed to be moderate.

Public health impact

The impact on public health is negligible, as the haemophilia B population is relatively small and the actual incidence of FIX inhibitor development in the target population is low.

2.7.3.3 Important potential risk: Thromboembolic events

Potential mechanisms

Local fibrin formation at sites of endothelial damage due to vascular disease may result in thrombus formation.

Evidence source and strength of evidence

This is a class risk for FIX products. No thromboembolic events have been reported in patients treated with nonacog beta pegol in clinical studies 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.[29] The strength of evidence for the risk of thromboembolic events in patients treated with nonacog beta pegol is considered low.

Characterisation of the risk

Frequency/seriousness/outcome

Clinical study data

Cumulatively, 2 non-serious events (in 1 patient) reported in PTPs from clinical studies have been captured by the MedDRA search term for the risk cumulatively (PTs Device occlusion [2 AEs]) However, the AEs were not true thromboembolic events.

Post-marketing data

One serious solicited case was reported from Haemophilia Infusion Program with PT Transient ischaemic attack. Injection site extravasation was assessed as the possible causality for the event.

Incidence and prevalence of thromboembolic events

A systematic review of prospective studies (1990–2001) about thrombotic events in relation to coagulation factor concentrates reported 11 cases of thrombophlebitis among 748 patients with haemophilia B, which corresponds to 1.47%.[29] The available data on mortality causes in the overall haemophilia population cover ischaemic heart disease (6% of total mortality cases), cerebrovascular disease (5%) and diseases of the circulatory system (17%).[10]

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.

Preventability

In patients with high risk, clinical surveillance for early signs of thrombotic and consumptive coagulopathy. The benefit of treatment with nonacog beta pegol should be weighed against the risk of these complications.

Impact on the benefit−risk balance of the product

The risk of thromboembolic events is a class risk for FIX products, which may affect cardiovascular and cerebrovascular morbidity and potentially mortality. The impact on the benefit−risk balance of the product is assessed to be low, considering the severity of the condition and the incidence of the events, as no cases have reported from clinical studies or in post-marketing reports.

Public health impact

The impact on public health is negligible, as the haemophilia B population is small and the actual incidence of thromboembolic events in the target population is low.

2.7.3.4 Important potential risk: Nephrotic syndrome following ITI

Potential mechanisms

Nephrotic syndrome following ITI is an unexplained and unusual immunological reaction.

Evidence source and strength of evidence

Evidence from the literature supports the high risk of developing nephrotic syndrome following ITI in patients with haemophilia B.[30] Nephrotic syndrome following ITI has not been reported in clinical studies 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.

Characterisation of the risk

Frequency/Seriousness/Outcome

No adverse events have been reported from post-marketing sources cumulatively. Nonacog beta pegol has not been investigated for ITI in clinical studies.

Incidence and prevalence of nephrotic syndrome following ITI

In patients with haemophilia B with FIX inhibitors, the use of ITI with a FIX product to reduce inhibitors has been shown to result in nephrotic syndrome in 30% of the patients.[30]

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.[31]

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.

Preventability

Monitoring of renal function may help identify patients on ITI who may develop nephrotic syndrome.

Impact on the benefit−risk balance of the product

The predicted incidence of events of nephrotic syndrome following ITI in the post-marketing setting is low given the overall poor success rate of ITI for treating patients with haemophilia B that have developed inhibitors. Considering that clinicians are likely to be reluctant to use ITI and that the incidence of inhibitor development in patients with haemophilia B is relatively low, the impact on the benefit−risk balance is assessed to be low despite the severity of the condition.

Public health impact

The impact on public health is negligible, as the haemophilia B population is small. Also, the predicted incidence of nephrotic syndrome following ITI in the target population is low since ITI is not expected to be frequently used in patients with haemophilia B due to the low success rate.

2.7.3.5 Important potential risk: Inadequate treatment due to assay overestimation of FIX activity

Potential mechanisms

In routine coagulation testing to assess FIX activity, an assay measuring activated partial thromboplastin time (aPTT) is commonly used. Reagent interference may occur when using this assay due to PEGylation of nonacog beta pegol and this may result in over- or underestimation of FIX activity. This could result in inadequate treatment of a bleed or in overdosing with nonacog beta pegol.

Evidence source and strength of evidence

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 clinical studies. Few adverse reactions due to an assay related overestimation of FIX activity levels have been reported from post marketing sources, however, complete assessment of the events could not be performed due to missing information.

Characterisation of the risk

FIX activity can be measured by the one-stage clotting assay or the two-stage chromogenic assay. The one-stage clotting assay is the most commonly used assay worldwide, but there is a PEG−aPTT interference which could result in over- or underestimation of FIX activity of approximately 50–600% depending on the aPTT reagent.[32-33] Silica-containing aPTT reagents are mainly those causing the overestimation of FIX activity.[34] A limited number of aPTT reagents give accurate results.[35] There is no interference when using the chromogenic assay, but this is less widely used, especially in the US. Only a few FIX chromogenic assays have been approved for diagnostic use in Europe. FIX chromogenic kits are not currently approved in the US (research use only) but are in the process of being developed for commercial use by other companies.

Overestimation of FIX activity could result in inadequate treatment of a patient followed by bleeding/continued bleeding. This could have serious consequences for the patient (e.g., a patient with intracranial bleeding).

Frequency/Seriousness/Outcome

Cumulatively, 23 adverse reactions due to an assay related overestimation of FIX activity levels have been reported from post marketing sources of which 2 events were serious. The most frequent PTs were Product dose omission issue (9 events), Therapeutic response decreased (5 events) and Drug ineffective (4 events). While 3 events had outcome recovered/recovering, one case reported an outcome not recovered. Outcome of majority of the events were unknown or not reported (19 events). A serious case of aggravated knee joint bleeding was reported with the outcome recovered. Considering the limited information and suspicion of subtherapeutic response, the

causality was assessed as possibly related to aggravation of haemarthrosis. The other serious case concerned an event 'Therapeutic product effect decreased' at/after surgery. As drug effect decreased is listed in safety information and important details of the event such as detailed description of the event along with the outcome, laboratory investigations, dosage and route of administration of the suspect drug, concomitant medication and treatment received were unavailable, complete medical assessment of the case could not be performed.

Incidence and prevalence

The incidence and prevalence of the risk-related AEs are unknown.

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).

Preventability

- Use of a chromogenic assay if available or use of a one-stage clotting assay qualified for use with nonacog beta pegol.
- Information about monitoring of FIX activity in the labelling.

Impact on the benefit−risk balance of the product

The actual impact on the benefit−risk balance of the product is currently assessed to be limited due to the lack of cases reported from post-marketing sources. Depending on the reporting rate of adverse events related to assay-related overestimation of FIX observed when nonacog beta pegol has been on the market for a longer period, the impact may change.

Public health impact

The impact on public health is expected to be negligible as the haemophilia B population is small.

2.7.3.6 Important potential risk: Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment

Potential mechanisms

This potential risk is based on nonclinical findings showing the presence of PEG in certain tissues in repeat-dose studies in rats and monkeys. No adverse events were associated with the presence of PEG. The risk does not address a specific clinical outcome, and it is unknown whether long-term exposure to PEG will have any clinical consequences. Thus, a mechanism has not been proposed.

Evidence source and strength of evidence

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 accumulation of PEG in any organ or tissue in humans nor clinical consequences have been established.

Characterisation of the risk

In repeat-dose toxicity studies in monkeys and rats, PEG was shown by immunohistochemical (IHC) staining to be present in blood in connective tissue and cytoplasm of epithelial cells of the choroid plexus of the brain. No other brain structures showed the presence of PEG. The presence of PEG was not associated with microscopic signs of cellular vacuolation or dysfunction. PEG was found in vesicles (lysosomes) in the epithelial cells of the choroid plexus in high-dose animals from the 26-week Rowett nude rat study, when assessed by transmission electron microscopy.[14] The PEG stored in lysosomes did not affect normal epithelial cell function as judged from the overall cell ultrastructure, including rough endoplasmic reticulum and polysomes and was thus not considered adverse.

A juvenile neurotoxicity study was conducted in male rats to evaluate effects on neurodevelopment, sexual maturation, and fertility following repeat-dosing of nonacog beta pegol. Male rats were dosed twice weekly from day 21 of age with nonacog beta pegol (120, 380 and 1200 IU/kg twice weekly) or vehicle for 10 weeks, followed by a dosing-free recovery period for 13 weeks. Overall, dosing nonacog beta pegol to juvenile rats did not result in any functional effects, as measured by neurobehavioural/neurocognitive tests, including motor activity, sensory function, learning and memory as well as growth, sexual maturation, and fertility.

Test item-related histopathological changes commonly observed in relation to the administration of pegylated compounds were observed in the pituitary gland (vacuolated macrophages in Rathke's cleft). Vacuolated macrophages were not considered as an adverse effect, but this vacuolization reflects the normal physiological function of the macrophages. No cellular inflammation or degeneration in relation to the vacuolated macrophages were observed.

PEG was detected by IHC staining present in the extravascular space and in epithelial cells within the choroid plexus, in five circumventricular organs (CVOs) and five motor neurons located in the brainstem. A diffuse stain for PEG was also observed in the nucleus tractus solitarius (NTS). The immunohistochemical stains in the CVO and cranial motor neurons increased dose dependently in the treatment period and there was a numerical reduction of PEG stain in the recovery period. No functional effects related to the PEG staining in the described areas have been observed.

Plasma and choroid plexus PEG exposure increased with dose and consecutive doses, PEG exposure decreased but remained detectable in plasma in the high dose group and in all dose groups in choroid plexus after a 13-week recovery period. PEG was not detectable in cerebrospinal fluid.

The distribution and excretion studies in rats and mice show that PEG is cleared from organ/tissues over time (including choroid plexus). Based on these data, estimated elimination half-lives of all organs (15–49 days) were calculated and used to create a model and to simulate plasma and tissue concentrations following repeated dosing in rats and in humans. The model was updated with data

from the juvenile toxicity study (for details about the juvenile study refer to Section 2.2.1). The results indicate that a maximum concentration (steady state) will be reached for most organs within 1 year and for choroid plexus within 4.5 years in humans. This was substantiated by PEG plasma concentration data in samples from patients in study NN7999-3774 documenting that steady-state plasma levels were achieved within the first 6 months of treatment. No unexpected safety findings have been seen.

The MedDRA search terms for this important potential risk have been chosen based on nonclinical data showing the presence of PEG in epithelial cells of the choroid plexus in rats and monkeys treated with nonacog beta pegol (SOCs Nervous system disorders and Psychiatric disorders) and based on known sites of PEG elimination, i.e., kidneys and liver (SMQs Acute renal failure and Drug related hepatic disorders, respectively).

Frequency/seriousness/outcome

All adverse events captured from clinical studies or post-marketing sources by the broad MedDRA search terms have been evaluated by Novo Nordisk as unlikely to be potential clinical consequences of long-term exposure to PEG based on, e.g., alternative aetiology, lack of temporal relationship, short duration of event and full recovery while receiving nonacog beta pegol or insufficient time of exposure.

Clinical study data

A total of 117 AEs (PUP - 45; PTP - 72) have been captured cumulatively by the broad MedDRA search terms and evaluated case by case. Around 90% were assessed as unlikely related to treatment with nonacog beta pegol by the investigator. The events which were possibly related to nonacog beta pegol (9 events) most commonly reported PT ‘Headache’ and the outcome of the majority of events was reported as recovered. Most of the AEs captured from clinical studies were non-serious (>90%) and with an outcome reported as ‘recovered’ or ‘recovering’ (>80%). Fourteen events had outcome not recovered and 3 cases of fatality were reported; 5 events lead to the withdrawal of nonacog beta pegol. Headache was the most frequently reported PT with 45 events.

Post-marketing data

Cumulatively, 59 AEs (in 44 cases) have been captured from post-marketing sources with nonacog beta pegol as the suspected drug in the MedDRA search for AEs potentially associated with the important potential risk. Most AEs captured from post-marketing sources were reported as non-serious (41 of 59 events) and most cases had limited information available. Headache (15 events), Dizziness (8 events) and Tremor (5 events) were the most frequently reported PTs of the events captured; notably, most (22 of 28 events) events of headache, dizziness and tremor were reported as nonserious. Of the 18 serious events, the outcome of 8 events was recovered / recovering, while 2 events did not recover. Two serious events (PTs Cerebral haemorrhage and Hepatic encephalopathy) with fatal outcome were reported with causality assessed as unlikely related to nonacog beta pegol.

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.

Preventability

No clinically relevant methods are available to prevent a potential accumulation of PEG. However, PEG will reach steady state and will not accumulate indefinitely.

Impact on the benefit−risk balance of the product

Possible clinical consequences of potential PEG accumulation are currently unknown. The majority of nonclinical data suggest that at clinically relevant doses PEG is inert and there are no functional changes or changes of toxicological relevance. Nonclinical and clinical safety data available for nonacog beta pegol and other relevant marketed pegylated products containing ≥40 kDa PEG (marketed for several years for long-term use in adults) have not shown any clinically relevant adverse reactions associated with PEG accumulation. Should a causal relationship be established between long-term exposure to PEG and any clinical consequences in patients treated with nonacog beta pegol, the impact will depend on the type, severity and incidence of adverse events.

Public health impact

The impact on public health is negligible, as the haemophilia B population is small.

2.7.3.7 Missing information: Females, including pregnant and lactating women

Evidence source

The safety concern is based on theoretical considerations.

Population in need of further characterisation:

Pregnant and lactating women were excluded from clinical development programme. No reproduction studies have been conducted with nonacog beta pegol since haemophilia B is primarily a male condition. It is unknown whether nonacog beta pegol is excreted in human breast milk.

2.8 Module SVIII: Summary of safety concerns

Table 2-14 Summary of safety concerns – nonacog beta pegol

Summary of safety concerns	
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 • Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment
Missing information	• Females, including pregnant or breastfeeding women

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

3 Pharmacovigilance plan

3.1 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

3.1.1 Specific adverse reaction follow-up questionnaires

Factor IX inhibitor questionnaire: During post-marketing surveillance, adverse events related to inhibitor development will be closely monitored. If inhibitors are suspected, a FIX inhibitor questionnaire will be utilised (Annex 4A). The objective of the questionnaire is to assess and characterise the risk of FIX inhibitor development with nonacog beta pegol. The questionnaire includes questions on treatment and inhibitor history as well as questions on the reported event. The form also documents relevant medical history and laboratory tests performed.

Hypersensitivity questionnaire: During post-marketing surveillance, adverse events concerning allergic reactions will be closely monitored. If an allergic /hypersensitivity reaction is reported, a questionnaire will be utilised. The objective of the form is to assess and characterise the risk of allergic reactions associated with nonacog beta pegol. The questionnaire is designed to enable better documentation of the signs and symptoms of a reported allergic reaction. The form also documents relevant medical history and laboratory tests performed. It will be utilised to collect important information to allow for a full assessment of causal relationship to nonacog beta pegol on a case by case basis (Annex 4B).

Thromboembolic events questionnaire: During post-marketing surveillance, thromboembolic events will be closely monitored. If a thromboembolic event is reported, a questionnaire will be utilised. The objective of the questionnaire is to assess and characterise the potential risk of thromboembolic associated with nonacog beta pegol. The form is designed to enable better documentation of the signs and symptoms of a reported thromboembolic event (Annex 4C).

Follow-up questions for post-marketing surveillance of the safety issue of potential clinical consequences of long-term PEG exposure: During post-marketing surveillance, CNS-related adverse events and events related to renal or hepatic impairment will be closely monitored. If any such adverse events are reported, follow-up questions will be used to collect important information to allow for a full assessment of causal relationship to nonacog beta pegol on a case by case basis (Annex 4D). The objective of the follow-up questions is to assess and characterise CNS-related adverse events as well as events related to renal or hepatic impairment that might potentially be due to long-term PEG exposure.

3.1.2 Other forms of routine pharmacovigilance activities

Aggregated analyses of safety data concerning events of potential relevance for the risk 'Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment' are included in the PSURs. The analyses also include non-serious adverse events from clinical studies.

3.2 Additional pharmacovigilance activities

3.2.1 NN7999-4031 PASS summary

Study title:

A non-interventional post-authorisation safety study (PASS) in male haemophilia B patients receiving nonacog beta pegol (N9-GP) prophylaxis treatment.

Rationale and study objectives:

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.

Exploratory objectives are to monitor possible clinical effects of long-term exposure to nonacog beta pegol prophylaxis in patients with haemophilia B, including optional assessments of kidney and liver function parameters, neurological function and the patients' PEG plasma level, in situations where this is allowed as part of a non-interventional study. Additional exploratory objectives are to further investigate health economic/patient reported outcomes (PROs).

Study design:

This is a prospective, multinational, non-interventional PASS in male haemophilia B patients without current inhibitors designed to obtain additional real-world post-authorisation exposure and safety information. Patients fulfilling the inclusion criteria can participate in the study regardless of previous treatment regime if any, allowing inclusion of patients previously exposed to nonacog beta pegol in the paradigm™ clinical development programme, but also patients exposed to other FIX products.

Patients will be treated with commercially available nonacog beta pegol according to local clinical practice at the discretion of the physician. Patients on any treatment regimen with N9-GP and patients undergoing surgical procedures receiving nonacog beta pegol for perioperative haemostasis can be included in the study.

A baseline visit will be documented for all patients after informed consent is signed. When all inclusion and exclusion criteria have been confirmed, baseline data can be obtained and recorded. Assessments will be documented when a patient visits the clinic according to local clinical practice until end of study visit.

Study visits will take place when patients attend visits at the clinic, as of local clinical practice. Data and results from assessments and laboratory sampling performed according to local clinical practice or upon physician's discretion will be recorded upon availability.

Study populations:

Male patients of any age with haemophilia B assigned to nonacog beta pegol prophylaxis treatment for which there is a negative FIX inhibitor test at study entry.

Milestones:

Planned duration of the enrolment is minimum 4 years.

Milestone	Date
Protocol submission	31 Jul 2018
Start of data collection Defined as first entry of patient data	01 Apr 2019
End of study Defined as last patient last visit (LPLV)	15 Dec 2027
End of data collection Defined as data base lock (DBL)	02 Feb 2028
Registration in the EU PAS Register	Obtained on 20 Nov 2018; EUPAS26592
Study progress report	06 Dec 2019 (data cut-off: 01 Dec 2019)
Study progress report 2	December 2020
Study progress report 3	After 31 May 2021 (aligned with international birth date [IBD] for nonacog beta pegol)
Study report	07 Jun 2028

Abbreviations: DBL = data base lock; IBD = international birth date; LPLV = last patient last visit.

3.2.2 NN7999-4413 PASS summary

Study title:

Adverse event data collection from external registries on nonacog beta pegol.

Rationale and study objectives:

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).

Study design:

This is as registry-based post-authorisation safety study (PASS) collecting data from existing third-party databases. The included registries are the PedNet Haemophilia Registry and EUHASS (European Haemophilia Safety Surveillance) and the study may include other international or national/local registries.

Study populations:

All patients with haemophilia B treated with nonacog beta pegol who reports adverse events to the PedNet Registry and the European Haemophilia Safety Surveillance System (EUHASS), and possibly other national or international registries.

A decision to initiate treatment with commercially available nonacog beta pegol has been made by the patient/Legally Acceptable Representative (LAR) and the treating physician before and independently from the decision to include the patient in the registries in scope.

Milestones

Milestones	Planned date
Start of data collection	01 Apr 2019
End of study	15 Dec 2027
End of data collection	02 Feb 2028
Reporting of study results	In PSURs based on annual reports from registry

Abbreviations: PSUR = periodic safety update report.

3.2.3 Clinical study NN7999-3774

Study title

Safety, efficacy and pharmacokinetics of nonacog beta pegol in previously treated children with haemophilia B.

Rationale and study objectives

The rationale for performing this study 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.

Primary objective

To evaluate immunogenicity of nonacog beta pegol in previously treated patients (PTP) ≤12 years of age.

Secondary objectives

To investigate the following in patients ≤12 years of age previously treated with a FIX product and with moderate to severe haemophilia B during the study period:

- Safety other than immunogenicity of nonacog beta pegol
- Efficacy of nonacog beta pegol in long-term prophylaxis treatment
- Pharmacokinetic properties of nonacog beta pegol
- To monitor the FIX consumption for prophylaxis and breakthrough bleeding episodes
- To evaluate patient reported outcomes (PRO) and assess health economic impact of treatment with nonacog beta pegol

Study design

This is an open-label, single-arm, multinational, non-controlled, confirmatory study investigating safety, efficacy and pharmacokinetics of nonacog beta pegol in prophylaxis and treatment of breakthrough bleeding episodes in previously treated children with haemophilia B (12 years of age and younger at inclusion), with an extension phase. The study consists of a main phase and an extension phase. The duration of the main phase for each patient was 52 weeks. After completion of the main phase, the patients could continue in an extension phase, lasting until nonacog beta pegol is commercially available in the relevant countries or if the nonacog beta pegol programme is terminated, unless otherwise required by national regulations. In the UK, the end of study was defined as 31 Oct 2018.

The patients were stratified into two age groups: 0–6 years and 7–12 years. A minimum of 10 patients in each age group had to complete the main phase of the study with at least 50 EDs. The study has one treatment arm where all the patients received nonacog beta pegol once weekly for prophylaxis. In the extension phase, the same dosing regimen is administered. In addition, nonacog beta pegol will be administered in case of breakthrough bleeding episodes during the main phase and extension phase.

Study populations

Inclusion criteria

- Informed consent obtained before any study-related activities
- Male patients with moderately severe or severe congenital haemophilia B with a FIX activity level ≤2% according to medical records
- Age ≤12 years (until patient turns 13 years, at time of inclusion)
- Body weight ≥10 kg
- History of at least 50 EDs to other FIX products
- The patient and/or parent(s)/caregiver is capable of assessing a bleeding episode, keeping an eDiary, capable of conducting home treatment and otherwise able to follow study procedures

Milestones

Milestones	Date
Protocol approval	15 Sep 2011
First patient first visit	16 May 2012
Last patient last visit	17 Nov 2023
CTR submission	08 May 2024

Abbreviations: CSR = clinical study report.

Safety results

- No patient developed inhibitory antibodies against FIX.
  - Overall estimated inhibitor rate with 1-sided 97.5% upper confidence limit was 0.0 (0.16) which was lower than the threshold of ≥0.6 BU over 52 weeks demonstrating adequate safety with regard to inhibitors development.
- No safety issues were identified
  - 685 AEs were reported in 24 patients, 9 SAEs were reported in 7 patients and 10 medical events of special interest (MESIs) reported in 7 patients
- No focal or global neuro-toxicity were observed

3.2.4 Clinical study NN7999-3895

Study title

Safety and efficacy of nonacog beta pegol (N9-GP) in previously untreated patients with haemophilia B.

Rationale and study objectives

The rationale for performing this study 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 studies 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 study 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

Study design

This is an interventional, multinational, multi-centre, open-label, single-arm, non-controlled study investigating the safety and efficacy of nonacog beta pegol in prophylaxis and treatment of breakthrough bleeding episodes in haemophilia B PUPs aged <6 years with FIX activity ≤2%.

The study has one treatment arm in which all patients will achieve at least 100 EDs of 40 IU/kg nonacog beta pegol.

The study consists of four phases:

- A screening visit (interval between visit [v0] and [v1]) is allowed until the first dose of nonacog beta pegol is required.
- A 1–3-year main phase, patient received either pre-prophylaxis (until 24 months of age or until 20 EDs) or prophylaxis treatment until 50 EDs.
- A 1-year extension phase, during which patients will receive nonacog beta pegol treatment for at least 50 EDs.
- A prophylaxis phase until the end of trial (EOT) where treatment with nonacog beta pegol will continue until last patient last visit (LPLV).

Study populations

Inclusion criteria

- Informed consent obtained before any study-related activities
- Male patients <6 years of age at the time of signing informed consent
- Patients with the diagnosis of haemophilia B (FIX activity level ≤2%) based on medical records or central laboratory results

- Previously untreated or exposed to FIX containing products less than or equal to 3 EDs

Milestones

Milestones	Date
Protocol approval	04 Nov 2013
First patient first visit	02 Jul 2014
Last patient last visit	27 Oct 2022
CTR submission	11 Apr 2023

Abbreviations: CSR = clinical study report.

Safety results

- No safety issues were identified and nonacog beta pegol was well tolerated.
  - The estimated overall FIX inhibitor incidence was 7.5%, which was within the expected range for the population.
  - No unexpected findings were identified based on long-term evaluation of neurological examinations and neurocognitive performance.

3.3 Summary table of additional pharmacovigilance activities

Table 3-1 Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)				
NN7999-4031 A non-interventional post-authorisation safety study (PASS) in male haemophilia B patients receiving nonacog beta pegol (N9-GP) prophylaxis treatment. Ongoing	Safety of nonacog beta pegol in prophylaxis during long-term routine use in patients with haemophilia B in the manner prescribed by the physicians.	• FIX inhibitors • Allergic/hypersensitivity reactions • Thromboembolic events • Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	Interim results	First interim: When 5 patients have had their first visit after one year of inclusion. Second interim: When 25 patients have had their first visit after one year of inclusion.
			Study progress reports	As a PAM, the reports will be submitted yearly by 14th December until the final study report submission.
			Submission of final results	Q2 2028 (planned study report finalisation: 07 Jun 2028)
Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit–risk)				
None	N/A	N/A	N/A	N/A

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 – Required additional pharmacovigilance activities (by the CHMP/PRAC or NCA)				
NN7999-4413 Non-interventional registry study (PASS) Adverse event data collection from external registries on nonacog beta pegol Ongoing	To investigate potential clinical effects of long-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/hypersensitivity reactions • Thromboembolic events • Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	End of study	15 Dec 2027
			End of data collection	02 Feb 2028
			Reporting of study results	PSURs based on annual reports from registry

Abbreviations: CSR = clinical study report; FIX = coagulation factor IX; N9-GP = nonacog beta pegol; N/A = not applicable; PAM = post-authorisation measure; PASS = post-authorisation safety study; PEG = polyethylene glycol.

4 Plans for post-authorisation efficacy studies

Currently, no post-authorisation efficacy studies are planned for nonacog beta pegol.

5 Risk minimisation measures

5.1 Routine risk minimisation measures

Table 5-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Important identified risks	
Allergic/hypersensitivity reactions	*Routine risk communication:* The identified risk of allergic or 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 risk minimisation measures beyond the Product Information*: None
FIX inhibitors	*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*: A recommendation to carefully monitor for signs of inhibitor development by appropriate clinical observations and laboratory tests is included in SmPC Section 4.4.

Safety concern	Routine risk minimisation measures
	Other risk minimisation measures beyond the Product Information: None
Important potential risks	
Thromboembolic events	*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
Nephrotic syndrome following ITI	*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
Inadequate treatment due to assay overestimation of FIX activity	*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
Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	*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
Missing information	
Females, including pregnant or breastfeeding women	*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*:

Safety concern	Routine risk minimisation measures
	None *Other risk minimisation measures beyond the Product Information:* None

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

5.2 Additional risk minimisation measures

Routine risk minimisation activities as described in Section 5.1 are considered sufficient to manage the safety concerns of the medicinal product.

5.3 Summary table of pharmacovigilance and risk minimisation activities by safety concern

Table 5-2 Pharmacovigilance and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Allergic/hypersensitivity reactions	*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	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Hypersensitivity questionnaire (Annex 4B) *Additional pharmacovigilance activities:* PASS (NN7999-4031) Clinical study (NN7999-3774, NN7999-3895) PASS registry study (NN7999-4413)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
FIX inhibitors	*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	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* FIX inhibitor questionnaire (Annex 4A) *Additional pharmacovigilance activities:* PASS (NN7999-4031) Clinical study (NN7999-3774, NN7999-3895) PASS registry study (NN7999-4413)
Important potential risks		
Thromboembolic events	*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	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Thromboembolic event questionnaires (Annex 4C) *Additional pharmacovigilance activities:* PASS (NN7999-4031) Clinical study (NN7999-3774, NN7999-3895) PASS registry study (NN7999-4413)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Nephrotic syndrome following ITI	*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	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None
Inadequate treatment due to assay overestimation of FIX activity	*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	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None
Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	*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	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* Targeted follow-up questions regarding hepatic and renal impairment and CNS-related adverse events (Annex 4D) Aggregated safety data analyses in PSURs *Additional pharmacovigilance activities:* PASS (NN7999-4031) Clinical study (NN7999-3774, NN7999-3895) PASS registry study (NN7999-4413)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing information		
Females, including pregnant or breastfeeding women	*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	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None

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

6 Summary of the 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.

6.1 The medicine and what it is used for

Refixia is authorised for treatment and prophylaxis of bleeding in patients 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*.

6.2 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.

6.2.1 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).

Table 6-1 List of important risks and missing information

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 • Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment
Missing information	• Females, including pregnant or breastfeeding women

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

6.2.2 Summary of important risks

An overview of important identified risks, important potential risks and missing information for Refixia is provided in Table 6-2, Table 6-3 and Table 6-4, respectively.

Table 6-2 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 studies 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 studies 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 studies (NN7999-3774 and NN7999-3895) PASS registry study (NN7999-4413) See Section 6.2.3 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 completed clinical study 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 studies 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 studies (NN7999-3774 and NN7999-3895) PASS registry study (NN7999-4413) See Section 6.2.3 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.

Table 6-3 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 studies 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.[29] 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 studies (NN7999-3774 and NN7999-3895) PASS registry study (NN7999-4413) See Section 6.2.3 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 studies 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 6.2.3 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 6.2.3 of this summary for an overview of the post-authorisation development plan.
Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) 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 accumulation of PEG in any organ or tissue in humans 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 study (NN7999-3774, NN7999-3895) PASS registry study (NN7999-4413) See Section 6.2.3 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.

Table 6-4 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.

6.2.3 Post-authorisation development plan

6.2.3.1 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.

6.2.3.2 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 study NN7999-3774

Purpose of the study: The main purpose for performing this study 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 study 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 studies 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 study 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.

7 Annexes

Table 7-1 Annexes

Annex	Title	Included (Yes/No)
1	EudraVigilance interface	No
2	Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	Yes
3	Protocols for proposed and ongoing studies in Categories 1–3 of the section "Summary table of additional pharmacovigilance activities" in RMP Part 3	Yes
4	Specific adverse event follow-up forms 4A: FIX inhibitor questionnaire 4B: Hypersensitivity questionnaire 4C: Thromboembolic event questionnaire 4D: Follow-up questions for post-marketing surveillance of CNS-related adverse events and events related to renal or hepatic impairment	Yes
5	Protocols for proposed and ongoing studies in RMP part IV	No
6	Details of proposed additional risk minimisation measures	No
7	Other supporting data (including referenced material)	No
8	Summary of changes to the risk management plan over time	Yes

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Annex 2: Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme

Table 1 List of all planned and ongoing studies

Study Title Category	Summary of objectives	Safety concerns addressed	Protocol link Milestones
NN7999-4031 PASS A Non-Interventional Post-Authorisation Safety Study in male haemophilia B patients receiving Nonacog Beta Pegol (N9-GP) prophylaxis treatment Category 1	Safety of nonacog beta pegol in prophylaxis during long-term routine use in patients with haemophilia B in the manner prescribed by the physicians.	• FIX inhibitors • Allergic/hypersensitivity reactions • Thromboembolic events • Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	Link to protocol **Interim results:** First interim: When 5 patients have had their first visit after one year of inclusion. Second interim: When 25 patients have had their first visit after one year of inclusion. **Study progress reports:** As a PAM, the reports will be submitted yearly by 14th December until the final study report submission. **Final study report:** 07 Jun 2028 (planned)
NN7999-4413 Non-interventional registry study (PASS) Adverse event data collection from external registries on nonacog beta pegol Category 3	To investigate potential clinical effects of long-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/hypersensitivity reactions • Thromboembolic events • Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	Link to protocol **End of data collection:** 02 Feb 2028 (planned)

Abbreviations: FIX = coagulation factor IX; PAM = post-authorisation measure; PASS = post-authorisation safety study; PEG = polyethylene glycol.

Table 2 List of completed studies

Study Title Category	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
Clinical trial NN7999-3774 (phase 3) Safety, efficacy and pharmacokinetics of nonacog beta pegol in previously treated children with haemophilia B Category 3	To evaluate immunogenicity of nonacog beta pegol in previously treated paediatric patients with haemophilia B.	• FIX inhibitors • Allergic/hypersensitivity reactions • Thromboembolic events • Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	08 May 2024 Link to report
Clinical trial NN7999-3895 (phase 3) Safety and efficacy of nonacog beta pegol (N9-GP) in previously untreated patients with haemophilia B Category 3	To investigate: • Incidence of inhibitory antibodies against FIX • Frequency of adverse events • Annualised bleeding rate • Haemostatic effect on treatment of bleeds	• FIX inhibitors • Allergic/Hypersensitivity reactions • Thromboembolic events • Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment	11 Apr 2023 Link to report

Abbreviations: FIX = coagulation factor IX; N9-GP = nonacog beta pegol; PEG = polyethylene glycol.

Annex 3: Protocols for proposed and ongoing studies in Categories 1–3 of the section "Summary table of additional pharmacovigilance activities" in RMP Part 3

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

None

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

None

Part C: Previously agreed protocols for ongoing studies and final protocols not reviewed by the competent authority

Approved protocols:

1. NN7999-4031 (PASS category 1): A non-interventional post-authorisation safety study (PASS) in male haemophilia B patients receiving nonacog beta pegol (N9-GP) prophylaxis treatment.

   Finally approved with procedure: EMEA/H/C/PSA/S/0041.2 (dated 13 Feb 2020)

2. NN7999-4413 (PASS category 3): Adverse event data collection from external registries on nonacog beta pegol.

   Approved as a category 3 study with procedure: EMEA/H/C/004178/0000 (dated 02 Jun 2017)

Link to Annex 2

Follow-up Information Request Form

Factor IX inhibitor
Nonacog beta pegol (rFIX)

No. of pages: ___ (including attached lab results)

Patient Identifier (e.g. initials, age, date of birth, patient number etc.): **Reported term:** **Argus No:**

(The information in this box is provided in by Novo Nordisk Safety Operations)

Dear Dr xxx,

Thank you for reporting your experience with nonacog beta pegol (rFIX) treatment to Novo Nordisk. You have reported the finding of a FIX inhibitor during treatment with nonacog beta pegol (rFIX).

This form contains questions for additional information. In case you have already provided the requested information, please mark the question as NA.

We would like to ask you for the following details:

Patient information

Please provide the date of haemophilia B diagnosis:

_____

Is the patient diagnosed with mild, moderate or severe haemophilia B?

□ mild
□ moderate
□ severe

Is the genotype of this patient known?

□ yes □ no

If yes please provide details of genotype:

_____
_____
_____
_____

Treatment with nonacog beta pegol

Please specify the total number of exposure days and/or duration of treatment with nonacog beta pegol:

□ 0-10 exposure days
□ 11-20 exposure days
□ 21-50 exposure days
□ 51-100 exposure days
□ >100 exposure days

Duration of treatment: _____

What was the vial strength of nonacog beta pegol?

□ 500 IU

□ 1000 IU

□ 2000 IU

□ 3000 IU

For what indication was nonacog beta pegol used?

□ Prophylaxis (prevention)
□ On-demand
□ Prevention of surgical bleed
□ Other, please specify_____

Please describe the dosage regimen of nonacog beta pegol that the patient followed prior to FIX inhibitor development:

_____
_____
_____

Treatment with FIX products other than nonacog beta pegol

Please specify the total number of exposure days and/or duration of treatment with any other FIX product prior to start of treatment with nonacog beta pegol:

□ 0-10 exposure days
□ 11-20 exposure days
□ 21-50 exposure days
□ 51-100 exposure days
□ >100 exposure days

Duration of treatment: _____

Please describe dosing regimens for FIX products, including recent switching of products:

_____
_____
_____
_____

Has the patient been tested for FIX inhibitors prior to the start of treatment with nonacog beta pegol?

□ yes □ no

If yes, provide date and result of the test below:

□ Inhibitors against FIX
Date: _____ Result:_____

□ FIX activity and clot solubility
Date: _____ Result:_____

For the current reported event of FIX inhibitors

Has testing for inhibitory or binding FIX antibodies against nonacog beta pegol (rFIX) been performed?

□ yes □ no

If yes, please specify the type of assays used, provide the results (e.g. Bethesda Unit) and your interpretation of these results:

_____
_____
_____
_____

Has FIX activity or clot stability testing been performed?

□ yes □ no

If yes, please specify the type of tests performed (including aPTT reagent if applicable), results and your interpretation of these results:

_____
_____
_____
_____

Have any additional medications (e.g. other FIX products) been used to treat bleeding episodes in the period prior to the reported event?

□ yes □ no

If yes, please provide name of the drug and date(s) of administration:

_____
_____
_____
_____

Has the patient experienced reduced response/lack of efficacy in connection with the inhibitor development?

□ yes □ no

If yes, please describe further _____
_____
_____
_____

Please provide any further information that you believe may be relevant:
(Your help in providing additional information regarding this case is highly appreciated)

_____

_____

_____

_____

_____

_____

_____

_____

Follow-up Information Request Form

Hypersensitivity questionnaire
Nonacog beta pegol (rFIX)

No. of pages: ___ (including attached lab results)

Patient Identifier (e.g. initials, age, date of birth, patient number etc.):
Reported term:
Argus No:

(The information in this box is provided in by Novo Nordisk Safety Operations)

Dear Dr xxx,

Thank you for reporting your experience with nonacog beta pegol (rFIX) treatment to Novo Nordisk. You have reported an event suggestive of an allergic reaction or anaphylaxis.

This request is for additional information. In case you have already provided a response to any of the questions please mark the question as NA.

We would like to ask you for the following details:

For the current reported event:

Did the patient have any of the following symptoms and/or laboratory findings (tick as many as appropriate)?

Dermatological/mucosal
□ generalised erythema
□ generalized urticaria (hives)
□ angioedema, specify site:_____
□ generalized pruritus with skin rash
□ generalized pruritus without skin rash
□ generalised prickle sensation
□ localized injection site urticaria
□ itchy eyes with or without chemosis

Cardiovascular
□ hypotension, based on measurement
□ clinical diagnosis of uncompensated shock, indicated by the combination of at least 3 of the following:
- tachycardia
- capillary refill time > 3s
- reduced central pulse volume
- decreased level of consciousness or loss of consciousness

□ clinical diagnosis of reduced peripheral circulation as indicated by the combination of at least 2 of the following:
- tachycardia
- capillary refill time > 3s without hypotension decreased level of consciousness

Other symptoms
_____
_____
_____
_____

Respiratory
□ bilateral wheeze
□ stridor
□ upper airway swelling (lip, tongue, throat, uvula, or larynx
□ respiratory distress, 2 or more of the following:
- tachypnoea
  increased use of accessory respiratory muscles
- recession
- cyanosis
- grunting

□ persistent dry cough
□ hoarse voice
□ difficulty breathing without wheeze or stridor
□ sensation of throat closure
□ sneezing, rhinorrhea

Gastrointestinal
□ diarrhoea
□ abdominal pain
□ nausea
□ vomiting

Laboratory
□ mast cell tryptase elevation
> upper normal limit
□ FIX inhibitory antibodies
Result: _____
_____

□ Other laboratory tests
Type and results:_____
_____
_____

How soon after administration of nonacog beta pegol (rFIX) did the patient experience the first signs/symptoms (minutes/hours/days)?

_____
_____

Please specify after how many exposures to nonacog beta pegol the described event occurred:

_____
_____

Please specify the treatment for the event and the outcome including the duration of the reaction:

_____
_____
_____
_____

Does the patient have any history or familial history of allergy or intolerances?

□ yes □ no

If yes please provide information concerning these allergies:

_____
_____
_____
_____
_____

Does the patient have any history of allergic reaction with other FIX containing products?

□ yes □ no

If yes, please provide details:

_____
_____
_____
_____
_____

Did the patient use any other medication at the time of the reaction?

□ yes □ no

If yes, please specify:

_____
_____
_____
_____
_____

Are there other factors that may have contributed to the allergic reaction?

□ yes □ no

If yes, please specify:

_____
_____
_____

Please provide any other information that may be relevant:
(Your help in providing additional information regarding this case is highly appreciated)

_____
_____
_____
_____
_____
_____
_____
_____
_____

Follow-up Information Request Form

Thromboembolic events
rFVIIa / N9-GP

Patient Identifier (e.g. initials, age, date of birth, patient number, etc.):

Product used: □ **rFVIIa (NovoSeven®, Niastase®)**

□ **N9-GP (Refixia®, Rebinyn®)**

Reported term(s):

Argus case no:

CCGlow / Local reference no.:

(The information in this box is provided by Novo Nordisk, Safety Operations)

Dear Dr._____,

Thank you for reporting your experience with the treatment to Novo Nordisk.
You have reported an event that suggests a Thromboembolic event.
This request is for additional information. Please provide details where relevant.

For the current reported thromboembolic event:

For what indication was the product used?

_____

When was the treatment with the product initiated?

_____

Please describe the time interval between the last administration of the product and the onset of the thromboembolic event?

□ Less than 6 hours
□ 6-12 hrs.
□ 12-18 hrs.
□ 1 day
□ 1 ½ days
□ 2 days
□ More than 2 days

What was the dose administered?

_____

Have other medications (e.g. other coagulation factors, tranexamic acid, platelets or discontinuation of antithrombotic agents) been used in the period of the reported event?

□ yes □ no

If yes, please provide name of the drug and date(s) of administration:

_____

_____

_____

Did the patient possess any of the following risk factors for thromboembolic events?

□ Cardiovascular disease
□ Diabetes Mellitus
□ Previous thromboembolic disease
□ Atherosclerotic disease
□ Hypercholesterolaemia / Hyperlipidaemia
□ Hypertension
□ Smoking
□ Obesity
□ Central venous catheter (CVC) or peripheral inserted central lines (PIC)
□ Cancer
□ Immobilisation
□ Surgery
□ Previous diagnosis of thromboembolic disease
□ Major trauma
□ Family history of thromboembolic disease
□ Disseminated Intravascular Coagulation (DIC)
□ Other: _____

Laboratory values* (if available):

	Date	Time	Result / units	Reference range
Activated partial thromboplastin time (aPTT)				
Prothrombin time (PT)				
Anti-thrombin				
C-reactive protein (CRP)				
D-dimer				
Troponin I				
Troponin T				
Fibrinogen				
Platelets				
Protein C				
Protein S				

Report of Myocardial Infarction
When did the myocardial infarction occur? _____

(Date/time)

Please provide a brief description of ECG findings: _____
_____
_____
_____

Was coronary angiography performed?
□ yes □ no

If yes, please describe results briefly: _____
_____
_____
_____
_____

Report of Cerebral infarction / Ischaemic stroke / Cerebrovascular accident (CVA)

When did the CVA occur? _____
(Date/time)

Which imaging modality was used to confirm the diagnosis of CVA?

□ Computerised Tomography (CT)
□ Magnetic Resonance Imaging (MRI)
□ Other (please specify):_____

Please describe results briefly, including signs of old infarctions:
_____
_____
_____

Report of Pulmonary embolism
When did the pulmonary embolism occur? _____
(Date/time)

Which imaging modality was used to confirm the diagnosis of pulmonary embolism?

□ Computerised Tomography (CT)
□ Pulmonary angiography
□ Ventilation-perfusion scintigraphy (V/Q scan / lung scintigraphy)
□ Magnetic Resonance Imaging (MRI)
□ Chest X-ray
□ Echocardiography
□ Other (please specify):_____

Please describe results briefly:_____
_____
_____
_____

Report of Deep Vein Thrombosis (DVT)

When did the DVT occur? _____
(Date/time)

Where was the DVT located? _____

Which imaging modality was used to confirm the diagnosis of DVT?

□ Duplex (Doppler) Ultrasound (DUS)
□ Computerised Tomography (CT) Venography
□ Magnetic Resonance Imaging (MRI)
□ Angiography
□ Phlebography
□ Other (please specify):_____

Please describe results briefly:

_____
_____
_____

Report of other thromboembolic event

When did the thromboembolic event occur? _____
(Date/time)

What was the type of the thromboembolic event:
□ Arterial
□ Venous
□ Mixed (arterial/venous)
□ Undetermined

What was the location of the thromboembolic event:
□ Arms
□ Legs
□ Hepatic
□ Mesenteric
□ Ophthalmic
□ Pelvic
□ Renal
□ Splenic
□ Vertebral
□ Aorta
□ Carotid artery
□ Jugular vein
□ Portal vein
□ Subclavian
□ Vena cava
□ Undetermined
□ Other (please specify):_____

Which imaging modality was used to confirm the diagnosis of the thromboembolic event?

□ Computerised Tomography
□ Contrast enhanced computerised tomography
□ Magnetic Resonance Imaging
□ Angiography
□ Duplex (Doppler) Ultrasound
□ Other (please specify):_____

Please describe results briefly:

_____
_____
_____

For all reports

Please provide any further information that you believe may be relevant to the assessment of this case (e.g. signs and symptoms, other clinical findings, etc.):

_____
_____
_____
_____
_____
_____

If batch number of the most recently administered product is available please supply here

_____

Form completed by: Date and Signature:

We thank you for your help in providing additional information that will help in the assessment of the events that you have reported in association with the use of a Novo Nordisk product.

Annex 4D: Follow-up questions for post-marketing surveillance of CNS-related adverse events and events related to renal or hepatic impairment

1 CNS-related events

1.1 Headache or similar type of reported event

- Describe headache (frequency, duration of headache, location etc.)
- Does the patient have any family history of headache? If yes, please provide details.
- Has the patient experienced unexplained headache (inconclusive after rigorous testing e.g. including imaging) before?
- Has the patient experienced this before? If yes, has there been worsening (in terms of severity or frequency) of the pre-existing condition?
- Has this condition been reported with other neurological findings? E.g., hemiparesis, changes in vision, hearing loss, etc.
- Has the patient experienced nausea and vomiting especially in the morning?
- Has the headache been triggered by specific factors like light, noise, food, etc.?
- Any imaging (CT scan) done to test for increased intracranial pressure or enlarged ventricles? If yes, please provide details.
- Any recent eye examination done? If yes, please provide details.
- Any lumbar puncture done? If yes, please provide details.
- Any cerebrospinal fluid analysis (cell count, microbiology, chemistry, etc.). If yes, please provide details.
- Please provide details of any treatment provided. Has the patient responded? If yes, please provide details.

1.2 Increased intracranial pressure

- Any medical history of brain tumour/brain metastasis and/or irradiation? If yes, please specify.
- Any medical history of head injury, brain haemorrhage, brain abscess or hydrocephalus? If yes, please specify.
- Were any of the following recent or present: meningitis, encephalitis, subdural hematoma or status epilepticus?

1.3 Seizure/convulsions or similar type of reported event

- Please state type and frequency of seizures.
- Has the patient experienced this before? If yes, is there a change in frequency or timing?
- Please state if this is an unexplained episode.
    - Is this a new or historical ICH (intracerebral haemorrhage)?
    - Has there been any brain lesion? Any acute illness (e.g. meningitis)? or
      Any medications taken that have a risk of convulsions? If yes, please provide the details.

- Has this condition been reported with other neurological findings? E.g., hemiparesis, changes in vision, hearing loss, etc. If yes, please provide details.
- Please provide details of any treatment provided. Has the patient responded? If yes, please provide details.

1.4 Developmental, Cognitive or Behavioural issue

- How has this development delay or missed milestone been identified? By whom?
- Please provide details of any treatment provided. Has the patient responded? If yes, please provide details.
- Has there been a change in cognitive function? How has this been confirmed? By whom?
- Please provide details of any treatment provided. Has the patient responded? If yes, please provide details.
- Has there been a change in behavioural function? How has this been confirmed? By whom?
- Has the patient experienced anxiety/depression/mood disorders at the same time? If yes, please provide details.

1.5 Rapid onset neurology (Infections and autoimmune diseases e.g. ADEM [acute disseminated encephalomyelitis]):

- Please state the details of the type of infection experienced: bacterial or viral
- Any lumbar puncture done? If yes, please provide details.
- Any CSF analysis (cell count, microbiology, chemistry, etc.). If yes, please provide details.
- Has there been any brain imaging done? (e.g. MRI, CT scan, etc.) If yes, please provide details.

2 Renal function altered

- Any relevant laboratory results (e.g., blood urea nitrogen (BUN), serum creatinine, creatinine clearance, urine albumin or protein, glomerular filtration rate [GFR], urinalysis, serum electrolyte)? (including baseline measurements and reference ranges). If yes, please provide details.
- Any recent change in drinking or eating pattern? If yes, please specify.
- Any recent treatment with drugs potentially affecting renal function (e.g. aminoglycosides, non-steroidal anti-inflammatory drugs [NSAIDS], intra venous contrast, allopurinol, ACE inhibitor or angiotensin receptor blockers [ARB])? If yes, please specify.
- Any recent history of decrease in renal perfusion due to volume depletion (severe vomiting/diarrhoea leading to dehydration), decreased cardiac output (e.g. due to heart failure, myocardial infarction or aortic aneurysm) or hypotension? If yes, please specify.
- Was the patient rehydrated? If yes, please provide the s-creatinine value after rehydration.
- Any recent major surgery (e.g. CABG)? If yes, please specify.
- Any recent history of urinary tract infection, streptococcal infection, food poisoning or change in diet (e.g. Atkins diet)? If yes, please specify.
- Any systemic autoimmune disease present? If yes, please specify.
- Any pre-existing altered renal function or chronic renal condition (e.g. chronic renal failure)? If yes, please specify.

- Has a referral been made to a nephrologist? If yes, please provide relevant medical information such as examinations and tests, and the nephrologist's conclusion.
- Any imaging studies performed (e.g. renal ultrasound, CT scan of kidneys, renal angio-imaging [conventional angiography, angio-CT, angio-MRI])? If yes, please provide the results.
- Any biopsy of the kidney(s) performed? If yes, please provide histology results
- Is the patient requiring continuous renal replacement therapy (CRRT)? If yes, provide the start date of therapy and modality of treatment. Is the CRRT still ongoing?
- Does the patient have G6PD (Glucose-6-phosphate dehydrogenase) deficiency?
- Is there any family history of renal disease? If, yes, please describe.

3 Hepatic disorders

- Any signs/symptoms associated with the event (e.g. anorexia, nausea, fatigue, jaundice or icterus, ascites, upper abdominal discomfort and vomiting)? If yes, please specify.
- What were the blood glucose levels at the time of event onset?
- Any liver enzyme tests (e.g. ALT, AST, ALP, GGT) or liver function tests (e.g. total bilirubin, serum albumin, PT, INR, coagulation factors) performed? If yes, please provide the results, including any prior values and values during the recovery phase.
- Please provide hepatitis serology. Any other viral diseases (e.g. cytomegalovirus [CMV], Epstein-Barr virus [EBV])? If yes, please provide details.
- Any examinations performed (e.g. liver biopsy or ultrasonography, CT-scan or MR-scan of the abdomen)? If yes, please provide the results.
- Any pre-existing liver disease including cirrhosis, hepatitis (all types including autoimmune), steatosis, fibrosis and cholestasis/cholelithiasis? If yes, please provide details.
- Any medical history of hypotension or right heart congestive failure which could have caused ischemic/hypoxic hepatopathy?
- Any relevant family history? If yes, please provide details.
- Any medical history of alcohol/drug abuse, food poisoning or misuse of medication? If yes, please provide details.
- What was the average weekly alcohol consumption prior to the event? (units per week)
- Has there been an episode of excessive (binge) drinking in the last 30 days prior to the event?
- Any prior or current treatment with medications known to be hepatotoxic (e.g. paracetamol)? If yes, please provide start and stop dates and dosage regimen
- Was the patient referred to a specialist?

Annex 8: Summary of changes to the risk management plan over time

Table-1 A list of all significant changes to the risk management plan over time

Version	Approval date Procedure	Change
2.4	Date of approval: 02 Jun 2017 Procedure number: EMEA/H/C/004178/0000	RMP filed for approval with the EMA <u>Safety concerns</u> *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:* • Previously untreated patients • Children below 12 years of age • Elderly • Females, including pregnant or breastfeeding women • Patients with HIV with high viral load and low CD4 count • Patients with a history of FIX inhibitors • Patients with a history of thromboembolic events • Patients on ITI regimen
3.0	Date of approval: NA Procedure number: EMEA/H/C/004178/IB/0019	<u>Safety concerns</u> *Important risks*: No important identified risks or important potential risks have been removed or reclassified. *Missing information*: As requested by the PRAC during the assessment procedure of the 2nd nonacog beta pegol PSUR (PSUSA/00010608/201806), the following changes have been proposed: • 'Previously untreated patients': Removed • 'Children below 12 years of age': Removed • 'Elderly': Removed. • 'Patients with HIV with high viral load and low CD4 count': Removed • 'Patients with a history of FIX inhibitors': Removed • 'Patients with a history of thromboembolic events': Removed • 'Patients on ITI regimen': Removed <u>Pharmacovigilance plan</u> *NN7999-4031 (PASS category 1):* The study title has been updated. Status: Ongoing.

Version	Approval date Procedure	Change
		NN7999-4413 (PASS category 3): As agreed with the EMA, this study has been added to ensure structured data collection relating to use of nonacog beta pegol in national and international registries (including the EUHASS registry and PedNet). The data collection was included as a pharmacovigilance activity in the previous RMP, but not as a study. Status: Ongoing. *Clinical trial NN7999-3774*: Due date of the final clinical trial report has been postponed to 2024 in agreement with the EMA due to the extension of the trial. *Clinical trial NN7999-3895*: Due date of the final clinical trial report has been postponed in agreement with the EMA to 2023 due to the extension of the trial. <u>Post-authorisation efficacy plan</u> No changes have been made (no studies are included). <u>Risk minimisation measures</u> No changes have been made <u>Annexes</u> *Annex 4C*: A specific adverse drug reaction follow up form has been added for thromboembolic events. It replaces the targeted follow-up questions included in Annex 7C of RMP Version 2.4. *Annex 4D*: Follow-up questions for CNS-related adverse events have been slightly modified to obtain improved characterisation of the events. Also, follow-up questions for events of renal or hepatic impairment have been included in Annex 4D.
3.1	Date of approval *(opinion) 27 May 2020* Procedure number: EMEA/H/C/004178/IB/0019	The update to RMP Version 3.1 comprised only a revision of the text under the header 'Impact on the benefit−risk profile of the product' in the characterisation of risks, Section 2.7.3.6 (Important potential risk: Accumulation of PEG in the brain [choroid plexus] and in other tissues/organs after long-term treatment) based on a request in the initial PRAC and CHMP assessment report received in response to the type IB variation application.
4.0	Date of approval: *21 Feb 2022* Procedure number: EMEA/H/C/004178/R/0025	The update to the RMP Version 4.0 comprises the following: • An update of the information in Table 3-1 of Section 3.3 (ongoing and planned additional pharmacovigilance activities) of the RMP and Annex 2 with milestones and due dates of interim results and progress reports for the category 1 PASS NN7999-4031, as requested by the EMA. • Module SV (Post-authorisation experience) was updated with post-marketing data received until the DLP (31 May 2021). Section 2.7.3 (Details of important identified risks, important potential risks, and missing information) was updated with safety data received from the ongoing clinical trials NN7999-3895 and NN7999-3774 and post-marketing sources as of the DLP (31 May 2021).

Version	Approval date Procedure	Change
Version 5.2	Date of approval: *04 Aug 2023* Procedure number: EMEA/H/C/004178/II/0032	The update to RMP Version 5.2 comprises the following: • Product information: Inclusion of a new strength of 3000IU approved for treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency) based on positive opinion received on 13 Oct 2022 via line extension procedure. • Non-clinical study: Data from non-clinical studies including the findings • juvenile neurotoxicity study in male rats has been updated. • Epidemiology and clinical trial exposure: Data from clinical trials (including 2 paediatric trials) and post-marketing sources (including exposure) and for epidemiology has been updated as of the data lock point. • Safety concerns: Re-naming of the important potential risk 'Accumulation of PEG in the brain (choroid plexus) and in other tissues/organs after long-term treatment' to 'Effects on organ function due to PEG residues in tissues/organs (e.g., brain, kidney) after long-term treatment'.
Version 6.0	Pending	The update to RMP Version 6.0 comprises the following: • Since the last last RMP update, two clinical studies NN7999-3895 and -3774 have been completed. Data pertaining to these studies has been updated in the RMP. • Additionally, data from clinical studies, post-marketing sources (including exposure) and epidemiological sources has been updated as of the data lock point (DLP).

Abbreviations: CD4 = cluster of differentiation 4; CHMP = Committee for Medicinal Products for Human Use; CNS = central nervous system; DLP = data lock point; EMA = European Medicines Agency; FIX = factor IX; HIV = human immunodeficiency virus; ITI = immune tolerance induction; NA = not applicable; PASS =post-authorisation safety study; PRAC = Pharmacovigilance Risk Assessment Committee; RMP = risk management plan.