AUSTRALIAN PRODUCT INFORMATION

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

1 NAME OF THE MEDICINE

Recombinant Coagulation Factor IX (rFIX), Nonacog gamma (rch)), rFIX

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

The product is available in the following strengths: 250 IU, 500 IU, 1000 IU, 2000 IU, and 3000 IU.

The product concentration differs for each strength as every strength is reconstituted with the accompanying 5 mL of Sterile Water for Injection (SWFI).

The specific activity of rFIX is ≥ 200 IU factor IX per mg.

Composition

Table 1. Unit Formulation: after reconstitution with Sterile Water for Injection to 5 mL

RIXUBIS	250 IU	500 IU	1000 IU	2000 IU	3000 IU
Active ingredient: Nonacog gamma [Recombinant Coagulation FIX (rch)]	250 IU	500 IU	1000 IU	2000 IU	3000 IU
Approximate Product Concentration: (IU rFIX per mL of reconstituted solution)	50 IU/mL	100 IU/mL	200 IU/mL	400 IU/mL	600 IU/mL

The amounts of the inactive ingredients are constant in all strengths. For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS -Table 13.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection

Appearance

White, lyophilised powder and diluent for solution, for intravenous administration.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

RIXUBIS is indicated for:

- Routine prophylaxis of bleeding episodes in patients with haemophilia B
- Treatment and prevention of bleeding episodes in patients with haemophilia B (congenital factor IX deficiency)
- Peri-operative management in patients with haemophilia B

4.2 DOSE AND METHOD OF ADMINISTRATION

General

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

It is recommended that prescribed doses of RIXUBIS are expressed as 'International Units' (written in full) of factor IX.

Patients and their caregivers should be adequately trained in the correct administration technique before self-administration of RIXUBIS in a home treatment setting can be considered.

The dosage and duration of the substitution therapy depend on the severity of the 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.

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. (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Inhibitors

Patients using RIXUBIS should be monitored 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. (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Dosage

A guide for calculating the dose for treatment of bleeding episodes is provided below:

Number of factor IX IU required	**=**	**body weight (in kg)**	**X**	**desired factor IX increase (%) or (IU/dL)**	**X**	**reciprocal of observed recovery (dL/kg)**

Patients ≥ 12 years of age
The calculation of the required dose of RIXUBIS can be based on the empirical finding that 1 IU RIXUBIS per kg body weight is expected to increase the circulating level of factor IX by 0.9 IU/dL of plasma (0.9% of normal) (range from 0.5 to 1.4 IU/dL).

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

Number of factor IX IU required	**=**	**body weight (in kg)**	**X**	**desired factor IX increase (%) or (IU/dL)**	**X**	**1.1 dL/kg**

Patients < 12 years of age

The calculation of the required dose of RIXUBIS can be based on the empirical finding that 1 IU 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) (range from 0.31 to 1.0 IU/dL).

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 IU required	**=**	**body weight (in kg)**	**X**	**desired factor IX increase (%) or (IU/dL)**	**X**	**1.4 dL/kg**

Due to the wide range of individual differences in incremental recovery, it is recommended to base the calculation of the required dose on the patient's individual incremental recovery using serial factor IX activity assays.

Doses administered should be titrated to the patient's clinical response and individual pharmacokinetics, in particular incremental recovery and half-life.

Treatment of Bleeding Episodes and Peri-operative Management

In the case of the following haemorrhagic events, the factor IX activity should not fall below the plasma factor IX activity levels (in % of normal or in IU/dL) in the corresponding period.

Table 2. Treatment of Bleeding Episodes and Peri-operative Management

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, including tooth extraction	30–60	Every 24 hours, at least 1 day, until healing is achieved.
Major	80–100 (pre- and postoperative)	Repeat infusion every 8–24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor IX activity of 30% to 60% (IU/dL)

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

Routine Prophylaxis

RIXUBIS can be administered for long-term prophylaxis against bleeding in patients with severe and moderately severe haemophilia B. The recommended dose for previously treated patients (PTPs) ≥ 12 years of age is 40 to 60 IU/kg twice weekly. The recommended dose for patients <12 years of age is 40 to 80 IU/kg twice weekly. Shorter dosage intervals or higher doses may become necessary depending upon the individual patient's pharmacokinetics, age, bleeding phenotype, and physical activity.

Method of administration

RIXUBIS is administered by intravenous (IV) infusion.

Administer RIXUBIS at room temperature using a rate that ensures the comfort of the patient, up to a maximum of 10 mL/min.

Do not administer RIXUBIS by continuous infusion.

Only use plastic syringes with this product.

Instructions for use

Administer RIXUBIS by intravenous (IV) infusion after reconstitution.

Initiate treatment under the supervision of a physician experienced in the treatment of haemophilia and continue treatment under supervision for a period of time. (See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE/Anaphylaxis and Severe Hypersensitivity Reactions)

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

Administer RIXUBIS at room temperature within 3 hours of reconstitution. RIXUBIS contains no antimicrobial preservative. It is for single use in one patient only. Discard any unused product.

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.

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 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; 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.

10. Remove the blue cap from the BAXJECT II device. Connect the syringe to the BAXJECT II device (Figure E). **Do not inject air**.

11. 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).

12. Disconnect the syringe; attach a suitable needle and inject intravenously as instructed 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.

13. Maximum infusion rate of 10 mL/min.

Figure A

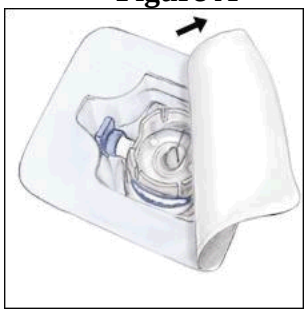


Figure B

Figure C

Figure D

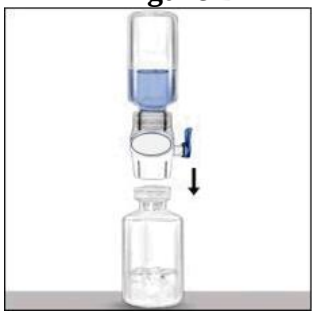


Figure E

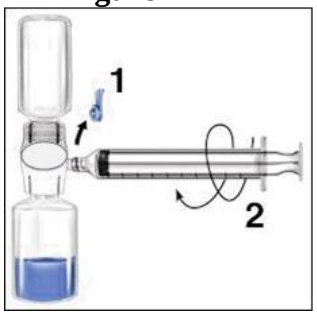
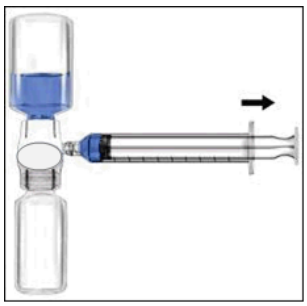


Figure F



4.3 CONTRAINDICATIONS

RIXUBIS is contraindicated in patients with known hypersensitivity to active substance, to excipients, or to hamster protein.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity Reactions

Hypersensitivity has been reported with RIXUBIS. Anaphylaxis and other hypersensitivity reactions to any type of factor IX concentrate are possible. 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.

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, the current medical standards for shock treatment should be observed.

Inhibitors - Nephrotic Syndrome

Patients with haemophilia B may develop neutralising 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 haemophilia centre 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.

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

Thromboembolism, DIC, Fibrinolysis

The use of factor IX products has been associated with the development of thromboembolic complications. Therefore, the use of 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 this product to patients with liver disease, to patients peri- and postoperatively, to newborn infants, or to other patients at risk for thromboembolic 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.

Use in the 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.

Monitoring Laboratory Tests

- Monitor factor IX activity levels by the one-stage clotting assay to confirm that adequate factor IX levels have been achieved and maintained, when clinically indicated (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION)
- 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 if factor IX inhibitor is present should be titred in Bethesda Units (BUs).

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interactions of recombinant coagulation factor IX products with other medicinal products are known.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of RIXUBIS on fertility have not been established.

Use in pregnancy

Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse Reactions from Clinical Trials

The following adverse reactions have been identified during clinical development of RIXUBIS from 2 completed studies and 2 ongoing studies* with 99 unique, male previously treated patients PTPs with haemophilia B receiving a total of 14,018 infusions.

Table 3. Clinical Trials Adverse Reactions

System Organ Class (SOC)	Preferred MedDRA Term	Frequency per Patient[a] N = 99		Frequency per Infusion[b] N = 14,018	
		Category	Number of patients (Percentage)	Category	Number of occurrences (Percentage)
NERVOUS SYSTEM DISORDERS	Dysgeusia	Common	1 (1.01%)	Rare	2 (0.014%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Pain in extremity	Common	1 (1.01%)	Very Rare	1 (0.007%)

Legend: Frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥1/10,000 - <1/1,000), Very Rare (<1/10,000)

[a] The frequency per patient is based on the number of patients experiencing an adverse event with an investigator assessment of at least possibly related, or when an investigator assessment of causality was unknown, considered at least possibly related by Baxter Healthcare Corporation.

[b] The frequency per infusion is based on the number of occurrences of adverse events with an investigator assessment of at least possibly related, or when an investigator assessment of causality was unknown, considered at least possibly related by Baxter Healthcare Corporation.

* Baxter Clinical Study 250901 (Pivotal) Completed
Baxter Clinical Study 251101 (Pediatric) Completed
Baxter Clinical Study 251001 (Continuation) Data cut-off date = 14 June 2013
Baxter Clinical Study 251002 (Surgery) Data cut-off date = 14 June 2013

Immunogenicity

Of the 99 PTPs exposed to RIXUBIS during clinical development, none developed inhibitory or treatment-related† total binding antibodies† to factor IX or antibodies to Chinese hamster ovary (CHO) proteins. One subject had a positive titer for rfurin that was not present when checked at a later time point and was therefore considered transient. No clinical adverse findings were observed in this subject.

†Defined as a more than 2 dilution-steps increase in specific titer compared to pre-study level.

Post-marketing Adverse Reactions

The following adverse reactions have been reported, listed by MedDRA (Version 17.01) System Organ Class (SOC), then by Preferred Term in order of severity.

IMMUNE SYSTEM DISORDERS: Hypersensitivity (including symptoms such as dyspnoea, pruritus).

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Urticaria, rash.

Class Reactions

- Disseminated intravascular coagulation, embolism (e.g., pulmonary embolism, venous thrombosis, arterial thrombosis)

- Anaphylactic reaction or hypersensitivity reactions (including symptoms such as angioedema, chest discomfort, hypotension, lethargy, nausea, vomiting, paraesthesia, restlessness, wheezing, dyspnoea)

See Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Reporting an adverse event

Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

No symptoms of overdose have been reported.

For information on the management of overdose, contact the Poisons Information Centre telephone: 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

RIXUBIS contains recombinant coagulation factor IX.

Mechanism of action

Recombinant coagulation factor IX is a single chain glycoprotein that is a member of the serine protease family of vitamin K-dependent coagulation factors. Recombinant coagulation factor IX is a recombinant DNA-based protein therapeutic which has structural and functional characteristics comparable to endogenous factor IX. Factor IX is activated by factor VIIa/tissue factor complex in the extrinsic pathway and by factor XIa in the intrinsic coagulation pathway. Activated factor IX, in combination with activated factor VIII, activates factor X. This results ultimately in the conversion of prothrombin to thrombin. Thrombin then converts fibrinogen into fibrin, and a clot can be formed. Factor IX activity is absent or greatly reduced in patients with haemophilia B, and substitution therapy may be required.

Haemophilia B is an X chromosome-linked recessive congenital disorder of blood coagulation due to decreased levels or complete lack 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. Replacement therapy increases the plasma level of factor IX, providing a temporary correction of the factor deficiency and the bleeding tendency.

Clinical trials

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

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 the prophylaxis and/or for the treatment of bleeding episodes on an on-demand basis. PTPs were defined as subjects who

were exposed to a factor IX-containing product on ≥ 150 days. All subjects had severe (factor IX level < 1%) or moderately severe (factor IX level ≤ 2%) haemophilia 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 haemostatic effect other than haemophilia B were excluded from participation. Fifty-nine (59) PTPs received RIXUBIS for prophylaxis. Fifty six (56) of these PTPs who received RIXUBIS for a minimum of 3 months, were included in the efficacy evaluation for prophylaxis (see Tables 4 and 5). An additional 14 PTPs received RIXUBIS for 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 enrolment. 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 annualized bleeding rate (ABR) was 33.9±17.37 ranging from 12.9 to 73.1.

Prophylaxis

The mean ABR on prophylaxis for all bleeds was 4.3, for spontaneous bleeds 1.7 and for joint bleeds 2.9 (see Table 4).

Table 4. Efficacy of Prophylaxis with RIXUBIS in 56 PTPs ≥ 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 bleeds	
% (n)	42.9% (24)

* 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.

Comparison with Historical Control

The mean total ABR of a historical control was compared with the mean total ABR resulting from twice-weekly treatment with RIXUBIS. The historical control is based on a meta-analysis of data from 12 studies published from 1976 to 2011 with a total of 276 hemophilia B patients (children and adults) treated on-demand with various factor IX products for a mean duration of 19.6 months. The mean total ABR was 20.0 (SD 39.4; 95% CI 15.3; 24.6, whereas the mean total ABR in the RIXUBIS prophylactic cohort (based on data of an interim analysis with n=56 with at least 3 months treatment), was 4.20 ± 5.75 (95% CI 2.66; 5.74). The difference was statistically significant (p < 0.001) with a reduction of total ABR by 79%.

Treatment of Bleeding Episodes

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 individualized 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 95.4% of all treated bleeding episodes. No bleeding episode had an efficacy rating of "none".

Prophylaxis and control of bleeding in PTPs < 12 years of age

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. 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 5).

Table 5. Efficacy of Prophylaxis of RIXUBIS in 23 PTPs < 12 years of age

Treatment duration (months)	
Mean ± SD	5.98 ± 0.712
Median (range)	5.95 (3.3–7.7)
Number of infusions per week*	
Mean ± SD	1.97 ± 0.082
Median (range)	1.97 (1.8–2.2)
Dose per infusion (IU/kg)*	
Mean ± SD	56.25 ± 8.341
Median (range)	55.63 (43.0–75.5)
Total annualized bleeding rate (ABR)	2.7 ± 3.14
Mean ± SD	2.0 (0.0–10.8)
Median (range)	
ABR for joint bleeds	
Mean ± SD	0.8 ± 1.76
Median (range)	0.0 (0.0–7.2)
ABR for spontaneous bleeds	
Mean ± SD	0.2 ± 0.66
Median (range)	0.0 (0.0–2.0)
Subjects with zero bleeds	
% (n)	39.1.% (9)
Subjects with spontaneous bleeds or bleeds of unknown origin	13.0% (3)
% (n)	

* 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. Treatment

was individualized based on the severity, cause and site of bleed. The majority (23; 88.5%) were treated with 1–2 infusions. The actual breakdown was (15; 57.7%) 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

The safety and efficacy in the perioperative setting was evaluated in an ongoing phase 3 prospective, open-label, uncontrolled, multicentre study in male PTPs with severe and moderately severe haemophilia B using RIXUBIS. The per-protocol efficacy analysis includes 13 surgeries performed in 13 patients between 19 and 54 years of age undergoing major or minor surgical, dental or other surgical invasive procedures. Ten (10) procedures were major including 6 orthopaedic and 1 dental surgery. Three procedures including 2 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 was maintained.

RIXUBIS was administered by bolus infusions.

Haemostasis was maintained throughout the study duration.

Table 6 shows the types of surgical procedures and the results of the assessment of the haemostatic response at various points in time.

Table 6. Efficacy of RIXUBIS for Surgical Procedures in PTPs

Procedure (# of patients/category)	**Assessment of Response[a]**		
	Intra-operative	**At time of drain removal or on post-operative day 3[b]**	**At Time of Discharge**
Removal of intramedullary nail (Major, n=1)	Excellent	Good	Excellent
Joint Replacement (Major, n=4)	Excellent	Good (2) Excellent (2)	Good (1) Excellent (3)
Intra articular injection left ankle (Minor, n=1)	Excellent	Not applicable	Good
Open synovectomy left elbow (Major, n=1)	Excellent	Excellent	Excellent
Excision of neurofibroma right calf (Major, n=1)	Excellent	Excellent	Excellent
Hernioplastic (Major, n=2)	Excellent	Excellent	Good (1) Excellent (1)
Tooth extraction (Major, n=1)	Excellent	Excellent	Excellent
Tooth extraction (Minor, n=2)	Excellent	Excellent	Excellent

a Where no drain was employed, response was assessed on postoperative day 3.
b Haemostatic response assessed by surgeon who performed procedure

Thrombogenicity
In all studies subjects were monitored for the presence of thrombosis. 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 phase 1/3 pivotal study (see Section 5.1 PHARMACODYNAMIC PROPERTIES/CLINICAL TRIALS and Section 5.2 PHARMACOKINETIC PROPERTIES), did not reveal any pattern indicative of clinically relevant thrombogenicity with either RIXUBIS or the comparator, and were not associated with adverse events.

5.2 PHARMACOKINETIC PROPERTIES

Previously treated patients ≥12 years of age

A randomized, 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 IV 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 mean and median doses of the comparator were 74.83 ± 2.51 and 74.92 IU/kg, respectively, with a range of 70.12 to 80 IU/kg. The pharmacokinetic parameters were calculated from factor IX activity 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 Table 7.

Table 7. Pharmacokinetic Parameters for RIXUBIS and Comparator (per-protocol analysis)

Parameter	RIXUBIS Initial cross-over study (N=25)	Comparator Initial cross-over study (N=25)	RIXUBIS Repeat Evaluation (N=23)
$AUC_{0\text{-}72h}$ (IU·h/dL)[a]			
Mean ± SD	1067.81 ± 238.42	1007.88 ± 236.64	1156.15 ± 259.44
Median (range)	1108.35 (696.07 - 1571.16)	1024.66 (650.08 - 1545.69)	1170.26 (753.85 - 1626.81)
Incremental recovery (IU/dL : IU/kg)[b]			
Mean ± SD	0.87 ± 0.22	0.76 ± 0.20	0.95 ± 0.25
Median (range)	0.88 (0.53 - 1.35)	0.73 (0.44 - 1.27)	0.93 (0.52 - 1.38
Half-life (h)			
Mean ± SD	26.70 ± 9.55	27.87 ± 9.22	25.36 ± 6.86
Median (range)	24.58 (15.83 - 52.34)	26.28 (17.59 - 64.29)	24.59 (16.24 - 42.20)
C_{max} (IU/dL)			
Mean ± SD	66.22 ± 15.80	58.24 ± 15.83	72.75 ± 19.73
Median (range)	68.10 (41.70 - 100.30)	55.90 (33.60 - 95.80)	72.40 (38.50 - 106.30)

Mean residence time (h) Mean ± SD Median (range)	 30.82 ± 7.26 28.93 (22.25 - 47.78)	 32.24 ±7.16 30.59 (25.40 - 60.70)	 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)	 2.20 (0.69) 1.98 (1.19 ; 3.92)	 1.79 ± 0.45 1.74 (1.12 - 2.72)
Clearance (dL/h/kg) Mean ± SD Median (range)	 0.0644 ± 0.0133 0.0622 (0.0426 ; 0.0912)	 0.0681 ± 0.0153 0.0655 (0.0438 - 0.1001)	 0.0602 ± 0.0146 0.0576 (0.0413 - 0.0945)

[a] Area under the plasma factor IX concentration x time curve from 0 to 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

The 90% confidence intervals for the AUC 0-72h /dose and AUC 0-72 h were within the margins of equivalence defined as 80% to 125%.
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 8.

Table 8. Incremental Recovery for RIXUBIS 30 minutes after infusion

Incremental recovery 30 min after infusion	**Exposure Day 1** **(N=73)**	**Week 5** **(N=71)**	**Week 13** **(N=68)**	**Week 26** **(N=55)**	**At study completion/ termination[b]** **(N=23)**
(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.

Previously treated patients <12 years of age

All 23 male subjects underwent an initial pharmacokinetic evaluation of RIXUBIS in a non-bleeding state as part of the combined phase 2/3 pediatric study. Subjects were randomized 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 Table 9.

Table 9. Pharmacokinetic Parameters for pediatric PTPs < 12 years of age (full analysis set)

Parameter	**< 6 years (N=11)**	**6 - < 12 years (N=12)**	**All (N=23)**
$AUC_{0\text{-}inf}$ (IU·h/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 (h) 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 (h)			
Mean ± SD	30.62±3.27	25.31±1.83	27.85±3.73
Median (range)	30.08 (26.2-36.2)	24.74 (23.7-30.3)	26.77 (23.7-36.2)
V_{ss}[b] (dL/kg)			
Mean ± SD	3.22 ± 0.52	2.21 ± 0.32	2.7 ± 0.67
Median (range)	3.16 (2.65-4.42)	2.185 (1.70-2.70)	2.69 (1.70-4.42)
Clearance (dL/[kg·h])			
Mean ± SD	0.1058 ± 0.01650	0.0874 ± 0.01213	0.0962 ± 0.01689
Median (range)	0.1050 (0.081-0.144)	0.0863 (0.069–0.108)	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 pediatric age groups. See Tables 10 - 12.

Table 10. Incremental Recovery for RIXUBIS 30 minutes after infusion Both pediatric age groups

Incremental recovery 30 min after infusion	**PK (Exposure Day 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	0.67 ± 0.16	0.68 ± 0.12	0.71 ± 0.13	0.72 ± 0.15
Median (range)	0.69 (0.31 – 1.00)	0.66 (0.48-0.92)	0.66 (0.51-1.00)	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.

Table 11. Incremental Recovery for RIXUBIS 30 minutes after infusion Pediatric patients < 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	0.59 ± 0.13	0.63 ± 0.10	0.68 ± 0.12	0.65 ± 0.13
Median (range)	0.59 (0.31-0.75)	0.6 (0.49-0.80)	0.66 (0.51-0.84)	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 Pediatric patients 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	0.73 ± 0.16	0.73 ± 0.13	0.73 ± 0.14	0.8 ± 0.14
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

Studies on carcinogenesis and mutagenesis of RIXUBIS, Coagulation factor IX (Recombinant), were not conducted, since no risk is anticipated for biotechnology-derived pharmaceuticals such as Coagulation factor IX (Recombinant).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The amounts of the inactive ingredients are constant in all strengths.

Table 13. Unit Formulation: after reconstitution with Sterile Water for Injection to 5 mL

RIXUBIS	250 IU	500 IU	1000 IU	2000 IU	3000 IU
Active ingredient: Nonacog gamma [Recombinant Coagulation FIX (rch)]	250 IU	500 IU	1000 IU	2000 IU	3000 IU
Inactive ingredient:	(mg)	(mg)	(mg)	(mg)	(mg)
L-Histidine	15.51	15.51	15.51	15.51	15.51
Sodium Chloride	17.54	17.54	17.54	17.54	17.54
Calcium Chloride	2.94	2.94	2.94	2.94	2.94
Mannitol	100.19	100.19	100.19	100.19	100.19
Sucrose	59.90	59.90	59.90	59.90	59.90
Polysorbate 80	0.25	0.25	0.25	0.25	0.25

Refer to Section 2 QUALITATIVE AND QUANTITATIVE COMPOSITION.

6.2 INCOMPATIBILITIES

This product must not be mixed with other medicinal products.

6.3 SHELF LIFE

36 months.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Storage

Store below 30°C.

Storage after reconstitution

Chemical and physical in-use stability has been demonstrated for 3 hours at temperatures up to 30°C.

Do not use beyond the expiration date printed on the vial or carton.

6.5 NATURE AND CONTENTS OF CONTAINER

Container type

RIXUBIS is a white or almost white lyophilised powder which is supplied in a single-dose Type I glass vial: 250 IU, 500 IU, 1000 IU, 2000 IU or 3000 IU. The vial is closed with a butyl rubber stopper. The components of this product are latex-free.

Each kit also contains 5mL of Sterile Water for Injection in a Type I glass vial and BAXJECT II Transfer device.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The recombinant human factor IX (rFIX) is a glycoprotein consisting of 415 amino acids. RIXUBIS is synthesised by a genetically engineered Chinese hamster ovary (CHO) cell line. No exogenous materials of human or animal origin are employed in the manufacture, purification, or formulation of the final product. The growth medium is chemically defined and the downstream process does not use monoclonal antibodies for the purification of RIXUBIS. The production process also includes two independent viral removal/inactivation steps: solvent detergent treatment and nanofiltration.

Biological potency is determined by a one-stage clotting assay, which employs a factor IX concentrate standard that is referenced to the World Health Organization (WHO) International Standard for factor IX concentrates.

CAS number

CAS No: 181054-95-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

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9 DATE OF FIRST APPROVAL

30 January 2014

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6 August 2018

Summary table of changes

Section Changed	Summary of new information
All	Australian PI updated to new TGA form.
All	Table numbers introduced to all tables.
2, 6.7	Text moved from section 2 to section 6.7
4.2, 4.4, 4.8, 5.2	Minor editorial changes including update to standard MedDRA terminology.
4.2	Minor editorial change to update sponsor name; Illustrations updated to remove sponsor name.
5.2	Incorrectly placed footnotes removed and renumbered.
6.7	Included CAS Number
8	Change in sponsor details