ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

RIXUBIS 250 IU powder and solvent for solution for injection
RIXUBIS 500 IU powder and solvent for solution for injection
RIXUBIS 1000 IU powder and solvent for solution for injection
RIXUBIS 2000 IU powder and solvent for solution for injection
RIXUBIS 3000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RIXUBIS 250 IU powder and solvent for solution for injection
One vial contains nominally 250 IU nonacog gamma, recombinant human coagulation factor IX (rDNA), corresponding to a concentration of 50 IU/ml after reconstitution with 5 ml solvent.

RIXUBIS 500 IU powder and solvent for solution for injection
One vial contains nominally 500 IU nonacog gamma, recombinant human coagulation factor IX (rDNA), corresponding to a concentration of 100 IU/ml after reconstitution with 5 ml solvent.

RIXUBIS 1000 IU powder and solvent for solution for injection
One vial contains nominally 1000 IU nonacog gamma, recombinant human coagulation factor IX (rDNA), corresponding to a concentration of 200 IU/ml after reconstitution with 5 ml solvent.

RIXUBIS 2000 IU powder and solvent for solution for injection
One vial contains nominally 2000 IU nonacog gamma, recombinant human coagulation factor IX (rDNA), corresponding to a concentration of 400 IU/ml after reconstitution with 5 ml solvent.

RIXUBIS 3000 IU powder and solvent for solution for injection
One vial contains nominally 3000 IU nonacog gamma, recombinant human coagulation factor IX (rDNA), corresponding to a concentration of 600 IU/ml after reconstitution with 5 ml solvent.

The potency (IU) is determined using the European Pharmacopoeia one stage clotting assay.
The specific activity of RIXUBIS is approximately 200-390 IU/mg protein.

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.

Excipient(s) with known effect:
One vial contains 19 mg sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
The powder is white to off-white. The solvent is clear and colourless.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).
RIXUBIS is indicated in patients of all age groups.

4.2 Posology and method of administration

Treatment should be under the supervision of a physician experienced in the treatment of haemophilia.

Treatment monitoring
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 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.

Posology
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 International Unit of factor IX activity is equivalent to that quantity of factor IX in one ml of normal human plasma.

Adult population
On demand treatment:
The calculation of the required dose of factor IX is based on the empirical finding that 1 International Unit 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 (further information see section 5.2).

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 haemarthrosis, 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 haemarthrosis, muscle bleeding or haematoma	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 resolved.
Surgery Minor surgery including tooth extraction	30 – 60	Every 24 hours, at least 1 day, until healing is achieved.
Major surgery	80 – 100 (pre- and postoperative)	Repeat infusion every 8 to 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 than 12 years of age:
On demand treatment
The calculation of the required dose of factor IX is based on the empirical finding that 1 International Unit 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 (further information see section 5.2).

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 (see above).

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.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.
Only plastic luer-lock syringes should be used with this product.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Known allergic reaction to hamster protein.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity
Allergic type hypersensitivity reactions have been reported with RIXUBIS. The product contains traces of hamster proteins. If symptoms of hypersensitivity occur, patients or their caregivers should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

The risk is highest during the early phases of initial exposure to factor IX concentrates in previously untreated patients (PUPs), in particular in patients with high-risk gene mutations. There have been reports in the literature showing an association between the occurrence of a factor IX inhibitor and allergic reactions, in particular in patients with a high-risk gene mutation. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor.

In case of shock, standard medical treatment for shock should be implemented.

Inhibitors
After repeated treatment with human coagulation factor IX (rDNA) products, patients should be monitored for the development of neutralising antibodies (inhibitors) that should be quantified in Bethesda Units (BU) using appropriate biological testing.

There have been reports in the literature showing a correlation between the occurrence of a factor IX inhibitor and allergic reactions. Therefore, patients experiencing allergic reactions should be evaluated for the presence of an inhibitor. It should be noted that patients with factor IX inhibitors may be at an increased risk of anaphylaxis with subsequent challenge with factor IX.

Because of the risk of allergic reactions with factor IX concentrates, the initial administrations of factor IX should, according to the treating physician's judgement, be performed under medical observation where proper medical care for allergic reactions could be provided.

Nephrotic syndrome
Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors.

Thromboembolism
Because of the potential risk of thrombotic complications, clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing when administering this product to patients with liver disease, to patients post-operatively, to new-born infants, or to patients at risk of thrombotic phenomena or DIC. In each of these situations, the benefit of treatment with RIXUBIS should be weighed against the risk of these complications.

Cardiovascular events
In patients with existing cardiovascular risk factors, substitution therapy with FIX may increase the cardiovascular risk.

Catheter-related complications
If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.

Excipient related considerations
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'. Depending on body weight and Posology of RIXUBIS, patients could receive more than one vial. This should be taken into consideration if the patient is on a controlled sodium diet.

Elderly
Clinical studies of RIXUBIS did not include subjects aged 65 and over. It is not known whether they respond differently from younger subjects. As for all patients, dose selection for an elderly patient should be individualised.

Paediatric population
The listed warnings and precautions apply both to adults and children.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor IX (rDNA) products with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of Factor IX in pregnant women. Animal reproduction studies have not been conducted with factor IX.
Factor IX should be used during pregnancy and breast-feeding only if clearly indicated.

Breast-feeding
It is unknown whether Factor IX/metabolites are excreted in human milk.

Fertility
There is no information on the effects of factor IX on fertility.

4.7 Effects on ability to drive and use machines

RIXUBIS has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely and may in some cases progress to severe anaphylaxis (including shock). In some cases, these reactions have progressed to severe anaphylaxis, and they have occurred in close temporal association with development of factor IX inhibitors (see also 4.4).
Nephrotic syndrome has been reported following attempted immune tolerance induction in haemophilia B patients with factor IX inhibitors and a history of allergic reactions.

Very rarely development of antibodies to hamster protein with related hypersensitivity reactions has been observed.

Patients with haemophilia B may develop neutralising antibodies (inhibitors) to factor IX. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

There is a potential risk of thromboembolic episodes following the administration of factor IX products, with a higher risk for low purity preparations. The use of low purity factor IX products has been associated with instances of myocardial infarction, disseminated intravascular coagulation, venous thrombosis and pulmonary embolism. The use of high purity factor IX is rarely associated with such adverse reactions.

Tabulated list of adverse reactions
Clinical studies with RIXUBIS included 99 subjects with at least one exposure to RIXUBIS reporting in total 5 adverse reactions. The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse Drug Reactions, from clinical trials and spontaneous reports		
MedDRA Standard System Organ Class	**Adverse reactions**	**Frequency per Patient**
Immune system disorders	Hypersensitivity [a)]	Not known
Nervous system disorders	Dysgeusia	Common
Musculoskeletal and connective tissue disorders	Pain in extremity	Common

a) ADR explained in the section below.

Description of selected adverse reactions

Hypersensitivity
Allergic type reactions have been manifested by dyspnoea, pruritus, generalised urticaria and rash.

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults. However, no data are available on previously untreated patients as only previously treated patients have been enrolled in the clinical studies; no immunogenicity investigation on inhibitor development was therefore made in this at risk population.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The effects of higher than recommended doses of RIXUBIS have not been characterised.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factor IX. ATC code: B02BD04.

Mechanism 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.

Pharmacodynamic effects
Haemophilia B is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor IX and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor IX is increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Clinical efficacy and safety
Prophylaxis and control of bleeding in previously treated patients 12 years and older
The efficacy of RIXUBIS has been evaluated in the open-label, uncontrolled part of a combined phase 1/3 study, in which a total of 73 male, previously treated patients (PTPs) between 12 and 59 years of age received RIXUBIS either for prophylaxis and/or for the treatment of bleeding episodes on an on-demand basis. All subjects had severe (factor IX level <1%) or moderately severe (factor IX level ≤2%) haemophilia B. Fifty-nine PTPs received RIXUBIS for prophylaxis. Fifty-six of these PTPs who received RIXUBIS for a minimum of 3 months were included in the efficacy evaluation for prophylaxis. An additional 14 PTPs received RIXUBIS for the treatment of bleeding episodes only. Subjects in the on-demand cohort had to have at least 12 documented bleeding episodes requiring treatment within 12 months prior to enrollment. The mean treatment duration in the on-demand cohort was 3.5±1.00 months (median 3.4, ranging from 1.2 to 5.1 months), the mean total annualised bleeding rate (ABR) was 33.9±17.37 with a median of 27.0, ranging from 12.9 to 73.1.

The median ABR on prophylaxis with RIXUBIS for all bleeds was 2.0, for spontaneous bleeds 0.0, and for joint bleeds 0.0. 24 subjects (42.9%) experienced zero bleeds.

A total of 249 bleeding episodes were treated with RIXUBIS, of which 197 were joint bleeds and 52 non-joint bleeds (soft tissue, muscle, body cavity, intracranial and other). Of a total of 249 bleeding episodes, 163 were moderate, 71 were minor, and 15 were major. Treatment was individualised based on the severity, cause and site of bleed. Of the 249 bleeding episodes, the majority (211; 84.7%) were treated with 1-2 infusions. Haemostatic efficacy at resolution of bleed was rated excellent or good in 96% of all treated bleeding episodes.

Prophylaxis and control of bleeding in PTPs below 12 years:
The efficacy of RIXUBIS has been evaluated in a combined phase 2/3 study, in which a total of 23 male PTPs between 1.8 and 11.8 years (median age 7.10 years) with 11 patients < 6 years, received RIXUBIS for prophylaxis and control of bleeding episodes. All subjects had severe (factor IX level <1%) or moderately severe (factor IX level ≤2%) haemophilia B. All 23 subjects received prophylactic treatment with RIXUBIS for a minimum of 3 months and were included in the efficacy evaluation for prophylaxis.

The median ABR was 2.0, for spontaneous bleeds 0.0 and for joint bleeds 0.0.
Nine subjects (39.1%) experienced zero bleeds.

A total of 26 bleeding episodes were treated with RIXUBIS, of which 23 bleeds were due to injury, 2 spontaneous and 1 of unknown origin. 19 bleeds were non-joint (soft tissue, muscle, body cavity, intracranial and other) and 7 were joint bleeds of which 1 was a bleed into a target joint. Of the 26 bleeding episodes, 15 were minor, 9 moderate, and 2 major. Treatment was individualised based on the severity, cause and site of bleed The majority (23; 88,5%) were treated with 1-2 infusions. Haemostatic efficacy at resolution of a bleed was rated excellent or good in 96.2% of all treated bleeding episodes.

Perioperative management:
The safety and efficacy in the perioperative setting was evaluated in a phase 3 prospective, open-label, uncontrolled, multicenter study in male PTPs with severe and moderately severe haemophilia B using RIXUBIS. The per-protocol efficacy analysis includes 37 surgeries performed in 27 patients between 17 and 57 years of age undergoing major or minor surgical, dental or other surgical invasive procedures. Twenty procedures were major including 13 orthopaedic and 3 dental surgeries. 17 procedures, including 10 dental extractions, were considered minor. Patients undergoing major surgeries had to perform a pharmacokinetic (PK) evaluation. All patients were dosed based on their most recent individual incremental recovery. The recommended initial loading dose of RIXUBIS was to ensure that during surgery, factor IX activity levels of 80-100% for major surgeries and 30-60% for minor surgeries were maintained. RIXUBIS was administered by bolus infusions.

Haemostasis was maintained throughout the study duration.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with RIXUBIS in previously untreated patients in the treatment and prophylaxis of bleeding in haemophilia B (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Previously treated patients 12 years and older:
A randomised, blinded, controlled, crossover pharmacokinetic study of RIXUBIS and a comparator was conducted in non-bleeding male subjects (≥15 years of age) as part of the combined phase 1/3 pivotal study. The subjects received either of the products as a single intravenous infusion. The mean (± SD) and median dose of RIXUBIS in the per protocol analysis set (n=25) were 74.69±2.37 and 74.25 IU/kg, respectively, with a range of 71.27 to 79.38 IU/kg. The

pharmacokinetic parameters were calculated from factor IX activitiy measurements in blood samples obtained up to 72 hours following each infusion.

The pharmacokinetic evaluation was repeated for RIXUBIS in an open-label, uncontrolled study with RIXUBIS in male subjects who participated in the initial PK crossover study and had received prophylaxis with RIXUBIS for 26±1 weeks (mean ± SD) and accumulated at least 30 exposure days (EDs) to RIXUBIS. The RIXUBIS dose range in the repeat pharmacokinetics study was 64.48 to 79.18 IU/kg (n=23).

Pharmacokinetic parameters for evaluable subjects (per-protocol analysis) are presented in the table below.

Parameter	**RIXUBIS Initial cross-over study (N=25)**	**RIXUBIS Repeat Evaluation (N=23)**
$AUC_{0\text{-}72h}$ (IU.hr/dL)[a] Mean±SD Median (range)	1067.81±238.42 1108.35 (696.07-1571.16)	1156.15±259.44 1170.26 (753.85-1626.81)
Incremental recovery at C_{max} (IU/dL:IU/kg)[b] Mean ±SD Median (range)	0.87±0.22 0.88 (0.53-1.35)	0.95±0.25 0.93 (0.52-1.38)
Half-life (hr) Mean±SD Median (range)	26.70±9.55 24.58 (15.83-52.34)	25.36±6.86 24.59 (16.24-42.20)
C_{max} (IU/dL) Mean±SD Median (range)	66.22±15.80 68.10 (41.70-100.30)	72.75±19.73 72.40 (38.50-106.30)
Mean residence time (hr) Mean±SD Median (range)	30.82±7.26 28.93 (22.25-47.78)	29.88±4.16 29.04 (21.32-37.52)
V_{ss}[c] (dL/kg) Mean±SD Median (range)	2.02±0.77 1.72 (1.10-3.94)	1.79±0.45 1.74 (1.12-2.72)
Clearance (dL/(kg.hr)) Mean±SD Median (range)	0.0644±0.0133 0.0622 (0.0426-0.0912)	0.0602±0.0146 0.0576 (0.0413-0.0945)

[a] Area under the plasma concentration-time curve from time 0-72 hours post-infusion.

[b] Calculated as (C_{max}-baseline factor IX) divided by the dose in IU/kg, where C_{max} is the maximal post-infusion factor IX measurement.

[c] Volume of distribution at steady state

Incremental recovery 30 minutes after infusion was determined for all subjects in the combined phase 1/3 study at exposure day 1, at their week 5, 13, and 26 visits, and at the time of study completion or termination, if it did not coincide with the week 26 visit. The data demonstrate that the incremental recovery is consistent over time (see table below).

	Exposure Day 1 (N=73)	**Week 5 (N=71)**	**Week 13 (N=68)**	**Week 26 (N=55)**	**At study completion/ termination[b] (N=23)**
Incremental recovery 30 min after infusion (IU/dL: IU/kg)[a] Mean±SD Median (range)	0.79±0.20 0.78 (0.26-1.35)	0.83±0.21 0.79 (0.46-1.48)	0.85±0.25 0.83 (0.14-1.47)	0.89±0.12 0.88 (0.52-1.29)	0.87±0.20 0.89 (0.52-1.32)

[a] Calculated as (C_{30min}-baseline factor IX) divided by the dose in IU/kg, where C_{30min} is the factor IX measurement 30 minutes after infusion.
[b] If not coinciding with week 26 visit.

Paediatric population (previously treated patients younger than 12 years)

All 23 male subjects underwent an initial pharmacokinetic evaluation of RIXUBIS in a non-bleeding state as part of the combined phase 2/3 paediatric study. Subjects were randomised to one of two blood sampling sequences to reduce the burden of frequent blood draws on the individual subjects. The mean (± SD) and median dose of RIXUBIS in the full analysis set (n=23)
was 75.50 ± 3.016 and 75.25 IU/kg, respectively, with a range of 70.0 to 83.6 IU/kg. The pharmacokinetic parameters were calculated from factor IX activity measurements in blood samples obtained up to 72 hours following the infusion.

Pharmacokinetic parameters for all subjects (full analysis set) are presented in the table below.

Parameter	**< 6years (N=11)**	**6 - < 12 years (N=12)**	**All (N=23)**
AUC_{inf} (IU.hr/dL)[a] Mean±SD Median (range)	723.7 ± 119.00 717.2 (488-947)	886.0 ± 133.66 863.7 (730-1138)	808.4 ± 149.14 802.9 (488-1138)
Half-life (hr) Mean±SD Median (range)	27.67 ± 2.66 27.28 (24.0-32.2)	23.15 ± 1.58 22.65 (21.8-27.4)	25.31 ± 3.13 24.48 (21.8-32.2)
Mean residence time (hr) Mean±SD Median (range)	30.62 ±3.27 30.08 (26.2-36.2)	25.31 ± 1.83 24.74 (23.7-30.3)	27.85 ± 3.73 26.77 (23.7-36.2)
V_{ss}[b] (dL/kg) Mean±SD Median (range)	3.22 ± 0.52 3.16 (2.65-4.42)	2.21 ± 0.32 2.185 (1.70-2.70)	2.7 ± 0.67 2.69 (1.70-4.42)
Clearance (dL/(kg.hr)) Mean±SD Median (range)	0.1058 ± 0.01650 0.1050 (0.081-0.144)	0.0874 ± 0.01213 0.0863 (0.069-0.108)	0.0962 ± 0.01689 0.0935 (0.069-0.144)

[a] Area under the plasma concentration-time curve from time 0 to infinity.
[b] Volume of distribution at steady state

Incremental recovery 30 minutes after infusion was determined for all subjects in the combined phase 2/3 study at the initial pharmacokinetic evaluation (exposure day 1), at week 5, 13, and 26 visits, and at the time of study completion or termination, if it did not coincide with the week 26 visit. The data demonstrate that the incremental recovery is consistent over time across all paediatric age groups. See tables below.

Incremental recovery for RIXUBIS 30 minutes after infusion, both paediatric age groups:

Incremental recovery 30 min after infusion	**PK (ED 1) All (N=22)**	**Week 5 All (N=23)**	**Week 13 All (N=21)**	**Week 26 All (N=21)**
(IU/dL: IU/kg)[a] Mean±SD Median (range)	0.67 ±0.16 0.69 (0.31 – 1.00)	0.68 ± 0.12 0.66 (0.48 – 0.92)	0.71 ± 0.13 0.66 (0.51-1.00)	0.72 ± 0.15 0.734 (0.51-1.01)

[a] Calculated as (C_{30min}-baseline factor IX) divided by the dose in IU/kg, where C_{30min} is the factor IX measurement 30 minutes after infusion.

Incremental recovery for RIXUBIS 30 minutes after infusion, paediatric patients < 6 years:

Incremental recovery 30 min after infusion	PK (ED 1) All (N=10)	Week 5 All (N=11)	Week 13 All (N=10)	Week 26 All (N=10)
(IU/dL: IU/kg)[a]	0.59 ± 0.13	0.63 ± 0.10	0.68 ± 0.12	0.65 ± 0.13
Mean±SD	0.59	0.6	0.66	0.61
Median (range)	(0.31-0.75)	(0.49-0.80)	(0.51-0.84)	(0.51-0.84)

[a] Calculated as (C_{30min}-baseline factor IX) divided by the dose in IU/kg, where C_{30min} is the factor IX measurement 30 minutes after infusion.

Incremental recovery for RIXUBIS 30 minutes after infusion, paediatric patients 6 to < 12 years:

Incremental recovery 30 min after infusion	PK (ED 1) All (N=12)	Week 5 All (N=12)	Week 13 All (N=11)	Week 26 All (N=11)
(IU/dL: IU/kg)[a]	0.73 ± 0.16	0.73 ± 0.13	0.73 ± 0.14	0.8 ± 0.14
Mean±SD Median (range)	0.71 (0.51-1.00)	0.70 (0.48-0.92)	0.70 (0.54 – 1.00)	0.78 (0.56-1.01)

[a] Calculated as (C_{30min}-baseline factor IX) divided by the dose in IU/kg, where C_{30min} is the factor IX measurement 30 minutes after infusion.

5.3 Preclinical safety data

RIXUBIS was not thrombogenic at a dose of 750 IU/kg in a rabbit stasis model (Wessler-Test).
RIXUBIS did not cause any adverse clinical, respiratory, or cardiovascular effects up to 450 IU/kg in cynomolgus monkeys.
No investigations on carcinogenicity, fertility impairment, and fetal development have been conducted.
RIXUBIS was well tolerated in single dose and repeated dose toxicity studies conducted in mice, rats and cynomolgus monkeys up to doses of 7500 IU/kg (single dose) and 750 IU/kg (repeated application).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Sucrose
Mannitol
Sodium chloride
Calcium chloride
L-Histidine
Polysorbate 80

Solvent
Sterilised water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Only plastic luer-lock syringes should be used with this product. Incorrect dosing can occur as a consequence of human coagulation factor IX adsorption to the internal surfaces of some infusion equipment.

6.3 Shelf life

3 years.
Chemical and physical in-use stability has been demonstrated for 3 hours at a temperature not above 30°C. From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. Do not refrigerate.

6.4 Special precautions for storage

Store below 30°C.
Do not freeze.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use

One pack contains a powder vial (type I glass) with a stopper (butyl rubber) and a flip-off seal, a vial containing 5 ml solvent (type I glass) with a stopper (chlorobutyl rubber, or bromobutyl rubber) and a flip-off seal and a needle-less reconstitution device (BAXJECT II).
Pack size of 1.

6.6 Special precautions for disposal and other handling

RIXUBIS is to be administered intravenously after reconstitution of the powder with the provided solvent.

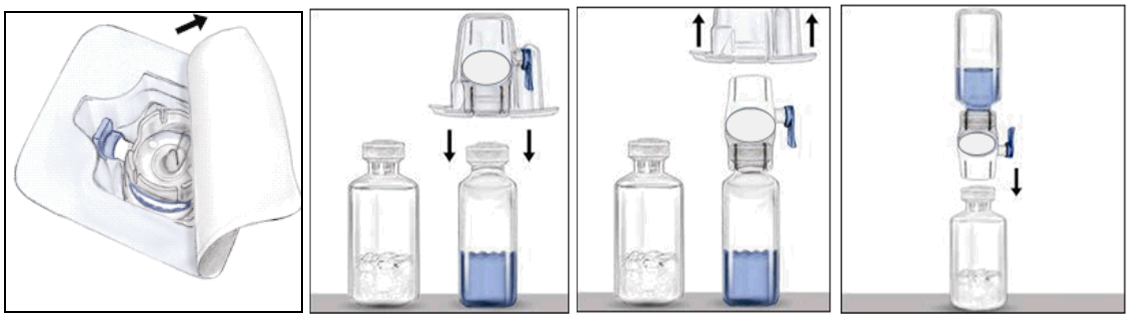
- For reconstitution use only the solvent and the reconstitution device (BAXJECT II) provided in the pack.
- For administration the use of a luer-lock syringe is required.
- Do not use if the BAXJECT II device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.

Reconstitution
Use Aseptic Technique

1. If the product is stored in a refrigerator, take both the RIXUBIS powder and solvent vials from the refrigerator and let them reach room temperature (between 15°C and 30°C).
2. Wash your hands thoroughly using soap and warm water.
3. Remove caps from powder and solvent vials.
4. Cleanse stoppers with alcohol swabs. Place the vials on a flat clean surface.
5. Open the package of BAXJECT II device by peeling away the paper lid without touching the inside (Fig. a). Do not remove the device from the package.
6. Turn the package over and insert the clear plastic spike through the solvent stopper. Grip the package at its edge and pull the package off BAXJECT II (Fig. b). Do not remove the blue cap from the BAXJECT II device.
7. With BAXJECT II attached to the solvent vial, invert the system so that the solvent vial is on top of the device. Insert the white plastic spike through the RIXUBIS stopper. The vacuum will draw the solvent into the RIXUBIS vial (Fig. c).

8. Swirl gently until all material is dissolved. The product dissolves rapidly (within 2 minutes). Be sure that RIXUBIS is completely dissolved, otherwise not all reconstituted solution will pass through the device filter. Reconstituted medicinal products should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

Fig. a **Fig. b** **Fig. c**

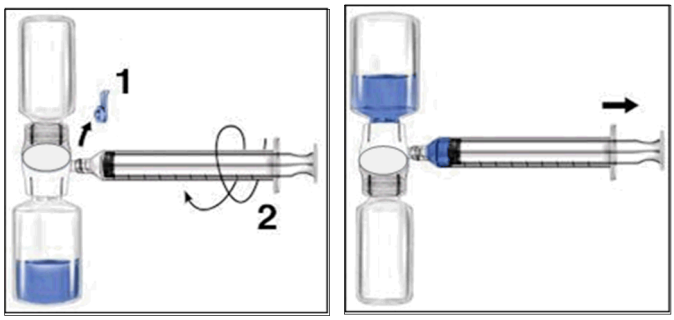


Do not refrigerate the preparation after reconstitution.
Use immediately.

Administration
Use Aseptic Technique

1. Remove the blue cap from BAXJECT II. **Do not draw air into the syringe**. Connect the syringe to BAXJECT II (Fig. d).
2. Invert the system (the vial with the reconstituted solution has to be on top). Draw the reconstituted solution into the syringe by pulling the plunger back slowly (Fig. e).
3. Disconnect the syringe.
4. Attach a butterfly needle to the syringe. Inject intravenously. The solution should be administered slowly, at a rate as determined by the patient's comfort level, not to exceed 10 ml per minute.

Fig. d **Fig. e**



Whenever possible, please record the name of the product and the batch number every time you use RIXUBIS (e.g. in your diary) to keep track of the products and product batches you have used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
Industriestrasse 67

A-1221 Vienna
Austria

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/970/001
EU/1/14/970/002
EU/1/14/970/003
EU/1/14/970/004
EU/1/14/970/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 December 2014
Date of latest renewal: 14 November 2019

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Takeda Manufacturing Austria AG
Uferstrasse 15
2304 Orth an der Donau
Austria

Takeda Manufacturing Singapore Pte. Ltd.
2A Woodlands Industrial Park D Street 2
Singapore 737779

Name and address of the manufacturers responsible for batch release

Baxalta Belgium Manufacturing SA
Boulevard René Branquart 80
B-7860 Lessines
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

RIXUBIS 250 IU powder and solvent for solution for injection
nonacog gamma (recombinant human coagulation factor IX)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 250 IU nonacog gamma, approx. 50 IU/ml after reconstitution with 5 ml solvent.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, sucrose, calcium chloride, histidine, mannitol, polysorbate 80.

Solvent: sterilised water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 powder vial, 1 solvent vial, 1 BAXJECT II device

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use, single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

Use immediately.

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/970/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RIXUBIS 250

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

RIXUBIS 250 IU powder for injection
nonacog gamma
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use injection.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 IU

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

RIXUBIS 500 IU powder and solvent for solution for injection
nonacog gamma (recombinant human coagulation factor IX)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 500 IU nonacog gamma, approx. 100 IU/ml after reconstitution with 5 ml solvent.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, sucrose, calcium chloride, histidine, mannitol, polysorbate 80.

Solvent: sterilised water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 powder vial, 1 solvent vial, 1 BAXJECT II device

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use, single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

Use immediately.

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/970/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RIXUBIS 500

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

RIXUBIS 500 IU powder for injection
nonacog gamma
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use injection.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 IU

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

RIXUBIS 1000 IU powder and solvent for solution for injection
nonacog gamma (recombinant human coagulation factor IX)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 1000 IU nonacog gamma, approx. 200 IU/ml after reconstitution with 5 ml solvent.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, sucrose, calcium chloride, histidine, mannitol, polysorbate 80.

Solvent: sterilised water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 powder vial, 1 solvent vial, 1 BAXJECT II device

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use, single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

Use immediately.

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/970/003

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RIXUBIS 1000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

RIXUBIS 1000 IU powder for injection
nonacog gamma
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use injection.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1000 IU

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

RIXUBIS 2000 IU powder and solvent for solution for injection
nonacog gamma (recombinant human coagulation factor IX)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 2000 IU nonacog gamma, approx. 400 IU/ml after reconstitution with 5 ml solvent.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, sucrose, calcium chloride, histidine, mannitol, polysorbate 80.

Solvent: sterilised water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 powder vial, 1 solvent vial, 1 BAXJECT II device

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use, single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

Use immediately.

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/970/004

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RIXUBIS 2000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

RIXUBIS 2000 IU powder for injection
nonacog gamma
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use injection.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2000 IU

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

RIXUBIS 3000 IU powder and solvent for solution for injection
nonacog gamma (recombinant human coagulation factor IX)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 3000 IU nonacog gamma, approx. 600 IU/ml after reconstitution with 5 ml solvent.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, sucrose, calcium chloride, histidine, mannitol, polysorbate 80.

Solvent: sterilised water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Contents: 1 powder vial, 1 solvent vial, 1 BAXJECT II device

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use, single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

Use immediately.

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Baxalta Innovations GmbH
A-1221 Vienna
Austria

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/970/005

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

RIXUBIS 3000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

RIXUBIS 3000 IU powder for injection
nonacog gamma
IV use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.
Single use injection.

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3000 IU

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL FOR THE SOLVENT

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Sterilised water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot:

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

RIXUBIS 250 IU powder and solvent for solution for injection
RIXUBIS 500 IU powder and solvent for solution for injection
RIXUBIS 1000 IU powder and solvent for solution for injection
RIXUBIS 2000 IU powder and solvent for solution for injection
RIXUBIS 3000 IU powder and solvent for solution for injection

nonacog gamma (recombinant human coagulation factor IX)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What RIXUBIS is and what it is used for

RIXUBIS contains the active substance nonacog gamma and is a coagulation factor IX product. Factor IX is a normal constituent of human blood necessary for effective blood clotting. RIXUBIS is used in patients with haemophilia B (Christmas disease, an inherited bleeding disorder caused by lack of factor IX). It works by replacing the missing factor IX to enable the patient's blood to clot.

RIXUBIS is used for the treatment and prevention of bleeding in patients with haemophilia B of all age groups.

2. What you need to know before you use RIXUBIS

Do not use RIXUBIS
- if you are allergic to nonacog gamma or any of the other ingredients of this medicine (listed in section 6)
- if you are allergic to hamster proteins

Warnings and precautions
Allergic-type hypersensitivity reactions are possible with RIXUBIS. Stop your infusion and contact your doctor immediately or seek emergency medical care if you experience early signs of hypersensitivity/allergic reactions like hives, rash, tightness of the chest, wheezing, low blood pressure or anaphylaxis (severe allergic reaction that can cause difficulty in swallowing and/or breathing, red or swollen face and/or hands). Your doctor may need to treat you promptly for these reactions. Your doctor may also do a blood test to check if you have developed activity-neutralising antibodies

(inhibitors) against your medicine, as inhibitors may develop together with allergies. Patients with factor IX inhibitors may be at an increased risk of anaphylaxis during future treatment with factor IX.

Talk to your doctor immediately if your bleeding does not stop as expected or if you experience a significant increase in your usage of RIXUBIS in order to control a bleed. Your doctor will do a blood test to check if you have developed activity-neutralising antibodies (inhibitors) against RIXUBIS. The risk for developing inhibitors 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.

The production of factor IX in the body is controlled by the factor IX gene. Patients who have specific mutations of their factor IX gene such as major deletion may be more likely to have factor IX inhibitors and an allergic reaction in the early period with any factor IX concentrate. Therefore if you are known to have such a mutation, your doctor will monitor you more closely for signs of an allergic reaction.

If you suffer from liver or cardiac disease or if you have recently had major surgery, please inform your doctor, as there is an increased risk for blood clotting (coagulation) complications.

Kidney disorders (nephrotic syndrome) have been reported following high doses of Factor IX in haemophilia B patients with factor IX inhibitors and a history of allergic reactions.

Whenever possible, please record the name of the product and the batch number every time you use RIXUBIS (e.g. in your diary) to keep track of the products and product batches you have used.

Other medicines and RIXUBIS
Tell your doctor if you are using or have recently used or might use any other medicines. No interactions of RIXUBIS with other medicines are known.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. Haemophilia B very rarely occurs in women.

Driving and using machines
RIXUBIS has no influence on the ability to drive and use machines.

RIXUBIS contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’. However, depending on your body weight and your dose of RIXUBIS, you could receive more than one vial. This should be taken into consideration if you are on a controlled sodium diet.

3. How to use RIXUBIS

Treatment with RIXUBIS will be started by a doctor who is experienced in the care of patients with haemophilia B.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Your doctor will decide the dose of RIXUBIS you will receive. This dose and duration will depend on the severity of your factor IX deficiency, on the location and extent of the bleeding and on your clinical condition, age and how quickly your body uses up factor IX which will have to be checked regularly.

RIXUBIS is administered by intravenous infusion (IV) after reconstitution of the powder with the provided solvent by your doctor or nurse. You or somebody else might also administer RIXUBIS as an injection but only after receiving adequate training.

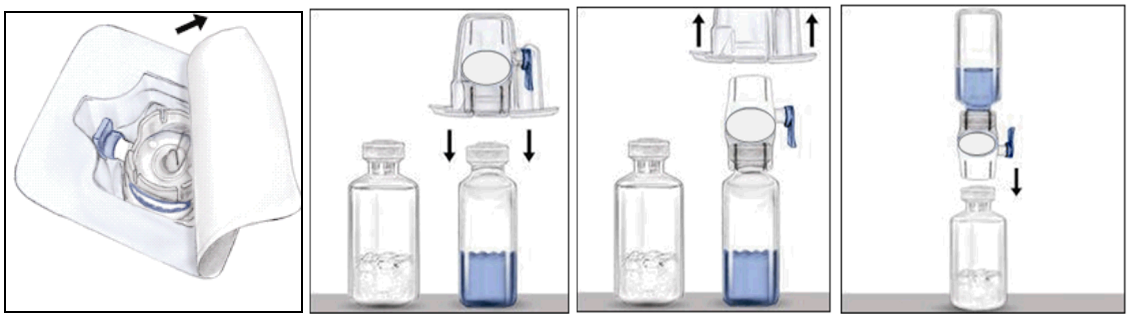
Reconstitution and administration

- For reconstitution use only the solvent and the reconstitution device (BAXJECT II) provided in the pack.
- For administration the use of a luer-lock syringe is required.
- Do not use if the BAXJECT II device, its sterile barrier system or its packaging is damaged or shows any sign of deterioration.

Reconstitution
Use Aseptic Technique

1. If the product is stored in a refrigerator, take both the RIXUBIS powder and solvent vials from the refrigerator and let them reach room temperature (between 15°C and 30°C).
2. Wash your hands thoroughly using soap and warm water.
3. Remove caps from powder and solvent vials.
4. Cleanse stoppers with alcohol swabs. Place the vials on a flat clean surface.
5. Open the package of BAXJECT II device by peeling away the paper lid without touching the inside (Fig. a). Do not remove the device from the package.
6. Turn the package over and insert the clear plastic spike through the solvent stopper. Grip the package at its edge and pull the package off BAXJECT II (Fig. b). Do not remove the blue cap from the BAXJECT II device.
7. With BAXJECT II attached to the solvent vial, invert the system so that the solvent vial is on top of the device. Insert the white plastic spike through the RIXUBIS stopper. The vacuum will draw the solvent into the RIXUBIS vial (Fig. c).
8. Swirl gently until all material is dissolved. The product dissolves rapidly (within 2 minutes). Be sure that RIXUBIS is completely dissolved, otherwise not all reconstituted solution will pass through the device filter. Reconstituted medicinal products should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear or slightly opalescent. Do not use solution that are cloudy or have deposits.

Fig. a **Fig. b** **Fig. c**



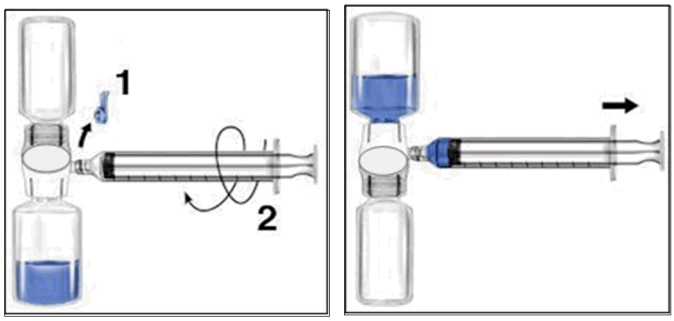
Do not refrigerate the preparation after reconstitution.
Use immediately.

Administration
Use Aseptic Technique

1. Remove the blue cap from BAXJECT II. **Do not draw air into the syringe**. Connect the syringe to BAXJECT II (Fig. d).
2. Invert the system (the vial with the reconstituted solution has to be on top). Draw the reconstituted solution into the syringe by pulling the plunger back slowly (Fig. e).
3. Disconnect the syringe.

4. Attach a butterfly needle to the syringe. Inject intravenously. The solution should be administered slowly, at a rate as determined by the patient's comfort level, not to exceed 10 ml per minute.

Fig. d **Fig. e**



Whenever possible, please record the name of the product and the batch number every time you use RIXUBIS (e.g. in your diary) to keep track of the products and product batches you have used.

Any unused product or waste material should be disposed of in accordance with local requirements.

If you use more RIXUBIS than you should
Always use RIXUBIS exactly as your doctor has told you. If you are not sure check with your doctor. If you injected more RIXUBIS than recommended, tell your doctor as soon as possible.

If you forget to use RIXUBIS
Do not inject a double dose to make up for a forgotten dose. Proceed with the next injection as scheduled and continue as advised by your doctor.

If you stop using RIXUBIS
Do not stop using RIXUBIS without consulting your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic-type hypersensitivity reactions are possible with RIXUBIS. Such reactions may include burning sensations and stinging at the infusion site, chills, flushing, lethargy, restlessness, tingling, hives, itching and rash, low blood pressure, fast heart rate, tightness of the chest, wheezing, swelling of the throat, anaphylaxis (severe allergic reaction), headache, nausea and vomiting. Please, contact your doctor immediately if you experience such signs. Your doctor may need to treat you promptly for these reactions (see section 2 'Warnings and precautions').

The following side effects have been observed with RIXUBIS:

Common side effects (may affect up to 1 in 10 patients)
- altered taste
- pain in limbs.

Side effects with unknown frequency (frequency cannot be estimated from the available data)
- allergic reactions (hypersensitivity).

Problems from exaggerated blood clotting (thromboembolic episodes) have not been observed with this product, but may occur with any factor IX products. These may include heart attack, blood clots in the veins or blood clots in the lung.

Reporting of side effects

If you get any side effects, talk to your doctor or, pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store RIXUBIS

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the outer box and vial label after EXP. The expiry date refers to the last day of that month.

Store below 30°C.
Do not freeze.

Use the reconstituted solution immediately.

Do not use RIXUBIS if the solution is not clear and colourless.

Do not throw away any medicines via waste water or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What RIXUBIS contains

- The active substance is nonacog gamma (recombinant human coagulation Factor IX). Each powder vials contains nominally 250, 500, 1000, 2000 or 3000 IU, corresponding to a concentration of 50, 100, 200, 400 or 600 IU/ml after reconstitution with 5 ml solvent.
- The other ingredients in the powder are sucrose, mannitol, sodium chloride, calcium chloride, L-histidine, polysorbate 80.

Solvent vial: 5 ml sterilised water for injections.

What RIXUBIS looks like and contents of the pack

RIXUBIS is provided as a powder and solvent for solution for injection.

The contents of the pack are:

- one vial of RIXUBIS 250, 500, 1000, 2000 or 3000 IU powder in a glass vial with a rubber stopper
- one vial of 5 ml sterilised water for injections in a glass vial with a rubber stopper
- one BAXJECT II (needle-less reconstitution device)

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Manufacturer

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Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Treatment monitoring
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 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.

Posology
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 International Unit of factor IX activity is equivalent to that quantity of factor IX in one ml of normal human plasma.

Adult population
On demand treatment:
The calculation of the required dose of factor IX is based on the empirical finding that 1 International Unit 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 (further information see section 5.2).

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 haemarthrosis, 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 haemarthrosis, muscle bleeding or haematoma	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 resolved.
Surgery Minor surgery including tooth extraction	30 – 60	Every 24 hours, at least 1 day, until healing is achieved.

Degree of haemorrhage/Type of surgical procedure	Factor IX level required (%) or (IU/dL)	Frequency of doses (hours)/Duration of therapy (days)
Major surgery	80 – 100 (pre- and postoperative)	Repeat infusion every 8 to 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 than 12 years:
On demand treatment
The calculation of the required dose of factor IX is based on the empirical finding that 1 International Unit (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 (further information see section 5.2).

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 (see above).

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.