EU RISK MANAGEMENT PLAN (RMP)

for

RIXUBIS (Nonacog gamma)

RMP Version number: 3.1

Date: 07-October-2024

EU Risk Management Plan for RIXUBIS (Nonacog gamma)

Administrative Information

RMP version to be assessed as part of this application:

RMP Version number: 3.1

Data lock point for this RMP: 30-June-2024

Date of final sign off: 07-October-2024

Rationale for submitting an updated RMP: This RMP is updated based on:

- Removal of safety topics "No clinical data on the use of RIXUBIS in previously untreated patients (PUPs)" and "No clinical data on the use of RIXUBIS in patients with severe chronic hepatic disease" from missing information; following the Pharmacovigilance Risk Assessment Committee (PRAC) recommendation (EMEA/H/C/PSUSA/00010320/202306);
- Reclassify the scope for PedNet and EUHASS registries (previously used to compensate for the lack of data on patients with severe chronic hepatic disease and PUPs, currently removed from the list of safety concerns) to further characterize all RIXUBIS safety concerns for long term safety follow-up;
- Completion of RIXUBIS India post-marketing study 251602

Summary of significant changes in this RMP in comparison to EU RMP version 2.1:

RMP Module:	**Significant Changes:**
Part I Product Overview	Aligned with the latest SmPC available. Pursuant to Article 23(3) of Regulation No (EU) 726/2004, Rixubis (nonacog gamma) is removed from the additional monitoring list as a new biological following five years of authorization along with the renewal, which was approved on 15-Nov-2019. Hence, additional monitoring in the EU updated to "No".
Part II Safety Specification	
• **Module SI Epidemiology of the indication(s) and target population(s)**	The Epidemiology data was updated in line with the updated DLP 30-June-2024.
• **Module SII Non-clinical part of the safety specification**	Not applicable
• **Module SIII Clinical trial exposure**	Updated as per the DLP 30-June-2024.
• **Module SIV Populations not studied in clinical trials**	Table SIV.1: Addition of a rationale for the removal of "No clinical data on the use of RIXUBIS on previously untreated patients (PUPs)" and "No clinical data on the use of RIXUBIS in patients with severe chronic hepatic disease" from missing information topics.
• **Module SV Post-authorisation experience**	Updated as per the DLP 30-June-2024.

RMP Module:	Significant Changes:
• **Module SVI Additional EU requirements for the safety specification**	Not applicable
• **Module SVII Identified and potential risks**	SVII.1: The list of safety concerns aligned as per the initial RMP. SVII.2: Removal of below safety topics from missing information: • "No clinical data on the use of RIXUBIS on previously untreated patients (PUPs)" and • "No clinical data on the use of RIXUBIS in patients with severe chronic hepatic disease". SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP modified to reflect the removal of the above-mentioned missing information topics, including reclassification of the scope for the additional pharmacovigilance activities EUHASS and PedNet registries applicable for the remaining list of safety concerns. SVII.3: Safety concerns aligned to reflect the removal of the above-mentioned missing information topics.
• **Module SVIII Summary of the safety concerns**	Removal of below safety topics from missing information: • "No clinical data on the use of RIXUBIS on previously untreated patients (PUPs)" • "No clinical data on the use of RIXUBIS in patients with severe chronic hepatic disease".
Part III Pharmacovigilance plan	Part III.2 Additional pharmacovigilance activity and Part III.3 Summary table of additional pharmacovigilance activities updated with the objective and safety concerns associated with the EUHASS registry and PedNet registry.
Part IV Plans for post-authorisation efficacy studies	Not applicable
Part V Risk minimisation measures	Pack size and legal status added under other routine risk minimisation measures beyond the Product Information. Removal of safety topics of "No clinical data on the use of RIXUBIS on previously untreated patients (PUPs)" and "No clinical data on the use of

RMP Module:	Significant Changes:
	RIXUBIS in patients with severe chronic hepatic disease" V.3 Summary of Pharmacovigilance Activities and Risk Minimisation Measures updated with the removal of safety topics of "No clinical data on the use of RIXUBIS on PUPs" and "No clinical data on the use of RIXUBIS in patients with severe chronic hepatic disease" and addition of EUHASS and PedNet registries for all the remaining safety concerns under additional pharmacovigilance activities.
Part VI Summary of the risk management plan	Part II.B updated with the removal of safety topics of "No clinical data on the use of RIXUBIS on PUPs" and "No clinical data on the use of RIXUBIS in patients with severe chronic hepatic disease" and also update of EUHASS and PedNet registries to make it clear it covers all the remaining safety concerns under additional pharmacovigilance activities. Part II.C.2. table was updated with the scope and objective of PedNet and EUHASS registries.
Part VII Annexes	Annex 2 was updated with the scope and objective of PedNet and EUHASS registries. Study 251602 was updated from ongoing to completed. Annex 4 included the latest Factor IX Inhibitor AE Questionnaire. Annex 7 was updated with the references.

Other RMP versions under evaluation:

Not applicable

Details of the currently approved EU RMP:

Version number: 2.1

Approved with procedure: EMEA/H/C/003771/R/0029

Date of approval (opinion date): 14-November-2019

QPPV name: **Jean-Marie Heim, MD**

QPPV signature: RMP signatures are kept on the file.

Please note that e-signature may also be performed by Deputy EUQPPV on behalf of the EU QPPV (i.e., 'per procurationem').

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List of Abbreviations

Abbreviation	Definition/Description
ALT	Alanine transaminase
aPCC	Activated factors Prothrombin Complex Concentrate
aPTT	Activated Partial Thromboplastin Clotting Time
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical classification system
BU	Bethesda Units
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese Hamster Ovary
DIC	Disseminated Intravascular Coagulation
DLP	Data Lock Point
DNA	Deoxyribonucleic Acid
eCTD	electronic Common Technical Document
EDs	Exposure Days
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EUHASS	European Haemophilia Safety Surveillance
FIX	Factor IX
INN	International Non-proprietary Names
INR	International Normalised Ratio
ISTH	International Society of Haemostasis and Thrombosis
ITI	Immune Tolerated Induction
IU	International Units
MTPs	Minimally Treated Patients

Abbreviation	Definition/Description
MAH	Marketing Authorisation Holder
NOAEL	No Observed Adverse Effect Level
PI	Product Information
PK	Pharmacokinetics
PL	Package Leaflet
PBRER	Periodic Benefit-Risk Evaluation Report
PCC	Prothrombin complex concentrate
PEG	Pegylated Glycol
PedNet	Pediatric Network on haemophilia management
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PTP	Previously Treated Patients
PUPs	Previously Untreated Patients
PWH	Patients with Haemophilia
QPPV	Qualified Person Responsible for Pharmacovigilance
rDNA	Recombinant Deoxyribonucleic Acid
rFVIIa	Recombinant Coagulation Factor VIIa
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SMR	Standardized Mortality Ratio
TAT	Thrombin-Antithrombin III
UK	United Kingdom
WFH	World Federation of Haemophilia

Part I: Product(s) Overview

Table Part I.1 – Product Overview

Active substance(s) **(INN or common name)**	Nonacog gamma
Pharmacotherapeutic group(s) (ATC Code)	Antihaemorrhagics, blood Coagulation factor IX (B02BD04)
Marketing Authorisation Holder	Baxalta Innovations GmbH (Baxalta is a subsidiary fully owned by Takeda)
Medicinal products to which this RMP refers	RIXUBIS
Invented name(s) in the European Economic Area (EEA)	RIXUBIS
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: RIXUBIS (recombinant coagulation factor IX) is a single-chain purified glycoprotein that has 415 amino acids. It is produced by recombinant deoxyribonucleic acid (DNA) technology in a Chinese hamster ovary (CHO) cell line. RIXUBIS is not derived from human blood or plasma products, and its manufacture does not include animal or human components. RIXUBIS contains no preservatives. Recombinant coagulation factor IX is a single-chain glycoprotein that is a member of the serine protease family of vitamin K-dependent coagulation factors.
	Summary of mode of action: RIXUBIS contains recombinant coagulation factor IX (nonacog gamma). Factor IX is a single-chain glycoprotein with a molecular mass of about 68,000 Dalton. It is a vitamin K-dependent coagulation factor, and it is synthesised in the liver. Factor IX is activated by factor XIa in the intrinsic coagulation pathway and by factor VII/tissue factor complex in the extrinsic pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot is formed.
	Important information about its composition: Nonacog gamma (recombinant coagulation factor IX) is a single-chain purified glycoprotein that has 415 amino acids. It is produced by recombinant DNA technology in a Chinese hamster ovary (CHO) cell line.

Hyperlink to the Product Information (PI)	Refer to eCTD Module 1.3.1 for proposed PI or latest approved PI.
Indication(s) in the EEA	Current: RIXUBIS is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency). RIXUBIS is indicated in patients of all age groups.
	Proposed: Not applicable
Dosage in the EEA	Current: Treatment should be under the supervision of a physician experienced in the treatment of haemophilia. <u>Treatment monitoring</u> During the course of treatment, appropriate determination of factor IX levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to factor IX, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor IX activity) is indispensable. To ensure that the desired factor IX activity plasma level has been attained, careful monitoring using an appropriate factor IX activity assay is advised and, if necessary, appropriate adjustments to the dose and the frequency of repeated infusions should be performed. When using an in vitro thromboplastin time (aPTT)-based one stage clotting assay for determining factor IX activity in patients' blood samples, plasma factor IX activity results can be significantly affected by both the type of activated partial thromboplastin time (aPTT) reagent and the reference standard used in the assay. This is of importance particularly when changing the laboratory and/or reagents used in the assay. <u>Posology</u> Dose and duration of the substitution therapy depends on the severity of the factor IX deficiency, on the location and extent of the bleeding, and on the patient's clinical condition, age and pharmacokinetic parameters of factor IX, such as incremental recovery and half-life. The number of units of factor IX administered is expressed in International Units (IU), which are related to the current WHO standard for factor IX products. Factor IX activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to an International Standard for factor IX in plasma). One IU of factor IX activity is equivalent to that quantity of factor IX in one mL of normal human plasma. *<u>Adult population</u>* <u>On-demand treatment</u>

The calculation of the required dose of factor IX is based on the empirical finding that 1 IU factor IX per kg body weight raises the plasma factor IX activity by 0.9 IU/dL (range from 0.5 to 1.4 IU/dL) or 0.9% of normal activity in patients 12 years and older.

The required dose is determined using the following formula:

Required units = body weight (kg) x desired factor IX rise (%) or (IU/dL) x reciprocal of observed recovery (dL/kg)

For an incremental recovery of 0.9 IU/dL per IU/kg, the dose is calculated as follows:

Required Units = body weight (kg) X desired factor IX rise (%) or (IU/dL) X 1.1 dL/kg

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

In the case of the following haemorrhagic events, the factor IX activity should not fall below the given plasma activity level (in % of normal or IU/dL) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery.

Degree of haemorrhage/ Type of surgical procedure	**Factor IX level required (%) or (IU/dL)**	**Frequency of doses (hours)/Duration of therapy (days)**
Haemorrhage		
Early hemarthrosis, muscle bleeding or oral bleeding	20-40	Repeat every 24 hours, at least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved
More extensive hemarthrosis, muscle bleeding, or hematoma	30-60	Repeat infusion every 24 hours for 3-4 days or more until pain and acute disability are resolved
Life-threatening haemorrhages	60-100	Repeat infusion every 8 to 24 hours until threat is achieved.
Surgery		
Minor, including tooth extraction	30-60	Every 24 hours, at least 1 day, until healing is achieved.
Major Surgery		

Major	80-100 (pre- and postoperative)	Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor IX activity of 30% to 60% (IU/dL)

Careful monitoring of replacement therapy is especially important in cases of major surgery or life-threatening haemorrhages.

Prophylaxis

For long-term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are 40 to 60 IU of factor IX per kilogram of body weight at intervals of 3 to 4 days for patients 12 years and older. In some cases, depending upon the individual patient´s pharmacokinetics, age, bleeding phenotype and physical activity, shorter dosage intervals or higher doses may be necessary.

Continuous infusion

Do not administer RIXUBIS by continuous infusion.

Paediatric population

Patients aged 12 to 17 years of age:

Posology is the same in adults and paediatric population from 12 to 17.

Patients less than12 years of age:

On-demand treatment:

The calculation of the required dose of factor IX is based on the empirical finding that 1 IU factor IX per kg body weight raises the plasma factor IX activity by 0.7 IU/dL (range from 0.31 to 1.0 IU/dL) or 0.7% of normal activity in patients less than 12 years of age.

The required dosage is determined using the following formula:

Patients less than 12 years:

Required Units = body weight (kg) X desired factor IX rise (%) or (IU/dL) X Reciprocal of observed recovery (dL/kg)

For an incremental recovery of 0.7 IU/dL per IU/kg, the dose is calculated as follows:

Required Units = body weight (kg) X desired factor IX rise (%) or (IU/dL) X 1.4 dL/kg

The same table as for adults can be used to guide dosing in bleeding episodes and surgery.

Prophylaxis:

The recommended dose range for paediatric patients less than 12 years is 40 to 80 IU/kg at intervals of 3 to 4 days. In some cases, depending upon the individual patient´s pharmacokinetics,

	age, bleeding phenotype and physical activity, shorter dosage intervals or higher doses may be necessary. Method of administration Intravenous use. In case of self-administration or administration by a caregiver appropriate training is needed. RIXUBIS should be administered using a rate that ensures the comfort of the patient, up to a maximum of 10 mL/min. After reconstitution, the solution is clear, colourless, free from foreign particles and has a pH of 6.8 to 7.2. The osmolality is greater than 240 m osmol/kg. Only plastic Luer-lock syringes should be used with this product.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: RIXUBIS 250 IU, 500 IU, 1000 IU, 2000 IU, 3000 IU Powder and solvent for solution for injection. The powder is white to off white. The solvent is clear and colourless. Each pack also contains 5 mL of Sterile Water for Injection in a Type I glass vial and a BAXJECT II Transfer device.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency)	
Incidence:	The estimate incidence (or prevalence at birth) of haemophilia B is 5.0/100,000 males for all haemophilia B and 1.5/100,000 males for severe haemophilia B (World Federation of Haemophilia [WHF], 2022). Applying these estimates to the current live birth population globally suggests that approximately 20,000 people with haemophilia will be born worldwide each year, of which about 7,000 are severe.
Prevalence:	The estimated prevalence (the percentage of the population affected), based on registry data from Australia, Canada, France, Italy, New Zealand, and the UK, is 3.8/100,000 males for all haemophilia B and 1.1/100,000 males for severe haemophilia B. The expected number of patients with haemophilia worldwide is 818,928, of which about 278,200 are severe.
Demographics of the target population in the indication:	Haemophilia occurs in all races and ethnic groups. The 2021 World Federation of Haemophilia (WFH) survey reported 79% male, 6% female, and remaining unknown or unreported.
The main existing treatment options:	Plasma-derived or recombinant factor IX (FIX) concentrates are the standard of care for haemophilia B. Standard half-life products are either plasma-derived or recombinant (e.g., RIXUBIS). Recombinant extended half-life products include either Fc fusion, albumin fusion, or glycoPEGylation, which extend dosing intervals to weekly or every other week. In severe haemophilia, the standard of care which is regular replacement therapy (prophylaxis) to prevent bleeding, starts early in life (before age 3) to prevent musculoskeletal complications from recurrent joint and muscle bleeds. Episodic (on-demand) replacement therapy is no longer considered a long-term treatment option.
Natural history of the indicated condition in the untreated population, including mortality and morbidity:	Haemorrhage is the leading cause of death in haemophilia, despite treatment advances, the increased availability of haemophilia treatment centers, the focus on comprehensive care, increased uptake of prophylaxis, and prevention and treatment of HIV. Results from a meta-analysis suggest that the life span of people with haemophilia is approaching that of general population. The all-cause standardized mortality ratio (SMR) decreased from 2.4 (95% CI: 1.9-3.0) prior to 2000 to 1.2 (95% CI: 1.0-1.4) after the year 2000. Similarly, an observational study in the Netherlands reported the median life expectancy of the haemophilia cohort increased from 66 years in 1973–1986 to 77 years of age in 2001–2018, a gain of 11 years. In the male general population, the median life expectancy increased from 79 years to 83 years of age during the same time frame.

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency)	
	The proportion of deaths from haemorrhage has remained unchanged pre- and post-2000. In a scoping review of studies published from 2005 to 2022, the prevalence of bleeding events was consistently higher in haemophilia populations compared to reference populations (haemorrhagic stroke, 1.4%-5.31% vs. 0.2%-0.97%; intracranial haemorrhage, 1.1%-10.8% vs. 0.04%-0.4%). Although 9 studies reported lower prevalence of arterial thrombosis (myocardial infarction/ stroke) in haemophilia vs. general populations, 5 studies reported higher or comparable prevalence in haemophilia. A retrospective study conducted in Norway examined haemophilia mortality over a 30-year period (1986-2018). Over this period, the most frequent causes of death shifted from haemophilia-related causes of death, such as haemorrhage and AIDS, to more age-related causes of death (e.g., cancer). The mean age at death for people with haemophilia varied by haemophilia severity: mild 71.7 years; moderate 67.3 years; and severe 50.2 years.
Important co-morbidities:	Bleeding episodes are the most common co-morbidity in haemophilia. Despite greater adherence to prophylactic regimens, people with haemophilia experience break-through bleedings which can be clinically overt, or subclinical, unrecognised, bleeding episodes that are associated with a risk of joint damage progression. Other complications include intracranial haemorrhages after minor trauma, hypovolemic shock events due to iliopsoas muscle bleeding, and airway compromise due to retropharyngeal bleedings. The most common co-morbidities reported in a study of hospitalised people with haemophilia in the US were: hypertension (33.4%), hyperlipidaemia (23.6%), and diabetes (21.1%). In children, hemarthrosis (11.4%), contusions (9.6%), and central line infections (9.3%) were the most common. In a scoping review of 14 studies, 9 reported lower prevalence of arterial thrombosis (myocardial infarction/stroke) in haemophilia vs general populations, and 5 studies reported higher or comparable prevalence in haemophilia.

Part II: Module SII – Non-clinical Part of the Safety Specification

Key safety findings from non-clinical studies and relevance to human usage:

Key Safety Findings	Relevance to human usage
Toxicity	
Single-dose Toxicity Two single-dose toxicity studies (Studies PV2380908 and CLEM 1933-012) were conducted in mice and cynomolgus monkeys. In the single-dose toxicity studies, mice and cynomolgus monkeys showed no signs of toxicity at the highest single intravenous dose tested with a no observed adverse effect level (NOAEL) of 7,500 IU/kg in mice and 750 IU/kg in monkeys. These NOAELs indicate a high margin of safety between the recommended maximum single-dose for humans of 150 IU/kg and the highest dose used in these single-dose studies without inducing adverse effects. In mice, no toxicologically relevant differences to BeneFIX and Mononine in any of the investigated parameters were detected	No signs of toxicity at the highest single intravenous dose. No toxicologically relevant differences to BeneFIX and Mononine in the parameters investigated. Assessment of single-dose toxicity in animal models supports the conclusion that RIXUBIS is safe for human use.
Repeat-dose Toxicity In the two repeat-dose toxicity studies (Study PV2390901 and CLEM 1933-014) conducted in rats and cynomolgus monkeys, results showed a NOAEL of 750 IU/kg in rats after 14 applications every other day (over 28 days) followed by a 14-day recovery period. In monkeys, no adverse effects were observed at a dose of 750 IU/kg administered every other day over 28 days (14 applications), followed by a 14-day recovery period.	No signs of toxicity in rats or monkeys after 14 applications every other day (28-day period) followed by a 14-day recovery period. Assessment of repeat-dose toxicity in animal models supports the conclusion that RIXUBIS is safe for human use.
Reproductive/Developmental Toxicity Non-clinical studies on reproductive and developmental toxicity or lactation were not conducted as haemophilia B predominantly effects the male population.	It is not known whether RIXUBIS affects the reproductive capacity or cause foetal harm when given to pregnant women. It is unknown if RIXUBIS is excreted in human milk. However, the mode of action (protein replacement drug) and the patient population (mainly male patients) do not indicate a risk for foetal harm.
Carcinogenicity Non-clinical studies on carcinogenicity have not been performed	In general, endogenous substances given as a replacement therapy, particularly where there is previous clinical experience with similar products, indicate no carcinogenicity risk.

Key Safety Findings	Relevance to human usage
Safety pharmacology	
General Pharmacology (e.g., cardiovascular [including QT interval prolongation], nervous system) Rabbits treated with RIXUBIS and BeneFIX showed comparable scores in a study of thrombogenic potential (Study PV2420905). RIXUBIS was not thrombogenic in the rabbit stasis model at a dose of 750 IU/kg body weight, representing 5-fold the maximum anticipated human dose. After spiking FIXa into RIXUBIS at the amounts present in BeneFIX (Study AU0411W01), similar Wessler scores were obtained as for BeneFIX, demonstrating a clear correlation between the FIXa content of the items tested and the resulting Wessler scores. General safety pharmacology evaluations (Study CLEM 1933-013) in conscious cynomolgus monkeys did not find deleterious effects of RIXUBIS on respiratory and cardiovascular parameters, and single intravenous infusions at dose levels of 75 or 450 IU/kg/day were well-tolerated.	The results of these studies suggest that thrombus formation, cardiovascular, or respiratory effects are unlikely to occur in patients treated with RIXUBIS at the maximum anticipated human dose of 150 IU/kg for bleeding episodes or surgical prophylaxis, and at the suggested dose of 50 IU/kg twice weekly for prophylactic treatment (with a range of 40-60 IU/kg, which may be increased to 75 IU/kg, if necessary) in patients above 12 years and 40-80 IU/kg in patients below 12 years of age).

Part II: Module SIII - Clinical trial exposure

Table SIII.1: Clinical Study Exposure and Person Time in Clinical Study

Cumulative for all* indications (person time):		
Duration of exposure	**Patients**	**Person time (days)**
60 days	113	33,196
120 days	85	30,381
180 days	77	29,253
Total person time	**154****	**34,770**

*All indications: prophylaxis, bleeding treatment, surgery, PK and others
Studies included: 250901, 251001, 251002, 251101 and 251602.
**Total 154 subjects exposed. Subjects may appear in more than one category

Person time per indication:		
Prophylactic		
Duration of exposure	**Patients**	**Person time (days)**
60 days	107	28,594
120 days	80	26,073
180 days	72	24,972
Total person time for indication	**147****	**30,200**

Studies included: 250901, 251001, 251002, 251101 and 251602.
** Total 154 subjects exposed. Subjects may appear in more than one category

Person time per indication:		
Bleeding treatment		
Duration of exposure	**Patients**	**Person time (days)**
5 days	74	2,303
15 days	45	2,069
25 days	30	1,788
Total person time for indication	**117****	**2,394**

Studies included: 250901, 251001, 251002, 251101 and 251602
** Total 154 subjects exposed. Subjects may appear in more than one category

Person time per indication:		
Surgery		
Duration of exposure	**Patients**	**Person time (days)**
5 days	21	348
15 days	17	324
25 days	11	253
Total person time for indication	**28****	**364**

Studies included: 250901, 251001, 251002, 251101 and 251602.
** Total 154 subjects exposed. Subjects may appear in more than one category

Table SIII.2: Age group and gender

Age group	**Patients**	**Person time (days)**
<6 years	10	2,778
6 - <12 years	15	3,919
12 - <16 years	7	1,220
>=16 years	122	26,853
Total	**154**	**34,770**

Studies included: 250901, 251001, 251002, 251101 and 251602

Gender	**Patients**	**Person time (days)**
Male	154	34,770
Total	**154**	**34,770**

Studies included: 250901, 251001, 251002, 251101 and 251602

Table SIII.3: Ethnic origin

Cumulative for all indications for ethnic origin groups (person time)		
Ethnic origin	**Patients**	**Person time (days)**
White	110	30,443
Black or African American	1	156
Japanese	5	551
Native Latin American	3	1,064

Cumulative for all indications for ethnic origin groups (person time)		
Ethnic origin	**Patients**	**Person time (days)**
Mestizo	2	426
Arabic	1	21
Indian	25	1,507
Chinese	6	550
Multiple	1	52
Total	**154**	**34,770**

Part II: Module SIV - Populations not studied in clinical trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Hypersensitivity to the active substance or to any of the excipients. Known allergic reaction to hamster protein	
Reason for exclusion:	As with any intravenous protein product, hypersensitivity reactions are possible. Patients with a history of allergic reactions/anaphylaxis to the active substance, excipients, or hamster protein should avoid use of RIXUBIS.
Is it considered to be included as missing information?:	No
Rationale:	Included as an identified risk

The subject has a history of FIX inhibitors with a titre ≥ 0.6 Bethesda Units (BU) (as determined by the Nijmegen modification of the Bethesda assay or the assay employed in the respective local and central laboratory) at any time prior to screening	
Reason for exclusion:	Subjects with FIX inhibitors at screening cannot be evaluated for product-related immunogenicity or for efficacy. FIX inhibitors partially or completely neutralise FIX activity in plasma which makes haemostatic efficacy evaluation impossible.
Is it considered to be included as missing information?:	No
Rationale:	Subjects with low titre low responding FIX inhibitors may continue receiving FIX concentrates in higher doses provided there are no concurrent severe allergic reactions. In subjects with high titre inhibitors and no concurrent severe allergic reactions, there is the option to undergo ITI with FIX concentrates. Therefore, subjects with inhibitors should not be excluded from treatment with RIXUBIS.

The subject has been diagnosed with an acquired haemostatic defect other than haemophilia B	
Reason for exclusion:	Clinical studies with RIXUBIS focused on patients with congenital haemophilia B. Other haemostatic disorders (acquired haemostatic disorders) may contribute to impaired clotting and may mask the ability to determine the

The subject has been diagnosed with an acquired haemostatic defect other than haemophilia B	
	efficacy of the product. Haemostatic disorders can be associated with a higher risk of thrombus or clot formation leading to stroke, myocardial infarction, pulmonary embolism, and possibly death.
Is it considered to be included as missing information?:	No
Rationale:	RIXUBIS is indicated for only haemophilia B to replace the missing factor FIX. However, use in patients with a history of other haemostatic disorders is not contraindicated; however, the benefits and risks of using the product should be carefully weighed against the patient's clinical condition.

The subject has evidence of an on-going or recent thrombotic disease, fibrinolysis or disseminated intravascular coagulation (DIC)	
Reason for exclusion:	Subjects with thrombotic disease were excluded to allow for determining the occurrence of thromboembolic events in those patients not at increased risk. Coagulation disorders can be associated with a higher risk of thrombus or clot formation leading to stroke, myocardial infarction, pulmonary embolism, and possibly death.
Is it considered to be included as missing information?:	No
Rationale:	Patients with coagulation disorders may benefit from RIXUBIS to aid in coagulation. Warnings regarding use in patients with coagulation disorders are discussed in SmPC Section 4.4. Therefore, coagulation disorders should not be an absolute contraindication and the benefits and risks of using the product should be carefully evaluated against each individual patient's clinical condition.

The subject has an abnormal renal function (serum creatinine > 1.5 times the upper limit of normal)	
Reason for exclusion:	Altered renal function may contribute to impaired or delayed coagulation.
Is it considered to be included as missing information?:	No

The subject has an abnormal renal function (serum creatinine > 1.5 times the upper limit of normal)	
Rationale:	Patients with altered renal function may benefit from RIXUBIS to aid in the treatment of bleeding. The benefits and risks of using the product should be carefully weighed against the patient's clinical condition.

The subject has active hepatic disease with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥ 5 times the upper limit of normal	
Reason for exclusion:	Altered liver function may contribute to impaired coagulation or coagulation complications.
Is it considered to be included as missing information?:	No
Rationale:	Patients with altered hepatic function may benefit from RIXUBIS to aid in the treatment of bleeding.

No clinical data on the use of RIXUBIS in geriatric patients	
Reason for exclusion:	Clinical studies of RIXUBIS did not include subjects aged 65 years and older. It is not known whether patients aged ≥ 65 years of age will respond differently from younger subjects. In the recently approved amendment to the continuation study protocol the upper age limit was increased to 70 years of age.
Is it considered to be included as missing information?:	No
Rationale:	It is not expected that the safety profile of RIXUBIS will be significantly different that in the target population.

The effects of RIXUBIS on male fertility have not been established in clinical trials	
Reason for exclusion:	There is no information on the effects of RIXUBIS on male fertility.
Is it considered to be included as missing information?:	No
Rationale:	Coagulation factor concentrates are commonly not considered to affect fertility based on the current scientific knowledge.

No clinical data on the use of RIXUBIS on previously untreated patients (PUPs)	
Reason for exclusion:	Clinical studies with RIXUBIS did not include PUPs.
Is it considered to be included as missing information?:	No
Rationale:	Patients at risk for inhibitor formation such as PUPs with high-risk gene mutations or patients with a previous history of hypersensitivity reactions to FIX concentrates or any of the components of RIXUBIS.

No clinical data on the use of RIXUBIS in patients with severe chronic hepatic disease	
Reason for exclusion:	Patients with severe chronic liver disease (as evidenced by an international normalised ratio (INR) >1.4 or AST and/or ALT exceeding five times the upper limit of normal) were excluded from RIXUBIS clinical studies.
Is it considered to be included as missing information?:	No
Rationale:	No clinical data on the use of RIXUBIS in patients with severe chronic hepatic disease, and insufficient data regarding the degree to which factor IX levels can be affected by the aPTT reagent in aPTT potency assay. Patients with hepatic impairment or severe liver disease (as evidenced by, but not limited to, any of the following: International Normalized Ratio (INR) > 1.4, hypoalbuminemia, portal vein hypertension (including presence of otherwise unexplained splenomegaly) and history of esophageal varices) were not included in clinical studies.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	

Type of special population	Exposure
Breastfeeding women	Not included in the clinical development program
Patients with relevant co-morbidities: • Patients with hepatic impairment • Patients with renal impairment • Elderly patients • PUPs • Children	Patients with a medical history of hepatitis (excluding those with active disease) and patients with a medical history of hepatitis or active hepatitis with ALT and/or AST not exceeding 5 times the upper limit of normal were included in clinical studies. Patients with severe chronic liver disease (as evidenced by an INR >1.4 or AST and/or ALT exceeding five times the upper limit of normal) were excluded from RIXUBIS clinical studies. Patients with active hepatitis may need to be monitored more closely than other patients. Patients with renal disease (serum creatinine >1.5 times the upper limit of normal) were excluded from clinical studies for RIXUBIS and are routinely excluded from clinical trial populations, as they can present with signs and symptoms attributable to these diseases which may severely limit the evaluation of safety in such trials Further, factor IX concentrates do not undergo metabolisation in the kidneys, and the mode of action and choice of therapy in haemophiliacs will not be influenced by this co-morbidity. Clinical studies of RIXUBIS did not include subjects aged 65 years and older. It is not known whether patients aged ≥65 years of age will respond differently from younger subjects. PUPs were not included in clinical studies with RIXUBIS. Therefore, the safety and efficacy of RIXUBIS in PUPs has not been established. Children were included in the clinical development programme.
Patients with a disease severity different form the inclusion criteria in the clinical trial population	Clinical studies included patients with severe (FIX level <1%) or moderately severe (FIX level ≤ 2%) haemophilia B. Clinical studies did not include patients with FIX level >2%. This is in line with the guideline on the clinical investigation of recombinant and human plasma-derived factor IX products (CHMP/BPWP/14552/09). Mild haemophilia B patients rarely need prophylactic treatment, and it can be anticipated that RIXUBIS will cover their needs for replacement of factor IX in the event of severe trauma or surgical interventions.

Type of special population	**Exposure**
Population with relevant different ethnic origin	Clinical studies with RIXUBIS did not exclude patients of certain ethnicities; however, the majority of patients studied were Caucasian. Black or African American, Japanese, Native Latin American, Mestizo, Arabic, and Indian populations were represented in clinical studies, but to a lesser extent. It is unlikely that the safety of RIXUBIS is affected by race or ethnicity.
Subpopulations carrying relevant genetic polymorphisms	Previously untreated patients may bear high risk gene mutations, which may be undiagnosed during the initial phase of exposure. There is an increased risk of inhibitor development and hypersensitivity reactions in PUPs with high-risk gene mutations (e.g., large deletions, nonsense mutations) during the first 20 exposure days (EDs) to any FIX concentrate. The risk of hypersensitivity reactions is also highest in this phase of initial exposure. Therefore, it is strongly recommended to monitor a patient in a treatment facility during the first 20 EDs to a FIX concentrate. Previously treated patients (PTP) with high-risk gene mutations (e.g., nonsense mutations) were included in clinical studies with RIXUBIS.

Part II: Module SV - Post-authorisation Experience

SV.1. Post-authorisation Exposure

SV.1.1. Method used to calculate exposure

Cumulatively from the first market of the product (October-2013) to 30-June-2024, approximately a total of 751,791,737 IU of RIXUBIS have been distributed worldwide.

The number of treatments and number of patients exposed to RIXUBIS were estimated based on the distribution data available through 30-June-2024. The proportion of patients who use RIXUBIS for prophylactic and on-demand treatment varies across countries and changes over time. Therefore, the estimated range of the potential number of patients assuming 100% of RIXUBIS distributed was used on-demand only and 100% of RIXUBIS distributed was used prophylactically only. An average weight per patient of 70 kg was assumed to estimate the dosing per recommendations on label.

Based on the data from a prospective, multi-center phase I/III study among 249 PTPs with severe (FIX level <1%) or moderately severe (FIX level ≤2%) haemophilia B.

The following assumptions were also made:

On-demand:

- The median dose of RIXUBIS per bleeding episode (up to 3 infusions per bleed) was 62.3 IU/kg; in a 70 kg patient, the total average dose per bleeding episode was 4,361 IU.
- The annual bleed rate in patients treated on-demand was 20.0 bleeds per year; the cumulative interval was 8.75 years (105 months/12 months/year) therefore, the number of bleeding episodes in the cumulative interval was 175.
- The average annual dose per patient using RIXUBIS exclusively on-demand is 87,220 IU per year (20 bleed/year * 4361 IU per bleed) and 7,268 IU/month [4361 IU per bleed * (20 bleeds/year / 12 months/year)].
- The average dose per patient using RIXUBIS exclusively on-demand is 784,980 IU in this interval (180 bleeds over 93 months * 4361 IU per bleed).

Prophylactic use:

- The average dose per treatment according to the label is 50 IU/kg. In a 70 kg person, a single prophylactic dose is 3,500 IU.
- The average annual dose per patient using RIXUBIS prophylactically is 30,333 IU per month and 364,000 IU per year (3500 IU * 2 dose/week * 52 weeks/year).
- The average dose per patient using RIXUBIS exclusively prophylactically is 2,820,969 IU in this interval (93 months * 30,333 IU per month).
- This estimation does not account for on-demand use of RIXUBIS in patients who have break-through bleeds.

SV.1.2. Exposure

Number of IUs sold	**751,791,737 IU**	
	On-Demand Use	**Prophylaxis Use**
Average treatment dose for a bleed (may include multiple infusions) for on-demand and to prevent a bleed for prophylaxis patient	62.3 IU/kg*	50 IU/kg*
Average treatment dose per bleed for on-demand patient and prevention dose for prophylaxis patient (avg. dose per bleeding episode x avg. weight [70 kg patient])	4,361 IU	3,500 IU

Number of IUs sold	751,791,737 IU	
	On-Demand Use	Prophylaxis Use
Estimated no. of cumulative patient treatments	172,390 treatments	214,798 treatments
Estimated average no. of patients during the cumulative interval	802 patients	192 patients

*DLP 30-June-2024.

Part II: Module SVI –- Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

The potential for misuse of RIXUBIS for illegal purposes has not been reported and is considered unlikely.

Part II: Module SVII – Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

None

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

None

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the PI are adhered to by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

None

Known risks that do not impact the risk-benefit profile

None

Other reasons for considering the risks not important:

None

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks	**Risk-benefit impact**
Hypersensitivity reactions (Including reactions/antibodies to CHO protein)	Hypersensitivity (Including reactions/antibodies to CHO protein) has been observed with RIXUBIS in post-marketing surveillance. The risk is highest during the early phases of initial exposure to FIX concentrates in PUPs, in particular in patients with high-risk gene mutations. No subjects developed hypersensitivity reactions (including reactions/antibodies to CHO protein) in clinical trials. Hypersensitivity is contraindicated in the local label.

Important Potential Risks	**Risk-benefit impact**
Inhibitor Formation	Patients with Haemophilia B may develop neutralising antibodies to FIX and inhibitor formation may result in lack of response to treatment and subsequent acute of bleeding episodes. Inhibitor formation has not been seen with RIXUBIS, however has been seen with products within the same class.

Important Potential Risks	**Risk-benefit impact**
Thromboembolic events (e.g., DIC and fibrinolysis)	There was no clinical evidence of thrombotic complications in any of the subjects throughout all clinical studies. The use of FIX products has been associated with the development of thromboembolic complications. Therefore, the use of FIX-containing products may be potentially hazardous in patients with DIC and in patients with signs of fibrinolysis. In DIC, blood clots may reduce blood supply to various organs such as the liver, brain, or kidney. Multiple organ failure may result. Thromboembolic events (e.g., DIC and fibrinolysis) has not been seen with RIXUBIS, however has been seen with products within the same class.
Nephrotic syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions	There have been no reports of nephrotic syndrome during clinical studies with RIXUBIS. Nephrotic syndrome may develop following attempted ITI in haemophilia B patients with FIX inhibitors. It is plausible that nephrotic syndrome in FIX deficient patients could lead to increased morbidity or even death; however, the specific rates are unknown. Nephrotic syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions has not been seen with RIXUBIS, however has been seen with products within the same class.
Lack of effect	There have been no reports of lack of effect in clinical studies with RIXUBIS. Severity and nature of the risk include lack of response in factor IX activity levels, lack of prophylactic coverage for bleeding episodes, with increased breakthrough bleeds and ultimately uncontrolled bleeding or severe hemorrhage. Careful monitoring using an appropriate factor IX activity assay is advised, and if necessary, appropriate adjustments to the dose and the frequency of repeated infusions should be performed.

Missing Information	**Risk-benefit impact**
No clinical data on use of RIXUBIS for ITI	With immune tolerance induction (ITI) factor IX concentrate is given regularly over a prolonged period of time until the body is trained to recognise and tolerate the factor IX concentrate. When ITI is successful, the inhibitors disappear and responses to factor IX concentrate return to normal.

Missing Information	Risk-benefit impact
	RIXUBIS should not be used for ITI. The safety and efficacy of using RIXUBIS for ITI has not been established.
No data on the use of RIXUBIS for continuous infusion	RIXUBIS should not be administered continuously. RIXUBIS should be administered as a single injection (bolus) at a rate determined by the patient's comfort level, but it should not exceed 10 mL per minute.
No clinical data on the use of RIXUBIS in PUPs	Clinical studies with RIXUBIS did not include PUPs. The risk for developing an inhibitor and hypersensitivity reactions is highest in patients who have not been treated with a factor IX replacement medicine before or in the early phases of treatment, i.e., for small children.
No clinical data on the use of RIXUBIS in patients with severe chronic hepatic disease	Clinical studies did not include patients with severe chronic liver disease. The safety and efficacy in patients with severe chronic liver disease is not known.
Insufficient data regarding the degree to which factor IX levels can be affected by the aPTT reagent in aPTT potency assay	Clinical studies did not assess how clotting evaluation assays examining factor IX levels can be affected by the different chemicals used.
No clinical data on the use of RIXUBIS in geriatric patient	Clinical studies with RIXUBIS did not include patients 65 years and older. It is not known whether patients 65 years and older would respond differently than younger patients.
The effects of RIXUBIS on male fertility have not been established in clinical trials	RIXUBIS is primarily used in male patients. There is no information on the effects of RIXUBIS on male fertility.

SVII.2. New Safety Concerns and Reclassification With a Submission of an Updated RMP

As requested in the PRAC recommendation ((EMEA/H/C/PSUSA/00010320/202306)), per the GVP module V rev.2, the safety topics related to PUPs and severe chronic hepatic disease are removed from missing information as the effect of RIXUBIS in PUPs is not expected to be different from the "normal" target population. Patients with hepatic impairment or severe liver disease (as evidenced by, but not limited to, any of the following: International Normalized Ratio (INR)>1.4, hypoalbuminemia, portal vein hypertension (including presence of otherwise unexplained splenomegaly) and history of esophageal varices) were not included in clinical studies. No clinical data on the use of RIXUBIS in PUPs and No clinical data on the use of RIXUBIS in patients with severe chronic hepatic disease will not be included in the list of safety concerns as there is no reasonable expectation that future pharmacovigilance activities could further characterise the safety profile of the product with respect to these areas of missing information.

Furthermore, the MAH proposes to reclassify the scope for PedNet and EUHASS registries (previously used to compensate for the lack of data on patients with severe chronic hepatic disease and PUPs, currently removed from the list of safety concerns) to further characterise all Rixubis safety concerns for long term safety follow-up.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Identified Risk: Hypersensitivity reactions (including reactions/antibodies to CHO protein)	
Potential mechanisms	Immune mediated response to RIXUBIS FIX or any of the constituents of the product.
Evidence source(s) and strength of evidence	Hypersensitivity reactions (including reactions/antibodies to CHO protein) has been reported in scientific literature and post-marketing surveillance.
Characterisation of the risk	Complications of FIX replacement therapy include severe allergic reactions to FIX and development of FIX-neutralising antibodies. Anaphylaxis is a serious complication of FIX infusions, particularly in individuals with a history of developing inhibitors. A recent retrospective study was conducted to describe the incidence of moderate to severe allergic reactions to FIX in subjects with haemophilia B, and they observed an allergic reaction to a FIX product in 3.89% of subjects . When the analyses were categorised into product type, it was shown that of those subjects receiving rFIX, 2.45% experienced an allergic reaction. This report is consistent with another study, in which a review of charts of haemophilia B patients was conducted. In this study, 1.8% of the patients receiving rFIX experienced a moderate to severe allergic reaction. It is also worth noting that in these studies the development of inhibitors and episodes of allergic reactions frequently occurred together. Several reported and published cases have linked these types of adverse events. In clinical studies with RIXUBIS, no subjects developed hypersensitivity reactions (including reactions/antibodies to CHO protein). Subjects in the RIXUBIS program were regularly monitored for and informed about the warning signs of hypersensitivity reactions. The occurrence of severe allergic reactions/anaphylaxis is a safety endpoint in the RIXUBIS clinical program.
Risk factors and risk groups	Patients with previous history of hypersensitivity to RIXUBIS or any other constituents of the product. The risk for hypersensitivity reactions is highest during the early phases of initial exposure to factor IX concentrates in PUPs), in particular in patients with high-risk gene mutation. Potential increased risk of hypersensitivity reactions in patients with inhibitors.
Preventability	Careful intake of patients' medical history for allergic/hypersensitivity reactions. Premedication with antihistamines in atopic patients and patients with allergic reactions in their medical history. Note history of past hypersensitivity reactions in the patient records. RIXUBIS is contraindicated in patients with known hypersensitivity to active substance, to excipients, or to hamster protein. PUPs with high risk gene mutations should be administered FIX in facilities with immediate access to paediatric resuscitation.
Impact on the risk-benefit balance of the product	Hypersensitivity reactions (including reactions/antibodies to CHO protein) will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The benefit-risk profile of RIXUBIS remains positive.

Important Identified Risk: Hypersensitivity reactions (including reactions/antibodies to CHO protein)	
Public health impact	In clinical studies, all events were mild or moderate in severity and the majority of events resolved without sequelae and did not require treatment.

Important Potential Risk: Inhibitor formation	
Potential mechanisms	Although the underlying mechanism of antibody generation against recombinant drug proteins (i.e., insulin, coagulation factors) is poorly understood, most cases appear to be the result of a breakdown of the body's typical immune tolerance to self-antigens. The lower number of patients developing inhibitors may be attributed to the extravascular distribution of FIX. Additional potential mechanism for lack of efficacy may involve factors such as the extent of bleeding, the patient's clinical condition, age, and pharmacokinetic parameters of factor IX, such as incremental recovery and half-life. In clinical studies with RIXUBIS, no subjects developed an inhibitory antibody to FIX with a titre ≥0.6 BU or developed treatment related positive binding antibodies to FIX. Binding antibodies with a titre of 1:20 or 1:40 were observed in 21 (21.2%) subjects. Eighteen (18) subjects were negative for total binding antibody to FIX at screening and had developed FIX antibodies of indeterminate specificity with titres of 1:20 or 1:40 (which could therefore not be confirmed for specificity in the competition assay and are within assay variability) at one or several time points during the study. Three (3) subjects had total binding antibodies to FIX of indeterminate specificity with a titre of 1:20 or 1:40, prior to the 1st exposure. The presence of total binding antibodies to FIX did not have an impact on PK, efficacy or safety.
Evidence source(s) and strength of evidence	Inhibitor formation has been reported in scientific literature, post-marketing surveillance and with other factor IX products of the same class.
Characterisation of the risk	In patients with haemophilia (PWH) B, approximately 30-45% have the severe form of the disease, and the development of inhibitory antibodies (which result in the neutralisation of coagulation factor activity following infusion of FIX) is seen in about 1–3% of those with severe haemophilia B . In a recent retrospective study, inhibitor formation was observed in 3.89% of haemophilia B subjects receiving a FIX product. When the analyses were categorised into product type, it was shown that of those subjects receiving rFIX, 1.84% developed inhibitors . This report is consistent with results from a prior study conducted by the authors in which inhibitor formation was observed in 1.8% of haemophilia B patients receiving rFIX. It is also worth noting that in these studies the development of inhibitors and episodes of allergic reactions frequently occurred together. Several reported and published cases have linked these types of adverse events. In PWH, inhibitor formation may be seen as lack of effect, and there are several clinical features that distinguish FIX inhibitors. Such as the relative lack of success of ITI . Data from the International Society of Haemostasis and Thrombosis (ISTH) registry on FIX inhibitors indicated that ITI was

Important Potential Risk: Inhibitor formation	
	successful in only 15% of the patients in whom it was attempted, which essentially constitutes a lack of effect in these patients. In clinical studies with RIXUBIS, no subjects developed an inhibitory antibody to FIX with a titre ≥0.6 BU or developed treatment related positive binding antibodies to FIX. Binding antibodies with a titre of 1:20 or 1:40 were observed in 21 (21.2%) subjects. Eighteen (18) subjects were negative for total binding antibody to FIX at screening and had developed FIX antibodies of indeterminate specificity with titre of 1:20 or 1:40 (which could therefore not be confirmed for specificity in the competition assay and are within assay variability) at one or several time points during the study. Three (3) subjects had total binding antibodies to FIX of indeterminate specificity with a titre of 1:20 or 1:40, prior to the 1st exposure. The presence of total binding antibodies to FIX did not have an impact on pharmacokinetics (PK), efficacy or safety.
Risk factors and risk groups	PUPs and Minimally Treated Patients (MTPs) with high risk gene mutations (such as large deletions, nonsense/stop mutations, gross deletions/insertions or complete gene deletion). Other risk factors include family history of inhibitors, association with atopia, effects of recent immunisations, race and age at first exposure.
Preventability	Patients using RIXUBIS should be regularly evaluated for the development of factor IX inhibitors by appropriate clinical observations (e.g., bleeding that is not controlled with an expected dose) and laboratory tests (factor IX activity levels). If bleeding cannot be controlled, an assay that measures factor IX inhibitor concentration should be performed. Inhibitor testing should also be performed if the patient develops severe allergic reactions or anaphylaxis when exposed to a FIX concentrate. PUPs with high risk gene mutations should be administered FIX in facilities with immediate access to paediatric resuscitation during the first 20 EDs.
Impact on the risk-benefit balance of the product	Inhibitor formation will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The benefit-risk profile of RIXUBIS remains positive.
Public health impact	Uncontrolled bleeding episodes may result in hospitalisation or life-threatening injury. Once an inhibitor exists, there may be lifelong costly therapy, e.g., with bypassing agents. Inhibitor occurrence may be related to allergic reactions. Severe allergic reactions may result in life-threatening anaphylaxis. Inhibitors reduce the efficacy of haemostatic treatment and clearly cause additional morbidity. Data on mortality are, however, conflicting. Some studies have reported increased mortality with inhibitors, whereas other reports showed no increase, suggesting that improved treatment of inhibitors may have improved outcome. One particular study which was conducted to determine the effect of FIX inhibitor formation on mortality, severe haemophilia B inhibitors developed at rates of 0.2 per 1000 years in those greater than five years of age. In haemophilia patients with HIV, inhibitor development did not increase mortality. However, in severe haemophilia without HIV, inhibitor development doubled mortality during 1977–92, but during 1993–99 mortality was identical with and without inhibitors. In severe haemophilia without HIV but with inhibitors, mortality from causes involving bleeding decreased during 1977–99 as did mortality involving intracranial haemorrhage.

Important Potential Risk: Thromboembolic events (e.g., DIC and fibrinolysis)	
Potential mechanisms	High and sustained levels of FIX with underlying risk factors may be associated with thromboembolic events.
Evidence source(s) and strength of evidence	Thromboembolic events (e.g., DIC and fibrinolysis) has been reported in scientific literature, post-marketing surveillance and with other factor IX products of the same class.
Characterisation of the risk	Thrombotic AEs after clotting factor concentrate administration are rarely reported, but the actual rate is unknown . Most thrombosis data pertain to the safety concerns associated with products containing activated factors (prothrombin complex concentrate (PCC), activated factors prothrombin complex concentrate (aPCC), recombinant coagulation factor VIIa [rFVIIa]) whereas information on thromboembolic complications in haemophilia is provided only by case reports or literature reviews . However, recently, a systematic review of prospective studies (1990–2011) reporting safety data of factor concentrates in PWH A, haemophilia B, and von Willebrand disease was conducted to identify the incidence and type of thrombotic AEs. This review included 71 studies, 15 (748 patients) of which were specific to haemophilia B. There were 11 thrombotic AEs, judged to be at least probably related to factor concentrates, identified in haemophilia B patients. However, there were no arterial thrombotic AEs reported, and local complications, such as thrombophlebitis represented virtually all (12/13) thrombotic AE reports in haemophilia B patients. The overall thrombotic event complication rate in haemophilia B patients was observed to be approximately 14.7 per 1,000 patients and 5.66 per 100,000 infusions. From this extensive safety data analysis, it can be concluded that the risk of thrombotic AEs to product infusion is small and mostly represented by mild AEs. There was one clinical study report (from study 251001) received, which described transient ischaemic attack, which was assessed as unlikely by Baxalta and unrelated by the investigator. In the RIXUBIS pivotal study (250901) thrombogenicity markers (prothrombin fragment 1.2 [F 1.2], thrombin-antithrombin III [TAT], and D-dimer) were evaluated in the PK portion of the study. In addition, all subjects have been regularly monitored for the occurrence of a thrombotic event. Out-of-range values for thrombogenicity markers (Thrombin-antithrombin III [TAT], Prothrombin fragment 1.2, and D-dimer), determined during the pharmacokinetic portion of study 250901 did not reveal any pattern indicative of clinically relevant thrombogenicity with either RIXUBIS or BeneFIX, and were not associated with AEs.
Risk factors and risk groups	Patients with liver disease, peri- and post-operative patients, new-born infants, or other patients at risk for thromboembolic events or DIC.
Preventability	Clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing, particularly in at risk patients.
Impact on the risk-benefit balance of the product	Thromboembolic events (e.g., DIC and fibrinolysis) will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The benefit-risk profile of RIXUBIS remains positive.
Public health impact	This may require prolonged hospitalisation, costly treatment and can have life-threatening or fatal outcomes.

Important Potential Risk: Nephrotic syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions	
Potential mechanisms	The manner of causation is not clear. One literature source speculated mechanism is a possible immune—complex-mediated reaction.
Evidence source(s) and strength of evidence	Nephrotic syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions has been reported in scientific literature and with other factor IX products of the same class.
Characterisation of the risk	Ewenstein BM, et.al. first described nephrotic syndrome as a complication of ITI performed in haemophilia B patients that develop inhibitors in association with an allergic phenotype. According to data from a FIX immune tolerance registry, the allergic complications of ITI occurred in subjects with an identified allergic phenotype and were accompanied by the development of nephrotic syndrome in 30% of subjects. There have been no reports of nephrotic syndrome during clinical studies with RIXUBIS.
Risk factors and risk groups	Patients using RIXUBIS regularly and patients with a history of factor IX inhibitors in association with an allergic phenotype.
Preventability	Patients should be regularly assessed for the development of factor IX inhibitors by appropriate clinical observation and laboratory test.
Impact on the risk-benefit balance of the product	Nephrotic syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions will continue to be monitored through routine pharmacovigilance and routine risk minimisation measures. The benefit-risk profile of RIXUBIS remains positive.
Public health impact	Prolonged hospitalisation, costly treatment. It is plausible that nephrotic syndrome could lead to increased morbidity or even death; however, the specific rates are unknown.

SVII.3.2. Presentation of the missing information

No clinical data on use of RIXUBIS for ITI	
Evidence source:	ITI means that factor IX concentrate is given regularly over a prolonged period of time until the body is trained to recognise and tolerate the factor IX concentrate without reacting (developing inhibitors) to it. When ITI is successful, the inhibitors disappear and your response to factor IX concentrates returns to normal. RIXUBIS should not be used for ITI. The safety and efficacy of using RIXUBIS for ITI has not been established. **Anticipated risk/consequence of the missing information:** Nephrotic syndrome has been reported following attempted ITI in haemophilia B patients with factor IX inhibitors.

No data on the use of RIXUBIS for continuous infusion	
Evidence source:	RIXUBIS should not be administered by continuous infusion. RIXUBIS should be administered as a single injection (bolus) at a rate determined by the patient's comfort level, but it should not exceed 10 mL per minute. **Anticipated risk/consequence of the missing information:** Continuous infusion is not recommended for administration of RIXUBIS. It potentially could lead to lack of efficacy.

Insufficient data regarding the degree to which factor IX levels can be affected by the aPTT reagent in aPTT potency assay	
Evidence source:	Clinical studies did not assess how clotting evaluation assays examining factor IX levels can be affected by the different chemicals used. **Anticipated risk/consequence of the missing information:** Caution should be taken when using the in vitro aPTT method as results can be significantly affected by the type of aPTT reagent and the reference standard used in the assay, therefore not getting reliable results. Routinely monitor for reports of variable factor IX levels affected by aPTT reagents in aPTT potency assay and identify trends in the reporting rate and severity of these reports.

Use in pregnancy and lactation	
Evidence source:	Clinical studies did not include patients that are pregnant or lactating. The safety in patients that are pregnant or lactating is unknown. Haemophilia B, or congenital FIX deficiency, is an X-linked bleeding disorder that mainly effects males. **Anticipated risk/consequence of the missing information:** Healthcare professionals need to balance the potential risks and only prescribe RIXUBIS is clearly needed as the risk may be different from the target population (males only). Routinely monitor for reports of use in patients with severe chronic hepatic disease and identify trends in the reporting rate and severity of these reports.

Part II: Module SVIII - Summary of the Safety Concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Hypersensitivity reactions (including reactions/antibodies to Chinese hamster ovary (CHO) protein)
Important potential risks	• Inhibitor formation • Thromboembolic events (e.g., DIC and fibrinolysis) • Nephrotic Syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions
Missing information	• No clinical data on use of RIXUBIS for ITI • No data on the use of RIXUBIS for continuous infusion • Insufficient data regarding the degree to which factor IX levels can be affected by the aPTT reagent in aPTT potency assay • Use in pregnancy and lactation

Part III: Pharmacovigilance Plan (Including Post-authorisation Safety Studies)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Targeted questionnaires are implemented for RIXUBIS to aid follow-up on specific safety concerns as described below. The forms are provided in Annex 4 of the RMP.

Safety Concern: Inhibitor formation - factor IX Inhibitor AE Questionnaire.

Other forms of routine pharmacovigilance activities:

Not applicable

III.2. Additional Pharmacovigilance Activities

Participation in registries (e.g., EUHASS registry and PedNet registry) and review of the data provided by the registries to evaluate for a potential signal. Regular surveillance reports are received from the EUHASS and PedNet registries with information they have collected on the safety of treatments for people with haemophilia and other bleeding disorders. EUHASS and PedNet are voluntary reporting networks in the EU. Additionally, an analysis of the surveillance reports received from EUHASS and PedNet is routinely provided in the PSURs/PBRERs.

EUHASS registry summary
Study short name and title: Participation in EUHASS registry and review of the data provided by the registry to further characterize the safety concerns for long term safety follow-up.
Rationale and study objectives: • To monitor the safety of treatments for people with inherited bleeding disorders in Europe. • To inform clinicians, regulators and other interested parties of the treatment patterns and AEs reported for these patients in Europe. • To set up a publicly available database of all the Haemophilia centres in Europe with details of how they can be accessed by patients, and information on relevant patient, doctor, nurse and physiotherapist organisations in each country. • To set up a publicly available directory containing information and publications lists for all the clotting factor products used in Europe to treat inherited bleeding disorders.
Study design: The MAH aims to collaborate with established EUHASS Registry to collect prospective AEs.
Study population: Patients with haemophilia B (for Rixubis use).
Milestones: Regular updates: Data will be reviewed on an on-going basis as part of signal detection and reported within PSURs/PBRERs when available.

PedNet registry summary
Study short name and title: Participation in PedNet registry and review of the data provided by the registry to further characterize the safety concerns for long term safety follow-up.
Rationale and study objectives: • To monitor the safety of treatments for people with inherited bleeding disorders in Europe. • To inform clinicians, regulators and other interested parties of the treatment patterns and AEs reported for these patients in Europe. • To set up a publicly available database of all the Haemophilia centres in Europe with details of how they can be accessed by patients, and information on relevant patient, doctor, nurse and physiotherapist organisations in each country. • To set up a publicly available directory containing information and publications lists for all the clotting factor products used in Europe to treat inherited bleeding disorders.
Study design: The MAH aims to collaborate with established PedNet Registry to collect prospective AEs.
Study population: Patients with haemophilia B (for Rixubis use).
Milestones: Regular updates: Data will be reviewed on an on-going basis as part of signal detection and reported within PSURs/PBRERs when available.

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: On-going 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				
None				
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				
None				
Category 3 - Required additional pharmacovigilance activities				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Participation in registries (e.g., EUHASS PedNet registries) and review of the data provided by the registries to further characterize the safety concerns for long term safety follow-up. Ongoing	The EUHASS and PedNet registries serve to collect further safety information in patients with hemophilia B.	• Hypersensitivity reactions (including reactions/antibodies to Chinese hamster ovary (CHO) protein) • Inhibitor formation • Thromboembolic events (e.g., DIC and fibrinolysis) • Nephrotic Syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions • No clinical data on use of RIXUBIS for ITI • No data on the use of RIXUBIS for continuous infusion • Insufficient data regarding the degree to which factor IX levels can be affected by the aPTT reagent in	Regular updates	Data will be reviewed on an on-going basis as part of signal detection and reported within PSUR/PBRERs when available.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
		aPTT potency assay • Use in pregnancy and lactation		

aPTT: Activated Partial Thromboplastin Clotting Time; DIC: Disseminated Intravascular Coagulation; FIX: Factor IX; ITI: Immune Tolerated Induction

Part IV: Plans for Post-authorisation Efficacy Studies

Not applicable.

Part V: Risk Minimisation Measures (Including Evaluation of the Effectiveness of Risk Minimisation Activities)

Risk minimisation plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified Risk	
Hypersensitivity reactions (including reactions/antibodies to CHO protein)	**Routine risk communication:** SmPC Section 4.3 – "Contraindications" SmPC Section 4.4 – "Special Warnings and Precautions for use" SmPC Section 4.8 – "Undesirable effects" PL Section 2 – "What you need to know before you use RIXUBIS" PL Section 4 – "Possible side effects" **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.3 – Patients with hypersensitivity to the active substance or to an of the excipients are contraindicated. SmPC Section 4.4 – Provides advise to immediately discontinue use with RIXUBIS if any early signs of hypersensitivity occur. PL Section 2 – Advises patients to stop their infusion if allergic-type reactions appear and to contact their doctor immediately. **Other routine risk minimisation measures beyond the PI:** Pack size. Prescription only medicine.
Important Potential Risk	
Inhibitor formation	**Routine risk communication:** SmPC Section 4.4 – "Special Warnings and Precautions for use" SmPC Section 4.8 – "Undesirable effects" PL Section 2 – "What you need to know before you use RIXUBIS" **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 – Recommendation for the development of neutralising antibodies monitoring. PL Section 2 – Advising the patient that the doctor may do blood tests to check if the patient has developed neutralising bodies. **Other routine risk minimisation measures beyond the PI:** Pack size. Prescription only medicine.

Safety concern	Routine risk minimisation activities
Thromboembolic event (e.g., DIC and fibrinolysis)	**Routine risk communication:** SmPC Section 4.4 – "Special Warnings and Precautions for use" SmPC Section 4.8 – "Undesirable effects" PL section 2 – "What you need to know before you use RIXUBIS" PL section 4 – "Possible side effects" **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.4 – Recommendations to monitor for early signs of thrombotic and consumptive coagulopathy when administering RIXUBIS to patients with liver disease, post-operative patients, new born infants and patients at risk of thrombotic phenomena or DIC. PL Section 2 – Patients should notify their doctor if they suffer from liver or cardiac disease or if they have had major surgery. **Other routine risk minimisation measures beyond the PI:** Pack size. Prescription only medicine.
Nephrotic syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions	**Routine risk communication:** SmPC Section 4.4 – "Special Warnings and Precautions for use" SmPC Section 4.8 – "Undesirable effects" **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Nephrotic syndrome has been reported following attempted ITI in haemophilia B patients with factor IX inhibitors. **Other routine risk minimisation measures beyond the PI:** Pack size. Prescription only medicine.
Missing Information	
No clinical data on the use of RIXUBIS for ITI	**Routine risk communication:** SmPC Section 4.4 – "Special Warnings and Precautions for use" SmPC Section 4.8 – "Undesirable effects" **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Nephrotic syndrome has been reported following attempted ITI in haemophilia B patients with factor IX inhibitors. **Other routine risk minimisation measures beyond the PI:** Pack size. Prescription only medicine.

Safety concern	Routine risk minimisation activities
No data on the use of RIXUBIS for continuous infusion	**Routine risk communication:** SmPC Section 4.2 – "Posology and method of administration" **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 – Recommends that you should not administer RIXUBIS by continuous infusion. **Other routine risk minimisation measures beyond the PI:** Pack size. Prescription only medicine.
Insufficient data regarding the degree to which factor IX levels can be affected by the aPTT reagent in an aPTT potency assay	**Routine risk communication:** SmPC Section 4.2 – "Posology and method of administration" **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.2 – Recommends physicians to take care when monitoring factor IX activity assay for determining factor IX in patient's blood samples **Other routine risk minimisation measures beyond the PI:** Pack size. Prescription only medicine.
Use in pregnancy and lactation	**Routine risk communication:** SmPC Section 4.6 – Fertility, pregnancy and lactation **Routine risk minimisation activities recommending specific clinical measures to address the risk:** SmPC Section 4.6 – There is no information regarding the use of factor IX during pregnancy and lactation. Recommends that factor IX should only be used if clearly indicated. **Other routine risk minimisation measures beyond the PI:** Pack size. Prescription only medicine.

PL= patient leaflet; SmPC=summary of product characteristics.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3. Summary of Risk Minimisation Measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks:		
Hypersensitivity reactions (including reactions/antibodies to CHO protein)	**Routine risk minimisation measures:** SmPC Sections 4.3, 4.4, 4.8 PL sections 2 and 4 **Additional risk minimisation measures:** No risk minimisation activities.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None. **Additional pharmacovigilance activities:** EUHASS and PedNet registries.
Important potential risks:		
Inhibitor formation	**Routine risk minimisation measures:** SmPC Sections 4.4, 4.8 PL Section 2. **Additional risk minimisation measures:** No risk minimisation activities.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Factor IX Inhibitor Questionnaire **Additional pharmacovigilance activities:** EUHASS and PedNet registries.
Thromboembolic event (e.g., DIC and fibrinolysis)	**Routine risk minimisation measures:** SmPC Section 4.4, 4.8 PL Sections 2, 4 **Additional risk minimisation measures:** No risk minimisation activities.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** EUHASS and PedNet registries.
Nephrotic syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions	**Routine risk minimisation measures:** **Additional risk minimisation measures:** No risk minimisation activities.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** EUHASS and PedNet registries.

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Missing Information		
No clinical data on the use of RIXUBIS for ITI	**Routine risk minimisation measures:** **Additional risk minimisation measures:** No risk minimisation activities.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** EUHASS and PedNet registries.
No data on the use of RIXUBIS for continuous infusion	**Routine risk minimisation measures:** SmPC Section 4.2. **Additional risk minimisation measures:** No risk minimisation activities.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** EUHASS and PedNet registries.
Insufficient data regarding the degree to which factor IX levels can be affected by the aPTT reagent in aPTT potency assay	**Routine risk minimisation measures:** SmPC Section 4.2. **Additional risk minimisation measures:** No risk minimisation activities.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** EUHASS and PedNet registries.
Use in pregnancy and lactation	**Routine risk minimisation measures:** SmPC Section 4.6 **Additional risk minimisation measures:** No risk minimisation activities.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** None **Additional pharmacovigilance activities:** EUHASS and PedNet registries.

Part VI: Summary of the Risk Management Plan

Summary of risk management plan for RIXUBIS (nonacog gamma)

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

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

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

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

I. The Medicine and What It Is Used For

RIXUBIS is authorised for treatment and prophylaxis of bleeding in patients with haemophilia B. It contains RIXUBIS as the active substance and it is given by injection.

Further information about the evaluation of RIXUBIS's benefits can be found in RIXUBIS's EPAR, including in its plain-language summary, available on the European medicines agency (EMA) website, under the medicine's webpage.

The link to the EPAR summary will be provided to the applicant as part of the cover letter in the CHMP opinion package. MAHs should use the same link for updates related to post-authorisation procedures.

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

Important risks of RIXUBIS, together with measures to minimise such risks and the proposed studies for learning more about RIXUBIS '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 PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, 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 RIXUBIS is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of RIXUBIS 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 RIXUBIS. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	• Hypersensitivity reactions (including reactions/antibodies to CHO protein)
Important potential risks	• Inhibitor formation • Thromboembolic events (e.g., DIC and fibrinolysis) • Nephrotic Syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions
Missing information	• No clinical data on use of RIXUBIS for ITI • No data on the use of RIXUBIS for continuous infusion • Insufficient data regarding the degree to which factor IX levels can be affected by the aPTT reagent in aPTT potency assay • Use in pregnancy and lactation

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Important Identified Risk – Hypersensitivity reactions (including reactions/antibodies to CHO protein)	
Evidence for linking the risk to the medicine	Hypersensitivity reactions (including reactions/antibodies to CHO protein) has been reported in scientific literature and post-marketing surveillance.
Risk factors and risk groups	Patients with previous history of hypersensitivity to RIXUBIS or any other constituents of the product. The risk for hypersensitivity reactions is highest during the early phases of initial exposure to factor IX concentrates in PUPs, in particular in patients with high-risk gene mutation. Potential increased risk of hypersensitivity reactions in patients with inhibitors.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4, and 4.8 PL section 2 and 4 **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance activities	EUHASS and PedNet registries See Section II.C of this summary for an overview of the post-authorisation development plan

Important Potential Risk – Inhibitor formation	
Evidence for linking the risk to the medicine	Inhibitor formation has been reported in scientific literature.

Important Potential Risk – Inhibitor formation	
Risk factors and risk groups	PUPs and MTPs with high-risk gene mutations (such as large deletions, nonsense/stop mutations, gross deletions/insertions or complete gene deletion). Other risk factors include family history of inhibitors, association with atopia, effects of recent immunisations, race and age at first exposure.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4, and 4.8. PL section 2 **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance activities	EUHASS and PedNet registries See Section II.C of this summary for an overview of the post-authorisation development plan

Important Potential Risk – Thromboembolic events (e.g., DIC and fibrinolysis)	
Evidence for linking the risk to the medicine	Thromboembolic events (e.g., DIC and fibrinolysis) has been reported in scientific literature, clinical study and other factor IX products.
Risk factors and risk groups	Patients with previous history of hypersensitivity to RIXUBIS or any other constituents of the product. The risk for hypersensitivity reactions is highest during the early phases of initial exposure to factor IX concentrates in PUPs, in particular in patients with high-risk gene mutation. Potential increased risk of hypersensitivity reactions in patients with inhibitors.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4, and 4.8. PL sections 2 and 4 **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance activities	EUHASS and PedNet registries See Section II.C of this summary for an overview of the post-authorisation development plan

Important Potential Risk – Nephrotic Syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions	
Evidence for linking the risk to the medicine	Nephrotic syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions has been reported in scientific literature.

Important Potential Risk – Nephrotic Syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions	
Risk factors and risk groups	Patients using RIXUBIS regularly and patients with a history of factor IX inhibitors in association with an allergic phenotype.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4, and 4.8 PL section 2 and 4 **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance activities	EUHASS and PedNet registries See Section II.C of this summary for an overview of the post-authorisation development plan

Missing Information – No clinical data on use of RIXUBIS for ITI	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.4, and 4.8. **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance activities	EUHASS and PedNet registries See Section II.C of this summary for an overview of the post-authorisation development plan

Missing Information – No data on the use of RIXUBIS for continuous infusion	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.2 **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance activities	EUHASS and PedNet registries See Section II.C of this summary for an overview of the post-authorisation development plan

Missing Information – Insufficient data regarding the degree to which factor IX levels can be affected by the aPTT reagent in an aPTT potency assay	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.2

Missing Information – Insufficient data regarding the degree to which factor IX levels can be affected by the aPTT reagent in an aPTT potency assay	
	Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	EUHASS and PedNet registries See Section II.C of this summary for an overview of the post-authorisation development plan

Missing Information – Use in Pregnancy and Lactation	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.6 **Additional risk minimisation measures:** No risk minimisation measures.
Additional pharmacovigilance activities	EUHASS and PedNet registries See Section II.C of this summary for an overview of the post-authorisation development plan

II.C. Post-authorisation Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorisation

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

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

Study name	Purpose of the study
Participation in registries (e.g., EUHASS and PedNet registries) and review of the data provided by the registries to further characterize the safety concerns for long term safety follow-up.	The EUHASS and PedNet registries serve to collect further safety information in patients with hemophilia B.

Part VII: Annexes

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Annex 4: Specific adverse drug reaction follow-up forms

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Annex 4: Specific adverse drug reaction follow-up forms

Annex 4.1: Factor IX Inhibitor AE Questionnaire

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to Takeda at:** **_____**

I. REPORTER INFORMATION

Name/Title:	Email:	
Postal Address:	Phone:	Fax:
Reporter Type: Select One		

2. PATIENT INFORMATION

Patient initials	Gender	Date of Birth or Age	Height	Weight
	Select One	DOB (ddmmmyyyy) or Age	☐cm ☐in	☐kg ☐lb

3. RELEVANT MEDICAL HISTORY ☐**None** ☐**Unknown** ☐**Not reported**

Diagnosis	Onset Date (ddmmmyyyy)	Cessation Date (ddmmmyyyy)	Check if ongoing?
			☐
			☐
			☐
			☐
			☐
			☐

Smoker? Select One If Yes, please state quantity:
Alcohol Use? Select One If Yes, please state quantity:
Allergies? Select One If Yes, please list allergies:

Severity of Hemophilia B: Select One Is there prior inhibitor history? ☐No ☐Yes

Information on last Factor IX Inhibitor

FIX Product received at time of last inhibitor detection:
Max inhibitory level during last episode: BU Date (ddmmmyyyy):
Local lab cut-off for positive inhibitor result: BU Date (ddmmmyyyy):
Did inhibitor resolve? ☐No ☐Yes
Previous Immune Tolerance Induction (ITII) at the time with other product? ☐No ☐Yes If yes, please complete below.
Date Started (ddmmmyyyy):
Regimen:
Exposure days at the time of 1st inhibitor (approximate) ☐<50 ☐50-150 ☐>150

Additional Medical History

Age at first Factor FIX exposure:
Is there a family history of hemophilia B? Select One
Is there a family history of inhibitor development? Select One
Please provide Hemophilia B genotype (if known): ☐Unknown ☐Not reported
Additional relevant inhibitor medical history? ☐ No ☐Yes Please list:

Case ID: **Patient/Study ID:**	**Send completed questionnaire by email to Takeda at:** **_____**

4. RELEVANT LAB DATA ☐ **Unknown** ☐ **Not Reported**

Test Name	Date (ddmmmyyyy)	Result	Normal Range

5. SUSPECT PRODUCT INFORMATION ☐**Unknown** ☐**Not Reported**

Takeda Trade Name	Lot#	Indication	Dose/Frequency/ Route of Administration	State Date (ddmmmyyyy)	Stop Date (ddmmmyyyy)	Check if Ongoing	Action taken with product
☐Rixubis ☐mmunine		Select One	Dose : Route: Freq:			☐	Select One
☐Rixubis ☐mmunine		Select One	Dose : Route: Freq:			☐	Select One
☐Rixubis ☐mmunine		Select One	Dose : Route: Freq:			☐	Select One
☐Rixubis ☐mmunine		Select One	Dose : Route: Freq:			☐	Select One
☐Rixubis ☐mmunine		Select One	Dose : Route: Freq:			☐	Select One

Factor IX substitution was given for:	☐ Prophylaxis ☐ On Demand ☐ Surgery ☐ Unknown ☐ Not reported
Exact number of RIXUBIS exposure days at time of inhibitor detection: If exact number of RIXIBUS exposure days is not known, please provide range:	☐ < 50 ☐ 50- 150 ☐ > 150
Exact number of Immunine exposure days at time of inhibitor detection: If exact number of Immunine exposure days is not known, please provide range:	☐ < 50 ☐ 50- 150 ☐ > 150
Exact number of all FIX product exposure days at time of inhibitor detection: If exact number of all FIX Product exposure days is not known, please provide range:	☐ < 50 ☐ 50- 150 ☐ > 150
Current factor IX therapy administered via:	☐ Bolus ☐ Continuous infusion ☐ Unknown ☐ Not reported

6. CONCOMITANT MEDICATION ☐**None** ☐**Unknown** ☐**Not reported**

Trade Name or Active Substance	Dose/Frequency/ Route of Administration	Start Date (ddmmmyyyy)	Stop Date (ddmmmyyyy)	Check if Ongoing
	Dose: Route: Freq:			☐
	Dose: Route: Freq:			☐

Case ID: Patient/Study ID:		Send completed questionnaire by email to Takeda at: _____		
	Dose: Route: Freq:			☐
	Dose: Route: Freq:			☐
	Dose: Route: Freq:			☐
	Dose: Route: Freq:			☐
	Dose: Route: Freq:			☐

7. FACTOR IX INHIBITOR INFORMATION

Date of inhibitor detection (ddmmmyyyy): ☐Unknown ☐Not reported
Inhibitor level at first laboratory detection: BU Date (ddmmmyyyy):
Max inhibitor level: BU Date (ddmmmyyyy):
Most recent inhibitor level: BU Date (ddmmmyyyy):
Local lab cut-off for positive inhibitor result: BU Date (ddmmmyyyy):
Assay Type?
Was inhibitor eradicated? ☐No ☐Yes (If yes, please provide Date (ddmmmyyyy):

Did the inhibitor involve any of the following? ☐No ☐Yes
If Yes, please specify:
☐Hospitalization from (ddmmmyyyy) to ddmmmyyyy)
☐Medically Significant ☐Life-Threatening ☐Disability ☐Death
Death on (ddmmmyyyy): Cause(s):

Is the Factor IX inhibitor related to treatment with the Takeda product? ☐No ☐Yes ☐Unknown
Has the patient recovered? ☐Recovered on (ddmmmyyyy) ☐Recovered with Sequelae ☐Recovering
☐Fatal ☐Not recovered ☐Unknown ☐Not reported

8. TREATMENT ☐None ☐Unknown ☐Not reported

Drug Name / Name of Non-Drug Name	Dose / Frequency / Route of Administration	Start Date (ddmmmyyyy)	Stop Date (ddmmmyyyy)	Check if Ongoing
	Dose : Route: Freq:			☐
	Dose : Route: Freq:			☐
	Dose : Route:			☐

Case ID: **Patient/Study ID:**		**Send completed questionnaire by email to Takeda at:** **_____**		
	Freq:			
	Dose : Route: Freq:			☐
	Dose : Route: Freq:			☐
	Dose : Route: Freq:			☐
	Dose : Route: Freq:			☐
	Dose : Route: Freq:			☐
	Dose : Route: Freq:			☐

Was immune tolerance induction (ITI) initiated? ☐No ☐Yes ☐Unknown ☐Not reported

(If yes, please answer below)

Date Started (ddmmmyyyy):

Regimen:

Inhibitor level at start of ITI: BU Date (ddmmmyyyy):

Maximum titer during ITI: BU Date (ddmmmyyyy):

Last inhibitor titer tested during ITI: BU Date (ddmmmyyyy):

Is the patient participating in an ITI trial? ☐No ☐Yes

If yes, please provide name of study:

ITI still ongoing? ☐No ☐Yes

9. ADDITIONAL INFORMATION

QUESTIONNAIRE COMPLETED BY	Printed Name:	Today's Date:
	Signature:	
	Address:	
	Contact Number:	Email:

Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Not applicable.