PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

RIXUBIS®

Recombinant Coagulation Factor IX (rFIX), Nonacog gamma for Injection

Lyophilized Powder, 250, 500, 1000, 2000 and 3000 International Units (IU) per vial,

Intravenous Injection

Coagulant

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RECENT MAJOR LABEL CHANGES

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

RIXUBIS (Recombinant Coagulation Factor IX (rFIX), Nonacog gamma for Injection) is indicated in adults and children with hemophilia B (congenital factor IX deficiency or Christmas disease) for:

- Control of bleeding episodes
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

1.1 Pediatrics

Pediatric Use (<12 years of age): Safety, efficacy and pharmacokinetics of RIXUBIS have been evaluated in 23 previously treated pediatric patients (see 8 ADVERSE EVENTS, 10 CLINICAL PHARMACOLOGY and 14 CLINICAL TRIALS).

1.2 Geriatrics

Geriatrics (> 65 years of age): Clinical studies of RIXUBIS did not include subjects aged 65 years 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 individualized.

2 CONTRAINDICATIONS

RIXUBIS contains trace amounts of Chinese Hamster ovary cell line (CHO). RIXUBIS is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation (including hamster protein), or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

General

Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia. The safety and efficacy of RIXUBIS administration by continuous infusion has not been established.

The dosage and duration of the replacement therapy depend on the severity of factor IX deficiency, the location and extent of bleeding, and the patient's clinical condition, age and pharmacokinetic parameters of factor IX, such as incremental recovery and half-life.

Monitor patients using an appropriate factor IX activity assay to ensure that the desired factor IX activity plasma has been attained. If necessary, adjust the dose and the frequency of repeated infusions as appropriate. Careful monitoring of replacement therapy is especially important in cases of major surgery or life-threatening hemorrhages.

Evaluate the patient for the development of factor IX inhibitors if the expected factor IX activity plasma levels are not attained or if bleeding is not controlled with an appropriate dose. (see 7 WARNINGS AND PRECAUTIONS)

Each vial of RIXUBIS has the factor IX (rFIX) potency in international units stated on the vial. Dosing of RIXUBIS may differ from that of plasma-derived factor IX products (see 10 CLINICAL

PHARMACOLOGY). Subjects at the low end of the observed factor IX recovery may require dose adjustment of RIXUBIS.

FIX potency results can be affected by the type of aPTT reagent and reference standard used in the assay; differences of up to 40% have been observed.

4.2 Recommended Dose and Dosage Adjustment

Method for Calculating Initial Estimated Dose

A guide for calculating the dose for treatment of bleeding episodes is provided in Table 1.

Table 1. Method for Calculating Initial Estimated Dose

Number of factor IX International Units required (IU)	=	Body Weight (kg)	x	Desired factor IX increase (% or U/dL)	x	Reciprocal of Observed recovery (IU/kg per IU/dL)

The calculation of the required dose of RIXUBIS is based on the empirical finding that one international unit of RIXUBIS per kg body weight is expected to increase the circulating level of factor IX by 0.7 IU/dL of plasma (0.7% of normal) for patients less than 12 years of age and by 0.9 IU/dL of plasma (0.9% of normal) (range from 0.5 to 1.4 IU/dL) in patients 12 years and older.

Incremental Recovery in Previously Treated Patients (PTPs)

It is recommended to base the calculation of the required dose on the patient's individual incremental recovery using serial factor IX activity assays due to the wide range of inter-individual differences in incremental recovery. Titrate the dose based on the patient's clinical response and individual pharmacokinetics, in particular incremental recovery and half-life.

Patients <12 Years of Age

For an incremental recovery of 0.7 IU/dL of plasma (0.7% of normal), the dose is calculated as follows:

Number of factor IX International Units required (IU)	=	Body Weight (kg)	x	Desired factor IX increase (% or U/dL)	x	1.4 dL/kg

Examples (assuming patient's baseline factor IX level is <1% of normal)

1. A dose of 1500 IU of RIXUBIS, administered to a 20 kg patient should be expected to result in a peak post-infusion factor IX increase of 1500 IU x {[0.7 IU/dL]/[IU/kg]}/[20 kg] = 53.6 IU/dL (53.6% of normal).

Patients ≥12 Years of Age

For an incremental recovery of 0.9 IU/dL of plasma (0.9% of normal), the dose is calculated as follows:

Table 2. Calculating Incremental Dose Adjustment

Number of factor IX International Units required (IU)	=	Body Weight (kg)	x	Desired factor IX increase (% or U/dL)	x	1.1 dL/kg

Examples (assuming patient's baseline factor IX level is <1% of normal):

1. A dose of 4550 IU RIXUBIS administered to a 70 kg patient should be expected to result in a peak post-infusion factor IX increase of 4550 IU x {[0.9 IU/dL]/[IU/kg]}/[70 kg] = 59 IU/dL (59% of normal).
2. A peak level of 70% is required in a 60 kg patient. In this situation, the appropriate dose would be 60 kg x 70 IU/dL/{[0.9 IU/dL]/[IU/kg]} = 4667 IU.

Treatment of Bleeding Episodes and Perioperative Management

A guide for dosing in the treatment of bleeding episodes and perioperative management is provided in Table 3 and Table 4, respectively. Ensure the factor IX activity level is achieved and maintained in the corresponding period.

Table 3. Dosing for Control and Prevention of Bleeding Episodes

Type of Bleeding Episodes	Circulating factor IX level Required (% or IU/dL)	Dosing Interval (hours)	Duration of Therapy
Minor Uncomplicated hemarthrosis, superficial muscular or soft tissue	20-30	12-24	Treat until bleeding stops and healing begins, about 1-2 days
Moderate Intramuscular or soft tissue with dissection, mucous membranes, or hematuria	25-50	12-24	Treat until bleeding stops and healing begins, about 2-7 days
Major Pharyngeal retropharyngeal, retroperitoneal, CNS	50-100	12-24	Treat until bleeding stops and healing begins, about 7-10 days

Adapted from Roberts HR, Eberst ME. Current management of hemophilia B. Hematol Oncol Clin North Am. 1993;7(6):1269-1280.

Table 4. Dosing for Perioperative Management

Type of Surgery	Circulating Factor IX Level Required (% or IU/dL)	Dosing Interval (hours)	Duration of Therapy (days)
Minor e.g. tooth extraction	30-60	24	Treat for at least 1 day, until healing begins
Major e.g. intracranial, intraabdominal, intrathoracic, joint replacement	80-100	8-24	Treat for 7-10 days, until bleeding stops and healing begins

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

Routine Prophylaxis

RIXUBIS can be administered for routine prophylaxis against bleeding in patients with severe and moderately severe hemophilia B. The recommended dose for previously treated patients (PTPs) is 40 to 80 IU/kg twice weekly for patients less than 12 years of age and is 40 to 60 IU/kg twice weekly for patients more than 12 years of age. Titration of dose may be necessary depending upon the individual patient's pharmacokinetics, age, bleeding pattern, and physical activity.

4.3 Reconstitution

Administer RIXUBIS by intravenous (IV) infusion after reconstitution.

Perform reconstitution, product administration, and handling of the administration set and needles with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs. Place needles in a sharps container after single use. Discard all equipment, including any reconstituted RIXUBIS, in an appropriate container.

RIXUBIS is a white or almost white lyophilized powder and is available in single-use vials which contain the following product strengths: 250 IU, 500 IU, 1000 IU, 2000 IU and 3000 IU

Each kit also contains 5 mL of Sterile Water for Injection and BAXJECT II Transfer device. Actual factor IX activity in international units is stated on the unit carton and vial label.

Table 5. Reconstitution using BAXJECT II

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
10 mL	5 mL	5 mL	50 IU/ml
10 mL	5 mL	5 mL	100 IU/ml
10 mL	5 mL	5 mL	200 IU/ml
10 mL	5 mL	5 mL	400 IU/ml
10 mL	5 mL	5 mL	600 IU/ml

Preparation and Reconstitution:

The procedures below are provided as general guidelines for the preparation and reconstitution of RIXUBIS. Always work on a clean surface and wash your hands before performing the following procedures:

1. Use aseptic technique during reconstitution procedure.
2. Allow the RIXUBIS vial (dry factor concentrate) and Sterile Water for Injection, USP vial (diluent) to reach room temperature.
3. Remove caps from the factor concentrate and diluent vials.
4. Cleanse stoppers with germicidal solution and allow to dry prior to use. Place the vials on a flat surface.
5. Open the BAXJECT II device package by peeling away the lid, without touching the inside (Figure A). **Do not remove the device from the package. Note that the BAXJECT II device is intended for use with a single vial of RIXUBIS and Sterile Water for Injection, USP only; therefore, reconstituting and withdrawing a second vial into the syringe requires a second BAXJECT II device.**
6. Turn the package over. Press straight down to fully insert the clear plastic spike through the diluent vial stopper (Figure B).
7. Grip the BAXJECT II package at its edge and pull the package off the device (Figure C). **Do not remove the blue cap from the BAXJECT II device.** Do not touch the exposed white plastic spike.

8. Turn the system over so that the diluent vial is on top. Quickly insert the white plastic spike fully into the RIXUBIS vial stopper by pushing straight down (Figure D). The vacuum will draw the diluent into the RIXUBIS vial.
9. Swirl gently until RIXUBIS is completely dissolved. **Do not refrigerate after reconstitution.** Use within 3 hours of reconstitution.

4.4 Administration

For intravenous use after reconstitution only.

- **The safety and efficacy of RIXUBIS administration by continuous infusion has not been established. Do not administer RIXUBIS by continuous infusion.** (see 7 WARNINGS AND PRECAUTIONS)
- Initiate treatment under the supervision of a physician experienced in the treatment of hemophilia. (see 7 WARNINGS AND PRECAUTIONS)
- Inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless in appearance. If not, do not use the solution and notify Takeda.
- Administer RIXUBIS at room temperature within 3 hours of reconstitution. Discard any unused product.
- Only use a plastic syringe with this product.

1. Remove the blue cap from the BAXJECT II device. Connect the syringe to the BAXJECT II device (Figure E). **Do not inject air.**
2. Turn the system upside down (factor concentrate vial now on top). Draw the factor concentrate into the syringe by pulling the plunger back slowly (Figure F).
3. Disconnect the syringe; attach a suitable needle and inject intravenously as instructed under **Administration by Bolus Infusion.** If a patient is to receive more than one vial of RIXUBIS, the contents of multiple vials may be drawn into the same syringe.
4. Maximum infusion rate of 10 mL/min.

Figure A

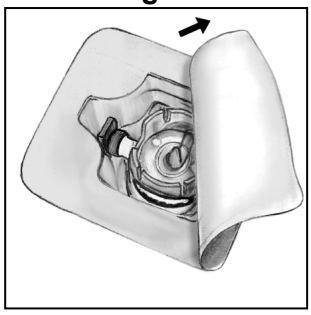


Figure B

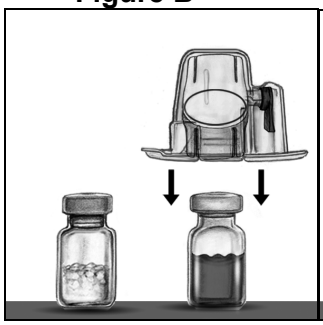


Figure C

Figure D

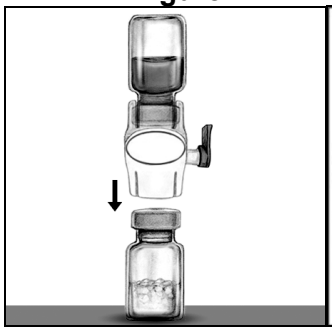


Figure E

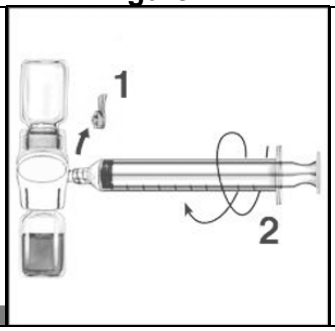
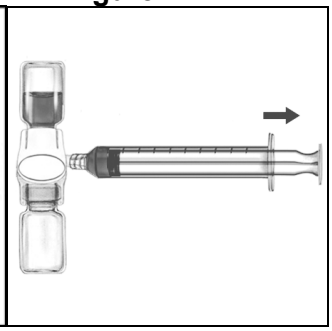


Figure F



5 OVERDOSAGE

No symptoms of overdose have been reported. As with other products of the same class, overdose may increase the risk for thrombotic and thromboembolic events (e.g., disseminated intravascular coagulation (DIC), pulmonary embolism, venous thrombosis, and arterial thrombosis).

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 6. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous Injection	Lyophilized Powder for Intravenous injection / 250, 500, 1000, 2000, 3000 International Units (IU) per vial reconstituted with 5 mL of water for injection	Calcium Chloride, L-Histidine, Mannitol, Polysorbate 80, Sodium Chloride, Sucrose

RIXUBIS is available in single-use vials which contain the following product strengths: 250 IU, 500 IU, 1000 IU, 2000 IU and 3000 IU.

Each kit also contains 5 mL of Sterile Water for Injection and BAXJECT II Transfer device. Actual factor IX activity in international units is stated on the unit carton and vial label.

7 WARNINGS AND PRECAUTIONS

General

Anaphylaxis and other hypersensitivity reactions have been reported with factor IX-containing products. Patients and/or their caregivers should be informed of the early signs of hypersensitivity reactions. They should be advised to discontinue use of the product immediately and contact their physician if such symptoms occur. 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. Early signs of anaphylaxis or allergic reactions include angioedema, chest-tightness, hypotension, lethargy, nausea, vomiting, paresthesia, restlessness, wheezing, and dyspnea.

In some cases, these reactions have progressed to severe anaphylaxis. In the case of shock, the current medical standards for treatment of shock should be observed. In case of severe allergic reactions, alternative hemostatic measures should be considered. Discontinue administration and initiate appropriate treatment if allergic or anaphylactic-type reactions occur.

There have been reports in the literature showing an association 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.

RIXUBIS contains trace amounts of hamster (CHO) proteins. Patients treated with this product may develop hypersensitivity to these non-human mammalian proteins.

Other factor IX products have had post-marketing reports of thrombotic events in patients receiving continuous-infusion through a central venous catheter, including life-threatening superior vena cava (SVC) syndrome in critically ill neonates.

Inhibitors
Patients with hemophilia B may develop neutralizing antibodies (inhibitors) to factor IX. Patients using RIXUBIS should be regularly evaluated for the development of factor IX inhibitors by appropriate clinical observations and laboratory tests. If expected plasma factor IX activity levels are not attained, or if bleeding is not controlled with an expected dose, an assay that measures factor IX inhibitor concentration should be performed.

If a patient develops an inhibitor, it is recommended that a specialized hemophilia center be contacted.

In patients with high titer factor IX inhibitors, RIXUBIS therapy may not be effective and other therapeutic options should be considered.

Patients with factor IX inhibitors are at an increased risk of severe hypersensitivity reactions or anaphylaxis if re-exposed to factor IX.

Monitoring and Laboratory Tests
Monitor factor IX activity levels by using an appropriate factor IX activity assay, e.g. the one-stage clotting assay, to confirm that adequate factor IX levels have been achieved and maintained, when clinically indicated (see 4 DOSAGE AND ADMINISTRATION). If necessary, appropriate adjustments to the dose and the frequency of repeated infusions should be performed.

Monitor for the development of inhibitors if expected factor IX activity plasma levels are not attained, or if bleeding is not controlled with the recommended dose of RIXUBIS. Assays used to determine factor IX inhibitors if present should be titred in Bethesda units.

Renal
Nephrotic Syndrome
Nephrotic syndrome has been reported following attempted immune tolerance induction in hemophilia B patients with factor IX inhibitors. The safety and efficacy of using RIXUBIS for immune tolerance induction has not been established.

Reproductive Health: Female and Male Potential

- **Fertility**

There is no information on the effects of RIXUBIS on fertility.

- **Teratogenic risk**

There are no data from the use of RIXUBIS in pregnant women (see 7.1.1 Pregnant Women).

Thromboembolic Complications
The use of factor IX products has been associated with the development of thromboembolic complications (e.g., pulmonary embolism, venous thrombosis, arterial thrombosis, cerebral artery thrombosis, superior vena cava obstruction). Factor IX-containing products may be potentially hazardous in patients with disseminated intravascular coagulation (DIC) and in patients with signs of fibrinolysis.

Clinical surveillance for early signs of thrombotic and consumptive coagulopathy should be initiated with appropriate biological testing, in particular when administering RIXUBIS to patients with liver disease, to patients peri- and post-operatively, to new born infants or to patients at risk for thrombotic events or DIC.

In patients with DIC or those at risk for DIC or thromboembolic events, the benefit of treatment with RIXUBIS should be weighed against the risk of these complications.

7.1 Special Populations

7.1.1 Pregnant Women

There are no data from the use of RIXUBIS in pregnant women. Healthcare providers should balance the potential risks and only prescribe RIXUBIS if clearly needed.

7.1.2 Breast-feeding

There are no data from the use of RIXUBIS in lactating women. Healthcare providers should balance the potential risks and only prescribe RIXUBIS if clearly needed.

7.1.3 Pediatrics

Pediatric Use (<12 years of age): Safety, efficacy and pharmacokinetics of RIXUBIS have been evaluated in 23 previously treated pediatric patients.

Incremental recovery was observed to be 22% lower in pediatric patients (<12 years) and dose adjustment is needed (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY sections). The mean incremental recovery (in ([IU/dL]/[IU/kg]) at the initial pharmacokinetics evaluation was 0.67 (±0.16) in subjects of both age cohorts, with lower values in the younger age cohort (0.59 ±0.13) and higher values in the older age group (0.73 ± 0.16). Clearance was higher in the younger age cohort, with a mean clearance of 10.6 ± 1.7 mL/(kg.hr) (median: 10.5; range: 8.1-14.4) in the <6 years age cohort compared to a mean clearance of 8.7 ± 1.2 mL/(kg.hr) (median: 8.6; range: 6.9-10.8) in the 6 to <12 years age cohort.

Also see 14 CLINICAL TRIALS section for prophylaxis and control of bleeding in patients <12 years of age.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Clinical studies of RIXUBIS did not include subjects aged 65 years and over. It is not known whether they respond differently from younger subjects. Dose selection for an elderly patient should be individualized. See 4 DOSAGE AND ADMINISTRATION.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reactions observed in >1% of subjects of RIXUBIS clinical trials were a positive Furin antibody test, dysgeusia and pain in extremity. See Table **7** for Summary of Adverse Reactions.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

During clinical development in a combined trial in 99 male previously treated patients (PTPs; exposed to a factor IX concentrate on ≥ 150 days) received at least 1 infusion of RIXUBIS for either on-demand treatment of bleeding episodes, in the perioperative management of major and minor surgical, dental, or other invasive procedures, for routine prophylaxis, or for the

evaluation of the pharmacokinetics of RIXUBIS. Eleven subjects (11.1%) were <6 years of age, 12 (12.1%) were 6 to <12 years of age, 3 (3.0%) were adolescents (12 to <16 years of age), and 73 (73.7%) were adults (16 years of age and older). The treated subjects received a total of 14,018 infusions with a median of 163 infusions of RIXUBIS (range - 8-327 infusions) for a median of 156 exposure days (range 8-316 days).

A total of 337 adverse events were reported in 80 (80.8%) of the 99 subjects.

Adverse reactions that occurred in >1% of subjects are shown in Table 7.

Table 7. Summary of Adverse Reactions

System Organ Class (SOC)	Events	Number of ARs (n)	Number of Subjects N = 99 n (%)	Percent per Infusion N=14018
Nervous System Disorders	Dysgeusia	2	1 (1.01%)	0.014%
Musculoskeletal and Connective Tissue Disorders	Pain in extremity	1	1 (1.01%)	0.007%
Investigations	Furin antibody test positive*	2	2 (2.02%)	0.014%

* See 14.4 Immunogenicity

8.5 Post-Market Adverse Drug Reactions

Immune System Disorders: Hypersensitivity (including symptoms such as dyspnea, pruritus)
Skin and Subcutaneous Tissue Disorders: Urticaria, rash

The following class adverse reactions have been seen with another recombinant factor IX: inadequate factor IX recovery, inhibitor development, anaphylaxis, angioedema, hypotension, and thrombosis.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Interactions have not been established.

9.3 Drug-Behavioural Interactions

Interactions with behavior have not been established.

9.4 Drug-Drug Interactions

Interactions with other drug products have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herbal Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

RIXUBIS temporarily replaces the missing clotting factor IX that is needed for effective hemostasis. The activated partial thromboplastin time (aPTT) is prolonged in people with hemophilia B. Treatment with factor IX concentrate may normalize the aPTT by temporarily replacing the factor IX.

10.2 Pharmacodynamics

The administration of RIXUBIS increases plasma levels of factor IX, and can temporarily correct the coagulation defect in these patients by decreasing aPTT.

10.3 Pharmacokinetics

PTPs ≥12 Years of Age

A randomized, blinded, controlled, crossover pharmacokinetic study of RIXUBIS and another commercial recombinant factor IX product was conducted in non-bleeding subjects (≥15 years of age). The subjects received either of the products as an IV infusion. The dose range of RIXUBIS and another recombinant factor IX product ranged from 71.27 to 79.38 IU/kg and 70.12 to 80 IU/kg respectively. The pharmacokinetic parameters were calculated from factor IX activity measurements in blood samples obtained up to 72 hours following each infusion.

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

Pharmacokinetic parameters for evaluable subjects (per-protocol analysis) are presented in Table 8. RIXUBIS was equivalent to another recombinant factor IX product based on AUC.

Table 8. Pharmacokinetic Parameters for RIXUBIS Following Single Repeat Dosing (≥12 years of age)

Parameter	Initial cross-over study (N=25)	Repeat Evaluation (N=23)
$AUC_{0\text{-}inf}$ (IU·hrs/dL)[a]		
Mean (SD)	1207 (242)	1305 (300)
Min ; Max	850 ; 1710	838 ; 1864
Incremental recovery at Cmax(IU/dL : IU/kg)[b]		
Mean (SD)	0.87 (0.22)	0.95 (0.25)
Min ; Max	0.53 ; 1.35	0.52 ; 1.38
Half-life (hrs)		
Mean (SD)	26.7 (9.6)	25.4 (6.9)
Min ; Max	15.8 ; 52.3	16.2 ; 42.2
Cmax (IU/dL)		
Mean ± SD	66.2 (15.8)	72.7 (19.7)
Min ; Max	41.7 ; 100.3	38.5 ; 106.3
Mean residence time (hrs)		
Mean ± SD	30.8 (7.3)	29.9 (4.2)
Min ; Max	22.3 ; 47.8	21.3 ; 37.5
V_{ss}[c] (mL/kg)		
Mean (SD)	201.9 (77.4)	178.6 (45.2)
Min ; Max	110.0 ; 394.0	112.0 ; 272.0

Parameter	Initial cross-over study (N=25)	Repeat Evaluation (N=23)
Clearance [mL/(kg·hr)] Mean (SD) Min ; Max	 6.4 (1.3) 4.3 ; 9.1	 6.0 (1.5) 4.1 ; 9.5
[a] Area under the plasma concentration-time curve from time 0 to infinity hours post-infusion. [b] Calculated as (Cmax – baseline factor IX) divided by the dose in IU/kg, where Cmax is the maximum post-infusion factor IX measurement. [c] Volume of distribution at steady state		

Data from PTPs who underwent repeat in vivo recovery testing for up to 26 weeks demonstrated that the incremental FIX recovery was consistent over time.

Incremental recovery 30 min after infusion was determined for all subjects in the combined 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 Table 9.

Table 9. Incremental Recovery for RIXUBIS 30 Minutes After Infusion (≥12 years of age)

	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.					

PTPs <12 Years of Age

Twenty-three male subjects underwent a pharmacokinetic evaluation of RIXUBIS as part of the combined pediatric trial (<6 years and 6-<12 years). The mean (±SD) and median dose were 75.5 ±3.0 and 75.3 IU/kg, respectively, with a range of 70.0 to 83.6 IU/kg. Non-linear mixed model (population PK) was used to estimate the pharmacokinetic parameters from factor IX activity measurements in blood samples obtained up to 60 hours following the infusion. Pharmacokinetic parameters for all subjects are presented in Table 10.

Table 10. Pharmacokinetic Parameters for PTPs

Parameter	≥ 12 years[a] (N=25)	6-<12 years (N=12)	<6 years (N=11)
$AUC_{0\text{-}inf}$ (IU • hr/dL)[a] Mean ±SD Median (range)	 1185 ± 273 1197 (783-1780)	 886 ± 134 864 (730-1138)	 724 ± 119 717 (488-947)
Half-life (hr) Mean ±SD Median (range)	 25.7±1.5 25.6 (22.8-29.0)	 23.2±1.6 22.6 (21.8-27.4)	 27.7 ± 2.7 27.3 (24.0-32.2)

Parameter	≥ 12 years[a] (N=25)	6-<12 years (N=12)	<6 years (N=11)
Mean residence time (hr) Mean±SD Median (range)	 30.2± 2.2 30.3 (25.9-33.9)	 25.3 ± 1.8 24.7 (23.7-30.3)	 30.6 ± 3.3 30.1 (26.2-36.2)
V_{ss}[b](mL/kg) Mean±SD Median (range)	 201.5 ± 47.2 190.2 (138-300)	 220.9 ± 31.7 218.5 (169.9-270.1)	 322.5 ± 52.3 315.7 (264.7-441.5)
Clearance (mL/[kg • hr]) Mean±SD Median (range)	 6.7 ± 1.5 6.43 (4.1-9.9)	 8.7 ±1.2 8.6 (6.9-10.8)	 10.6 ± 1.7 10.5 (8.1-14.4)

[a]Non-linear mixed model (population PK) was applied on the reduced 4 blood samples (30 min, 6 hr, 24 hr, and 60 hr)
[b]Volume of distribution at steady state

Incremental recovery 30 minutes after infusion was determined for all subjects in the combined trial during the pharmacokinetic evaluation (exposure day 1), at week 5, 13 and 26 visits, and at the time of trial 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 pediatric age groups. (see Table 11 and Table 12)

Table 11. Incremental Recovery for RIXUBIS 30 Minutes After Infusion (<6 years of age)

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

Table 12. Incremental Recovery for RIXUBIS 30 Minutes After Infusion (6 to <12 years of age)

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

11 STORAGE, STABILITY AND DISPOSAL

- Refrigerated temperature 2° to 8°C (35 to 46°F) for 36 months or
- Room temperature not to exceed 30°C (86°F) for up to 36 months.
- Do not freeze.
- Do not use beyond the expiration date printed on the carton or vial.

12 SPECIAL HANDLING INSTRUCTIONS

Inspect parenteral drug products for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless in appearance. If not, do not use the solution and notify Takeda immediately.

RIXUBIS is to be reconstituted with the provided Sterile Water for Injection (SWFI). Administer RIXUBIS within 3 hours of reconstitution.

This product must not be mixed with other medicinal products.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

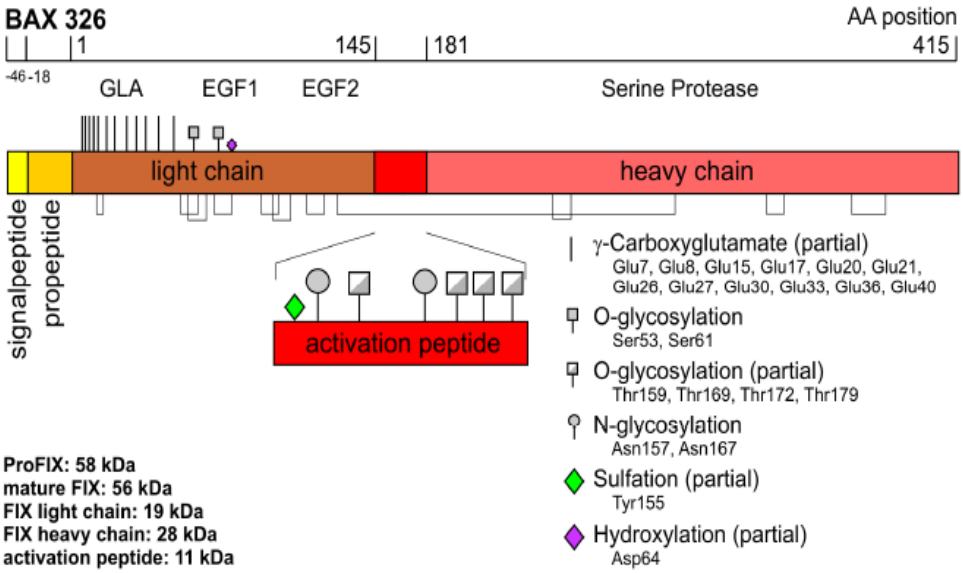
Drug Substance

Proper name: Recombinant Coagulation Factor IX (rFIX), Nonacog gamma

Chemical name: Recombinant Coagulation Factor IX (rFIX), Nonacog gamma

Molecular formula and molecular mass: The molecular formula for the peptide backbone of FVIIa, including the 12 Gla residues and 11 disulfide bonds is: $C_{2053}H_{3114}N_{558}O_{665}S_{25}$. The theoretical average molecular mass for the protein backbone of mature factor IX according to the above formula is 47,054 Da

Structural formula



Physicochemical properties: RIXUBIS is synthesized in the production CHO cells as a single chain polypeptide and secreted in its mature 415 amino acid form into the fermentation medium. The molecule consists of several discrete functional domains, including a Gla domain, two epidermal growth factor (EGF) domains, an activation peptide and the catalytic domain. As in other vitamin K-dependent proteins, RIXUBIS undergoes a number of post-translational maturation events prior to secretion (cleavage of pre-pro leader sequence, glycosylation, gamma-carboxylation, and partial sulfation and hydroxylation).

Pharmaceutical standard: The potency (in international units, IU) is determined using an in vitro one-stage clotting assay against the World Health Organization (WHO) International Standard for Factor IX concentrate. One IU is the amount of factor IX activity present in 1 mL of pooled, normal human plasma. The specific activity of RIXUBIS is greater than or equal to 200 IU per milligram of protein.

Product Characteristics
RIXUBIS [Recombinant Coagulation Factor IX (rFIX)] is a purified protein produced by recombinant DNA technology. It has a primary amino acid sequence that is identical to the Ala-148 allelic form of plasma-derived factor IX, and has structural and functional characteristics similar to those of endogenous factor IX. RIXUBIS is produced by a genetically engineered Chinese hamster ovary (CHO) cell line that is extensively characterized. No human or animal proteins are added during any stage of manufacturing or formulation of RIXUBIS.

RIXUBIS is not derived from human blood or plasma products, and its manufacture does not include animal or human components. RIXUBIS contains no preservatives.

The CHO cell line secretes recombinant factor IX into a defined cell culture medium that does not contain any proteins derived from animal or human sources as well as hormones, and the recombinant factor IX is purified by a chromatography purification process that does not require a monoclonal antibody step. The process includes validated virus inactivation/removal steps, namely solvent/detergent (S/D) treatment and 15 nm nanofiltration. The S/D treatment has the ability to inactivate lipid-enveloped viruses, whereas the nanofiltration step has the ability to remove both lipid-enveloped and non-lipid-enveloped viruses. RIXUBIS is predominantly a single component by SDS-polyacrylamide gel electrophoresis evaluation.

RIXUBIS is formulated as a sterile, nonpyrogenic, lyophilized powder preparation.

RIXUBIS is intended for intravenous (IV) infusion. It is available in single-use vials containing the labeled amount of factor IX activity, expressed in IU. Factor IX preactivation, the percent of FIXa/FIX as measured by activity assays, is ≤0.10%. Each vial contains nominally 250, 500, 1000, 2000, or 3000 IU of Coagulation Factor IX (Recombinant). After reconstitution of the lyophilized drug product, the concentrations of excipients are 20 mM L-histidine, 60 mM sodium chloride, 4 mM calcium chloride, 110 mM mannitol, 35 mM sucrose, 0.005% polysorbate 80. All dosage strengths yield a clear, colorless solution upon reconstitution.

Viral Inactivation
Three barriers have been introduced to the manufacture of rFIX to prevent viruses from entering the final product: 1) testing for adventitious viruses performed on the cell culture bulk harvest, 2) the Solvent Detergent (S/D) treatment step used in the rFIX BDS purification process and 3) a 15 nm nanofiltration step. S/D treatment and nanofiltration are dedicated, effective virus inactivation/removal steps and have been introduced to provide an additional safety margin for the final product. Complete inactivation to below the limits of detection of the assay was observed during the S/D treatment of three different enveloped model viruses (i.e X-MuLV, BVDV, PRV). The nanofiltration step for rFIX has also been demonstrated to effectively remove enveloped (i.e. X-MuLV and BVDV) and non-enveloped (i.e. MMV and Reovirus-3) viruses from the product.

Altogether very high margins of safety with regards to adventitious viruses is demonstrated.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Prophylaxis and Control of Bleeding in PTPs ≥12 Years of Age

The efficacy of RIXUBIS has been evaluated in one completed prospective, open-label, uncontrolled multicenter combined study, in which a total of 73 male PTPs between 12 and 65 years of age received RIXUBIS either for prophylaxis or on-demand treatment. In addition, a prospective open-label uncontrolled multicenter study where 30 PTPs underwent minor or major

surgeries receiving RIXUBIS for perioperative management has been completed. PTPs were defined as subjects who were exposed to a factor IX containing products for ≥150 days. All subjects had severe (factor IX level <1%) or moderately severe (factor IX level ≤2%) hemophilia B. Subjects with a history of or a detectable FIX inhibitor ≥0.6 BU, a history with severe allergic reactions following exposure to FIX, evidence of a severe chronic liver disease (INR >1.4), impaired renal function, a CD4 count <200 cells/mm^3 or any hemostatic effect other than hemophilia B were excluded from participation. The majority of subjects (88%) had arthropathy at screening and target joints (66%).

14.2 Study Results

Routine Prophylaxis

Fifty-nine (59) PTPs received RIXUBIS for prophylaxis. Fifty-six (56) of these PTPs who received the product for a minimum of 3 months were included in the efficacy evaluation for prophylaxis (see Table 13). The prophylactic regimen consisted of 40 to 60 international units/kg of RIXUBIS twice weekly. The mean total annualized bleeding rate (ABR) was 4.3 for all bleeds, 1.7 for spontaneous bleeds, and 2.9 for joint bleeds (Table 14). The median total ABR was 2.0 with a range of 0 to 23.4.

Table 13. Efficacy of Prophylaxis with RIXUBIS in 56 PTPs with ≥ 3 months of exposure to RIXUBIS (≥ 12 years of age)

Treatment duration (months)	
Mean ± SD	6.0 ± 0.65
Median (range)	6.0 (5.4 - 9.1)
Number of infusions per week*	
Mean ± SD	1.8 ± 0.11
Median (range)	1.8 (1.5 - 1.9)
Dose per infusion (IU/kg)	
Mean ± SD	49.4 ± 4.92
Median (range)	50.5 (40.0 - 62.8)
Total annualized bleeding rate (ABR)	
Mean ± SD	4.3 ± 5.80
Median (range)	2.0 (0.0 - 23.4)
ABR for joint bleeds	
Mean ± SD	2.9 ± 4.25
Median (range)	0.0 (0.0 - 21.5)
ABR for spontaneous bleeds	
Mean ± SD	1.7 ± 3.26
Median (range)	0.0 (0.0 - 15.6)
Subjects with zero bleeding episodes	
% (n)	42.9% (24)
Subjects Number of Exposure Days	
Mean ± SD	56.3 ±7.2
Median (range)	54.0 (50 - 83)

* The prophylactic regimen consisted of 40 to 60 IU/kg RIXUBIS twice weekly. The individual dose could be increased up to 75 IU/kg twice weekly.

On-Demand Treatment

An additional 14 PTPs from an on-demand cohort received RIXUBIS for treatment of bleeding episodes only. Subjects in this cohort had to have at least 12 documented bleeding episodes

requiring treatment within 12 months prior to enrollment. The mean treatment duration was 3.5 ± 1.00 months (median 3.4, ranging from 1.2 to 5.1 months) and, the mean total annualized bleeding rate (ABR) was 33.9 ± 17.37 with a median of 27.0 ranging from 12.9 to 73.1.

Treatment of Bleeding Episodes in PTPs ≥ 12 Years of Age

A total of 249 bleeding episodes were treated with RIXUBIS, of which 115 were recorded for subjects who had breakthrough bleeding episodes while on prophylaxis and, 134 bleeds were recorded for those who received on demand treatment only. There were 197 were joint bleeds and 52 non-joint bleeds (soft tissue, muscle, body cavity, intracranial and other). Of the total of 249 bleeding episodes, 163 were moderate, 71 were minor, and 15 were major. Treatment was individualized based on the severity, cause and site of bleed. Of the total of 249 bleeding episodes, the majority (211; 84.7%) were treated with 1-2 infusions.

Hemostatic efficacy at resolution of a bleed was rated excellent (full relief of pain and cessation of objective signs of bleeding after a single infusion; no additional infusion is required for the control of bleeding) or good (definite pain relief and/or improvement in signs of bleeding after a single infusion; possibly requires more than one infusion for complete resolution) in 96% of all treated bleeding episodes.

Prophylaxis and Control of Bleeding in PTPs <12 years of age

The efficacy of RIXUBIS has been evaluated in a clinical trial, in which a total of 23 male, (PTPs) between 1.8 and 11.8 years (median age 7.10 years) with 11 subjects <6 years, received RIXUBIS for prophylaxis and control of bleeding episodes. PTPs were defined as subjects who were exposed to a factor IX-containing product on ≥ 150 days for subjects aged 6 to <12 years and on ≥50 days for subjects aged <6 years. All subjects had severe (factor IX level <1%) or moderately severe (factor IX level ≤2%) hemophilia B. Subjects with a history of or a detectable FIX inhibitor ≥ 0.6 BU, a history of severe allergic reactions following exposure to FIX, evidence of severe chronic liver disease (INR>1.4), impaired renal function, a CD4 count <200 cells/mm3 or any hemostatic effect other than hemophilia B were excluded from participation. All 23 subjects received prophylactic treatment with RIXUBIS for a minimum of 3 months and were included in the efficacy evaluation for prophylaxis (see Table 14). The ABR reduced or remained zero in 15 of 23 subjects, and increased in 8 of 23 subjects. The mean ABR for all 23 subjects was 2.7 (±3.14) (medium: 2.0; range: 0.0-10.8).

Table 14. Efficacy of Prophylaxis with RIXUBIS in 23 PTPs with 6 months of exposure to Rixubis (< 12 years of age)

Treatment duration (months) Mean ± SD Median (range)	 5.98 (0.712) 5.95 (3.3-7.7)
Number of infusions per week* Mean ± SD Median (range)	 1.97 (0.082) 1.97 (1.8-2.2)
Dose per infusion (IU/kg) Mean ± SD Median (range)	 56.25 (8.341) 55.63 (43.0 – 75.5)
Total annualized bleeding rate (ABR) Mean ± SD Median (range)	 2.7 ± 3.14 2.0 (0.0 – 10.8)
ABR for joint bleeds Mean ± SD Median (range)	 0.8 ± 1.76 0.0 (0.0 – 7.2)
ABR for spontaneous bleeds Mean ± SD Median (range)	 0.2 ± 0.66 0.0 (0.0 – 2.0)
Subjects with zero bleeding episodes % (n)	 39.1% (9)
Subjects Number of Exposure Days Mean ± SD Median (range)	 53.6 (6.11) 53.0 (35-70)

* The prophylactic regimen consisted of 40 to 80 IU/kg RIXUBIS twice weekly.

Treatment of Bleeding Episodes in PTPs <12 years of age

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 (Minor: little or no pain; little or no change in the range of motion of affected joint (if joint bleeding event); mild restriction of mobility and activity; Moderate: mild to moderate pain; some decrease in range of motion of affected joint (if joint bleeding event); moderate decrease mobility and activity; Major/life threatening: significant pain; substantial decrease in range of motion of affected joint (if joint bleeding event); incapacity; life threatening). Treatment was individualized based on the severity, cause and site of bleed. Bleeding was controlled in all episodes. The majority (23; 88.5%) were treated with 1 to 2 infusions. Of the treated bleeding episodes 15 (57.75) received 1 infusion, 8 (30.8%) received 2 infusions, and 3 (11.5%) were treated with 3 infusions. Hemostatic efficacy at resolution of a bleed was rated excellent or good in 96.2% of all treated bleeding episodes.

Perioperative Management Study

The efficacy of RIXUBIS in perioperative management was evaluated in 38 surgeries performed in 28 previously treated patients (PTPs) between 17 and 57 years of age undergoing major or minor surgical (see Table 4 for definition of major and minor), dental or other surgical invasive procedures. Twenty-One (21) procedures were considered major including 14 orthopedic surgeries and 7 non-orthopedic surgeries (3 abdominal, 3 dental, 1 surgical excision of tumor

from soft tissue). Seventeen (17) procedures, including 11 dental surgeries and 6 orthopedic surgeries (5 intra-articular injections and 1 synoviorthesis), were considered minor.

Patients undergoing major surgeries had to perform a pharmacokinetics 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. None of the subjects analyzed (including 2 subjects who only received RIXUBIS for a PK infusion) resulted in the development of inhibitors to FIX or total binding antibodies to FIX. All adverse events were considered unrelated to treatment except one adverse event of hemorrhagic anemia which was considered 'possibly related' by the investigator. In summary, the results indicate that RIXUBIS is safe and well tolerated and efficacious in surgical hemostasis. Table 15 shows the types of surgical procedures and the results of the assessment of the hemostatic response at various points in time.

Table 15. Efficacy of RIXUBIS for Surgical Procedures in PTPs

Procedure (category, # of subjects)	Assessment of Response		
	Intra-operative	At time of drain removal or on post-operative day 3*	At Time of Discharge
Joint replacement (eg, hip, knee, ankle) (Major, n=10)	Excellent (9) Good (1)	Good (3) Excellent (7)	Excellent (3) Good (5) Fair (2)
Total right knee arthroplasty (Major, n=1)	Excellent	Excellent	Excellent
Removal of intramedullary nail (Major, n=1)	Excellent	Good	Excellent
Open synovectomy (Major, n=2)	Excellent (2)	Excellent (1) Good (1)	Excellent (1) Good (1)
Hernioplasty (Major, n=2)	Excellent (2)	Excellent (2)	Excellent (1) Good (1)
Excision neurofibroma (Major, n=1)	Excellent	Excellent	Excellent
Laparoscopic Cholecystectomy (Major, n=1)	Excellent	Excellent	Excellent
Dental implant (Major, n=2)	Excellent (2)	Excellent (2)	Excellent (2)
Tooth extraction (Major, n=1)	Excellent	Excellent	Excellent
Intra-articular infiltration (orthopedic) (Minor, n=4)	Excellent (4)	N/A (4)	Excellent (4)
Intra-articular injection (non-orthopedic) (Minor, n=1)	Excellent	N/A	Excellent
Synoviorthesis (Minor, n=1)	Excellent	N/A	Excellent
Tooth extraction (Minor, n=10)	Excellent (10)	Excellent (1) N/A (9)	Excellent (10)
Dental implant (Minor, n=1)	Excellent	N/A	Excellent

N/A = not applicable
* Where no drain was employed, response was assessed on postoperative day 3.

14.4 Immunogenicity

All 99 subjects were monitored for inhibitory and binding antibodies to factor IX, and binding antibodies to CHO protein and furin, at the following time points: at screening, at 72 hours following the first infusion of RIXUBIS and the commercial recombinant factor IX product in the crossover portion of the pharmacokinetic study, after 5 and 13 weeks following first exposure to RIXUBIS, and thereafter every 3 months. Antibodies against furin were tested by an in-house enzyme-linked immunosorbent assay (ELISA). A titer of 1:20 or 1:40 was considered to be indeterminate for the above validated assay, as these titers were too low to be verified by the confirmatory assay.

No subjects developed neutralizing antibodies to factor IX. Twenty-One subjects (21.2%) developed low-titer, non-neutralizing antibodies against factor IX at one or more time points. Three of these 21 subjects were found to have these antibodies at screening, prior to receiving RIXUBIS. Six of the 21 subjects were pediatric (2 subjects in <6 years of age cohort, 4 subjects in 6 to<12 years age cohort). No clinical adverse findings were observed in any of these 21 subjects.

Nineteen subjects (19.2 %) had signals for antibodies against furin (indeterminate specificity). Five of these 19 subjects expressed signals for antibodies at screening, prior to RIXUBIS treatment. An additional subject had an antibody signal after treatment with the comparator product and prior to RIXUBIS treatment. Two additional subjects had a positive titer of 1:80 that was not present when checked at a later time point and therefore considered transient. Two of the 19 subjects were pediatric (6 to <12 years age cohort). All post-treatment antibody titer increased in these two pediatric subjects were <2 dilution steps and therefore considered unrelated to treatment. No clinical adverse findings were observed in any of these 19 subjects.

In a study of 500 normal volunteers, using the same assay as in the clinical trial, 7% had titers of 1:20 or 1:40 and 1.2% had higher titers ranging from 1:80 to 1:320. These antibodies are thought to be part of a natural immune system response. To date, these antibodies have not been associated with any clinical adverse findings.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease.

Thrombogenicity

In all studies, subjects were monitored for the presence of thrombosis (see 7 WARNINGS AND PRECAUTIONS). There was no clinical evidence of thrombotic complications in any of the subjects.

Out-of-range values for thrombogenicity markers (Thrombin-antithrombin III [TAT], Prothrombin fragment 1.2, and D-dimer), determined during the pharmacokinetic portion of the combined study, did not reveal any pattern indicative of clinically relevant thrombogenicity with either RIXUBIS or a comparator factor IX-containing product, and were not associated with adverse events.

16 NON-CLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Nonclinical studies evaluating the carcinogenic and mutagenic potential of RIXUBIS have not been conducted.

No adverse effects on reproductive organs were observed by macroscopic and microscopic pathological investigations in repeated dose toxicity studies. No investigations on impairment of fertility have been conducted.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

RIXUBIS®
Recombinant Coagulation Factor IX (rFIX), Nonacog gamma for Injection

Read this carefully before you start taking **RIXUBIS** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RIXUBIS**.

What is RIXUBIS used for?

RIXUBIS is a medicine used to replace clotting factor (Factor IX) that is missing in people with hemophilia B. Hemophilia B is also called congenital factor IX deficiency or Christmas disease. Hemophilia B is an inherited bleeding disorder that prevents blood from clotting normally.

- RIXUBIS is used to prevent and control bleeding in adults and children with hemophilia B.
- Your healthcare provider may give you RIXUBIS when you have surgery.
- RIXUBIS can reduce the number of bleeding episodes when used regularly (prophylaxis).

How does RIXUBIS work?

RIXUBIS temporarily replaces the missing clotting factor IX that is needed for effective hemostasis.

What are the ingredients in RIXUBIS?

Medicinal ingredients: Recombinant Coagulation Factor IX (rFIX), Nonacog gamma
Non-medicinal ingredients: Calcium Chloride, L-Histidine, Mannitol, Polysorbate 80, Sodium Chloride, Sucrose

RIXUBIS comes in the following dosage forms:

RIXUBIS comes in five different dosage strengths 250 International Units (IU), 500 IU, 1000 IU, 2000 IU and 3000 IU.

The actual strength will be imprinted on the label and on the box. The five different strengths are color coded, as follows:

Light-blue	Dosage strength of approximately 250 International Units per vial
Pink	Dosage strength of approximately 500 International Units per vial
Green	Dosage strength of approximately 1000 International Units per vial
Orange	Dosage strength of approximately 2000 International Units per vial
Silver	Dosage strength of approximately 3000 International Units per vial

Always check the actual dosage strength printed on the label to make sure you are using the strength prescribed by your healthcare provider. Always check the expiration date printed on the carton. Do not use the product after the expiration date printed on the carton and the vial.

Do not use RIXUBIS if you:

- are allergic to hamsters.
- are allergic to any ingredients in RIXUBIS.

Tell your healthcare provider if you are pregnant or breastfeeding because RIXUBIS may not be right for you.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RIXUBIS. Talk about any health conditions or problems you may have, including if you:

- are pregnant or planning to become pregnant. It is not known if RIXUBIS may harm your unborn baby.
- are breast feeding or planning to breast feed. It is not known if RIXUBIS passes into your milk and if it can harm your baby.
- have or have had any medical problems.
- have any allergies, including allergies to hamsters.
- are at risk of developing blood clots.
- have liver disease.
- have recently had surgery or are planning to have surgery.
- have been told that you have inhibitors to factor IX (because RIXUBIS may not work for you).

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following medications may interact with RIXUBIS:

There are no known interactions of RIXUBIS with other medications.

How to take RIXUBIS:

For intravenous use only.

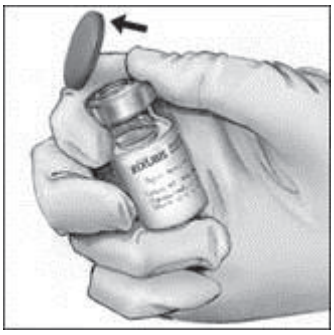
Do not attempt to do an infusion to yourself unless you have been taught how by your healthcare provider or hemophilia center.

See below for step-by-step instructions for reconstituting RIXUBIS.

Always follow the specific instructions given by your healthcare provider. The steps listed below are general guidelines for using RIXUBIS. If you are unsure of the procedures, please call your healthcare provider before using.

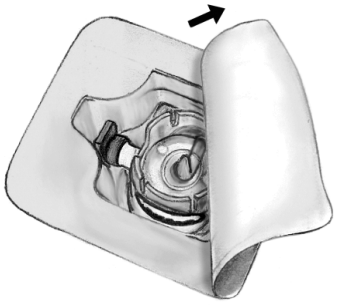
Dispose of all materials, including any leftover reconstituted RIXUBIS product, in an appropriate container.

1. Prepare a clean flat surface and gather all the materials you will need for the infusion. Check the expiration date, and let the vial with the RIXUBIS concentrate and the vial with the Sterile Water for Injection, USP (diluent) warm up to room temperature. Wash your hands and put on clean exam gloves. If infusing yourself at home, the use of gloves is optional.
2. Remove caps from the RIXUBIS concentrate and diluent vials to expose the centers of the rubber stoppers.



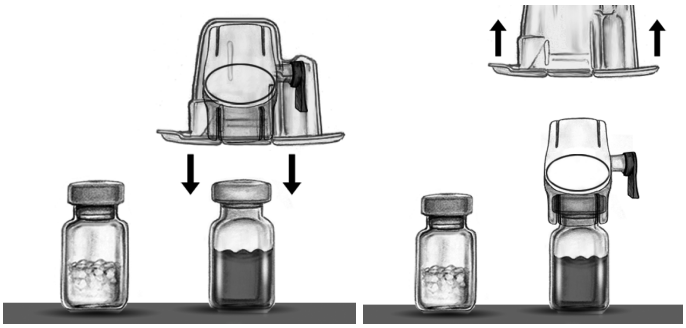
3. Disinfect the stoppers with an alcohol swab (or other suitable solution suggested by your healthcare provider or hemophilia center) by rubbing the stoppers firmly for several seconds and allow them to dry prior to use. Place the vials on a flat surface.

4. Open the BAXJECT II device package by peeling away the lid, without touching the inside of the package. **Do not remove the BAXJECT II device from the package**.



5. Turn the package with the BAXJECT II device upside down and place it over the top of the diluent vial. Fully insert the clear plastic spike of the device into the center of the diluent vial's stopper by pushing straight down. Grip the package at its edge and lift it off the device. Be careful not to touch the white plastic spike. **Do not remove the blue cap from the BAXJECT II device.**

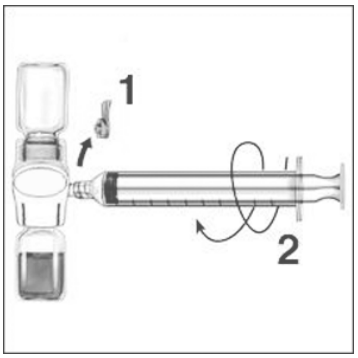
The diluent vial now has the BAXJECT II device connected to it and is ready to be connected to the RIXUBIS vial.



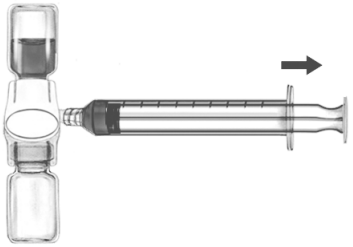
6. To connect the diluent vial to the RIXUBIS vial, turn the diluent vial over and place it on top of the vial containing RIXUBIS concentrate. Fully insert the white plastic spike into the RIXUBIS vial's stopper by pushing straight down. Diluent will flow into the RIXUBIS vial. This should be done right away to keep the liquid free of germs.

7. Swirl the connected vials gently and continuously until RIXUBIS is completely dissolved. **Do not shake**. The RIXUBIS solution should look clear and colorless. If not, do not use it and notify Takeda immediately.

8. Take off the blue cap from the BAXJECT II device and connect the syringe. **Be careful to not inject air.**

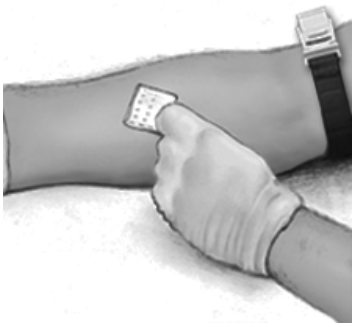


9. Turn over the connected vials so that the RIXUBIS vial is on top. Draw the RIXUBIS solution into the syringe by pulling back the plunger slowly. Disconnect the syringe from the vials. Attach the infusion needle to the syringe using a winged (butterfly) infusion set, if available. Point the needle up and remove any air bubbles by gently tapping the syringe with your finger and slowly and carefully pushing air out of the syringe and needle.

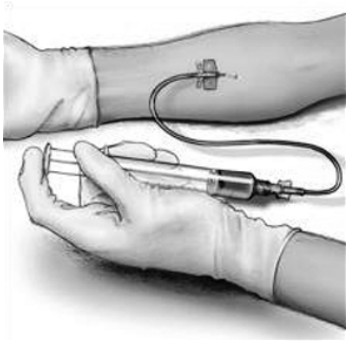


10. If you are using more than one vial of RIXUBIS, the contents of more than one vial may be drawn into the same syringe**. Make sure you mix each vial of RIXUBIS with the Sterile Water for Injection, USP that is provided in the box (**Following Steps 1-9). You will need a separate BAXJECT II device to mix each additional vial of RIXUBIS.

Apply a tourniquet and get the infusion site ready by wiping the skin well with an alcohol swab (or other suitable solution suggested by your healthcare provider or hemophilia center).



11. Insert the needle into the vein and remove the tourniquet. **Slowly infuse RIXUBIS. Do not infuse any faster than 10 mL per minute.**



12. Take the needle out of the vein and use sterile gauze to put pressure on the infusion site for several minutes.

Do not recap the needle. Place it with the used syringe in a hard-walled Sharps container for proper disposal.

Remove the peel-off label from the RIXUBIS vial and place it in your logbook. Clean any spilled blood with a freshly prepared mixture of 1 part bleach and 9 parts water, soap and water, or any household disinfecting solution.

13. Dispose of the used vials and BAXJECT II system in your hard-walled Sharps container without taking them apart. Do not dispose of these supplies in ordinary household trash.

Usual dose:
Your doctor will determine the dose of RIXUBIS you will receive.

The dose, duration and frequency of infusions you receive will be influenced by the severity of your factor IX deficiency, the location, extent of bleeding and age.

Call your healthcare provider right away if bleeding is not controlled after using RIXUBIS.
Your healthcare provider will prescribe the dose that you should take.

Your healthcare provider may need to take blood tests from time to time.
Talk to your healthcare provider before traveling. Plan to bring enough RIXUBIS for your treatment during this time.

Overdose:
No symptoms of overdose have been reported. As with other products of the same class, overdose may increase the risk for thrombotic and thromboembolic events (e.g., extensive blood clotting in multiple vessels, clotting in arteries or veins with examples in the leg and or lung vessels).

If you think you, or a person you are caring for, have taken too much RIXUBIS, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of this medicine, check with your doctor as soon as possible for instructions.

What are possible side effects from using RIXUBIS?
These are not all the possible side effects you may feel when using RIXUBIS. If you experience any side effects not listed here, contact your healthcare professional. You can ask your healthcare provider for information that is written for healthcare professionals.

Allergic reactions may occur with RIXUBIS. Call your doctor or get emergency treatment right away if you get a rash or hives, itching, tightness of the throat, chest pain or tightness, difficulty breathing, light headedness, dizziness, nausea or fainting.

Some common side effects of RIXUBIS were stomach flu like symptoms (such as nausea, vomiting and stomach pain), runny nose, sore throat, headache and diarrhea.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
- Refrigerated temperature 2° to 8°C (35 to 46°F) for 36 months or
- Room temperature not to exceed 30°C (86°F) for up to 36 months
- Do not freeze.
- Do not use beyond the expiration date printed on the carton or vial.
- Reconstituted product (after mixing dry product with wet diluent) must be used within 3 hours and cannot be stored or refrigerated. Discard any RIXUBIS left in the vial at the end of your infusion.

Keep out of reach and sight of children.

If you want more information about RIXUBIS:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html ; the manufacturer's website www.takeda.com/en-ca/rixubispm, or by calling 1-800-268-2772.

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