Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for nonacog gamma

Proprietary Product Name: Rixubis

Sponsor: Baxter Healthcare Pty Ltd

April 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of common abbreviations

Abbreviation	Meaning
ABR	Annualised bleeding rate
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration versus time curve
$AUC_{0\text{-}72\ h}$	Area under the plasma concentration versus time curve from 0 to 72 hours post-infusion
$AUC_{0\text{-}\infty}$ or $AUC_{0\text{-}inf}$	Area under the plasma concentration versus time curve from time 0 to infinity
BDS	Bulk Drug Substance
BE	Bleeding episode
BU	Bethesda Unit
CHO	Chinese hamster ovary
CL	Clearance
DIC	Disseminated intravascular coagulation
DMC	Data Monitoring Committee
eCRF	Electronic case report form
EC	Ethics committee
ED	Exposure day
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ER	Emergency room
FAS	Full Analysis Set
FDP	Finished Drug Product
FIX	Factor IX

Abbreviation	Meaning
GCP	Good clinical practice
GP	General practitioner
h	Hour(s)
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR QoL	Health-related quality of life
hs-CRP	High-sensitive C-reactive protein
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
INR	International normalised ratio
IP	Investigational product
IR	Incremental recovery
ITI	Immune tolerance induction
IU	International units
MRT	Mean residence time
NOAEL	No observable adverse event level
PK	Pharmacokinetic
PTP	Previously treated patients
rFIX	Recombinant Factor IX
SAE	Serious adverse event
SAER	Serious adverse event report
SPC	Summary of product characteristics
SWFI	Sterile water for injection
T½	Elimination phase half-life
Vss	Volume of distribution at steady state

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	30 January 2014
Active ingredient:	Nonacog gamma
Product name:	Rixubis
Sponsor's name and address:	Baxter Healthcare Pty Ltd 1 Baxter Drive Old Toongabbie NSW 2146
Dose form:	Lyophilised powder and solvent for solution for injection
Strengths:	250, 500, 1000, 2000 and 3000 IU
Containers:	Single-use glass vials
Pack size:	1 powder vial, 1 WFI vial and 1 BaxJect II needleless transfer Device
Approved therapeutic use:	*Routine prophylaxis of bleeding episodes in patients 12 years and older with haemophilia B.* *Treatment and prevention of bleeding episodes in patients 12 years and older with haemophilia B (congenital factor IX deficiency).* *Peri-operative management in patients 12 years and older with haemophilia B.*
Route of administration:	Intravenous
Dosage:	See Rixubis PI
ARTG numbers:	204767 - 250 IU 204769 - 500 IU 204766 - 1000 IU 204768 - 2000 IU 204765 - 3000 IU

Product background

Haemophilia B (congenital factor IX (FIX) deficiency; Christmas disease) is an X-chromosomal-linked bleeding disorder with an incidence of approximately one in 30,000 live male births. Haemophilia B is the second most common type of haemophilia and is five

times rarer than haemophilia A. The World Federation of Hemophilia (WFH) reported a worldwide prevalence of 399,000 subjects with haemophilia, of which there are an estimated 80,000 patients with haemophilia B. In approximately 30% of haemophilia B cases, there is no family history of the disorder and the condition is the result of a spontaneous gene mutation.

Historically, haemophilia patients were only treated when they had bleeding episodes (on-demand). One of the main reasons on-demand treatment has been used is the high cost and limited supply of FIX products. However, it has become known that treatment of severe haemophilia with frequent, periodic prophylactic FIX infusions can have significant medical and quality of life benefits. On prophylaxis, adequate plasma levels of FIX for haemostasis are maintained, approximating a non-diseased state. Prophylaxis treatment started at a young age would facilitate a complete lack of bleeding episodes, maintain healthy joints, and can lead to functionally normal lives. Thus, prophylaxis is preferred over on-demand therapy as it prevents most of the irreversible long-term effects brought about by bleeding.

Rixubis is a recombinant FIX (rFIX) product, with structural and functional characteristics comparable to endogenous FIX. It is synthesised by a recombinant Chinese Hamster Ovary (CHO) cell clone in suspension culture which coexpresses rFIX and recombinant human wild-type Furin [rFurin], a proteolytic enzyme which facilitates complete cleavage of the FIX propeptide. The CHO cell culture medium is a chemically defined medium developed by Baxter, and the downstream process does not use monoclonal antibodies for the purification. No materials of human or animal origin are employed in the manufacture, purification, or formulation of the final product, thus reducing the risk of transmission of adventitious agents.

Properly processed plasma-derived products are considered virally-safe, but the discovery of any new human pathogen (such as West Nile virus, SARS and blood-borne prions) leads to apprehension within the haemophilia community. Due to the absence of exposure to any human-derived proteins during manufacturing and formulation, Rixubis has an inherently improved viral safety profile compared with plasma derived FIX products.

Baxter's rFIX product was designated an orphan drug on 3 October 2012, under a different product name (Fixtera).

This AusPAR describes the application by Baxter Healthcare Pty Ltd (the sponsor) to seek approval for Rixubis to be registered with the following indications:

> *Routine prophylaxis of bleeding episodes in patients 12 years and older with haemophilia B.*
>
> *Treatment and prevention of bleeding episodes in patients 12 years and older with haemophilia B (congenital factor IX deficiency).*
>
> *Peri-operative management in patients 12 years and older with haemophilia B.*

Regulatory status

The product received initial ARTG Registration on 5 February 2014.

Rixubis has received approval in the United States and applications for registration have been lodged in other countries.

Table 1: Overseas regulatory status of Rixubis

Country	Application Status	Status date	Approved Indications
United States of America	Approved	Submission: 30 Aug 2012 Approval: 26 June 2013	Rixubis (Coagulation Factor IX [Recombinant]) is an anti-haemophilic factor indicated for: Control and prevention of bleeding episodes in adults with haemophilia B. Perioperative management in adults with haemophilia B. Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adults with haemophilia B.
European Union	Pending evaluation	Submission: 25 Oct 2013	NA
Switzerland	Pending evaluation	Submission: 16 Jan 2013	NA
Canada	Pending evaluation	Submission: 27 June 2013	NA

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

Quality findings

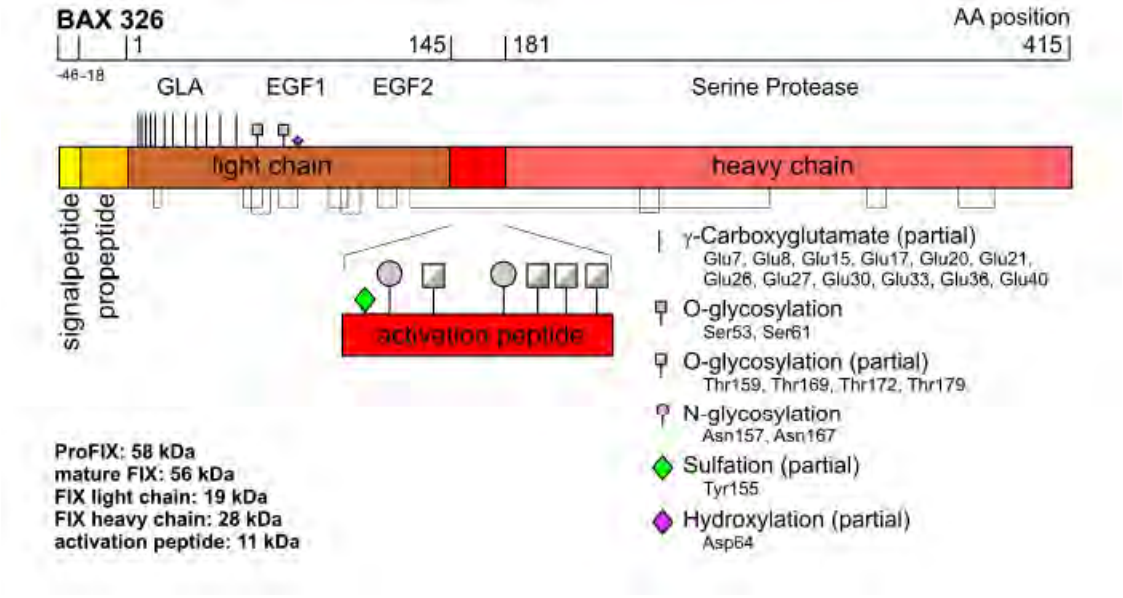
Drug substance

Rixubis rFIX is a purified protein that has 415 amino acids in a single polypeptide chain. It has a primary amino acid sequence comparable to the Ala148 allelic form of plasma–derived FIX, but some post-translational modifications of the recombinant molecule are different from those found in the plasma-derived molecule.

rFIX is a glycoprotein that is secreted by genetically engineered mammalian cells derived from a CHO cell line. Rixubis is synthesised as a single chain polypeptide and secreted in its mature form. 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.

Drug Substance FIX belongs to the vitamin-K-dependent blood coagulation factors and is part of the intrinsic blood coagulation system. After FIX (54-57 kDa) has been activated to activated FIX (FIXa), it has a molecular weight of approximately47 kDa due to the release of the activation peptide (approximately11 kDa). FIXa consists of an approximately 28 kDa heavy chain and an approximately18 kDa light chain connected by a disulfide bond (Human Protein Data). rFIX, Rixubis is expressed by a recombinant CHO cell line in a fermentation process, which is free from human or animal derived proteins.

Figure 1: Structure of Rixubis



Drug product

The Rixubis Final Drug Product (FDP) consists of a lyophilised powder for solution for injection. The proposed nominal dosage strengths are 250, 500, 1000, 2000 and 3000 IU/vial. Each dosage strength is reconstituted using Sterile Water for Injection (sWFI) and mixed prior to intravenous injection.

rFIX FDP is formulated as a sterile, non-pyrogenic, white or off-white, lyophilised powder preparation for intravenous injection and is stabilised with a mixture of sugars and salts. The Rixubis FDP is supplied in single-dose glass vial.

Quality summary and conclusions

It is recommended that approval for registration of Rixubis not be given until the sponsor has provided satisfactory answers to the questions below.

Question 1: ß-D Glucan

(1, 3)-ß-D Glucan molecules can be found in the cell walls of most yeasts and moulds and can induce inflammatory responses. Glucans may contaminate cell culture raw materials,

air quality samples, and cellulose filter preparations. Glucans are known to cause false positive results in endotoxin assays, triggering unnecessary investigations.

ß-Glucan analysis was performed at a contract lab using the Endosafe-PTS Glucan assay technology. In this analysis, sample sets from the downstream process starting with the load of the fermentation broth to the capture column (FLT-L) and ending with the final drug substance (CNN-E). The data indicate that a dramatic decrease of the ß-Glucan amount was obtained after the first downstream purification step. More than 99.99% (more than a three log^{10} reductions) of the initial ß Glucan content was removed during the eluate capture chromatography (CPN) step. The ß-Glucan content of the drug substance samples was below the analytical range of the method. The sponsor should be asked if there was any evidence of false positive results in endotoxin assays.

Question 2

Quantitative monosaccharide determination showed comparable and consistent amounts within the limits of the method. Quantitative sialic acid (N-acetyl-neuraminic acid) determination showed that the amounts of sialic acid on the terminal ends of the glycans are consistent within the limits of the method. Detected amounts of N-glycolyl-neuraminic acid, a potentially immunogenic variant of sialic acid, were less than ≤ 0.2% of total sialic acids. In addition the presence of an O-acetylated variant Neu5.9Ac2 was determined to be present (up to 2.5%).

The sponsor states that because this variant was also found in licensed, marketed, recombinant, and plasma derived FIX drug products, this variant was not considered as critical. The evaluator feels that further comment should be sought from the sponsor on this point.

Question 3

Has final nomenclature and art work for packaging and labels been prepared for evaluation?

Evaluation of sponsor's responses to questions

Response to question 1

Evidence of false positive results cannot be provided as the validation of the Endotoxin/LAL method has been performed using ß-glucan blocker. Therefore there are no false positive results.

The response is self-explanatory and acceptable.

Response to question 2

Data on N-glycolyneuraminc acid (Neu5Gc, NGNA) was provided in the characterisation section of the market application. Table 2 was provided below for reference.

The data demonstrate that the Neu5Ac is clearly the most predominant species, with the Neu5Gc and Neu5.9Ac2 contributing less than 3% to the total sialic acid amount. This is considered to be adequate based on the following reasons:

- CHO cell lines are known to incorporate small amounts of the non-human sialic acid like N glycolylneuraminic acid (NGNA). The amount of NGNA incorporated is dependent on cell clone and culture conditions.

- There is evidence that the presence of significant amounts of NGNA on a bio-therapeutic drug (1.84 mol SA/mol of product, nearly 100% NGNA) can impact product half-life and clearance (CL) whereas no NGNA specific immune response was seen with a product carrying a low NGNA content (0.1% NGNA of total SA content. These studies were both done with mAb drugs monoclonal (see Ghaderi D. et al, 2010[1]). Similarly, administration of rEPO containing about 1% NGNA of total sialic acids did not show any allergic side effects associated with the production of NGNA – specific antibodies (Noguchi A., et. al, 1996[2]). In addition, the anticoagulant drug Atryn (made of goat milk) is a licensed product for human use containing a high content of NGNA.

Table 2: Data on glycolyneuraminc acid (Neu5Gc, NGNA)

Rixubis	[nmol Neu5Ac/mg FIX[1]]	% Neu5Gc [Area%]	% Neu5.9Ac2 [Area%]
ORRNCNN11001E01	157	0.05	2.4
ORRNCNN11001E07	165	0.11	2.4
ORRNCNN11001E14	174	0.15	2.2
ORRNCNN11019E01	128	0.09	2.5
ORRNCNN11119E04	152	0.12	2.5
ORRNCNN11038E02	134	0.07	2.5
ORRNCNN11038E14	138	0.12	2.2
ORRNCNN11038E27	151	0.16	2.2
ORRNCNN11038E28	156	0.17	2.2
Comparator FDP 500IU	n.a.2	0.02	0.8
Comparator FDP 1000IU	n.a. 2	0.03	0.8
Comparator FDP 2000IU	n.a. 2	0.01	1.1
Comparator FDP 500IU	170.9 3	0.07	1.6
Plasma drived FIX H19708E	152.53	0.0	1.4

1: Values are release values and the complete data set for all BDS samples can be found in the batch analysis data.
2: Quantitative determination of Neu5Ac in the licensed, marketed, rFIX product samples is not possible due to matrix components interfering with recovery of sialic acids. Calculation of relative peak areas is

[1] Ghaderi D et al 2010. Implications of the presence of N-glycolylneuraminic acid in recombinant therapeutic glycoproteins. Nature Biotechnology 28(8):863-7
[2] Noguchi, A et al. 1996. Failure of human immunoresponse to N-glycolylneuraminic acid epitope contained in recombinant human erythropoietin. Nephron; 72(4):599-603

valid under the assumption that the influence of the matrix components is the same for all sialic acid variants.
3: For these samples a buffer exchange was done before analysis.

The sialic acid species identified and quantified from the characterisation of representative process validation batches (three different cell culture production runs as well as the beginning middle and end of one campaign) demonstrate that the sialic acid species concentrations are consistent inter and intra campaign and those other than the Neu5Ac species are low. Consequently the NGNA amount in Rixubis is considered not to impact safety and efficacy of the Rixubis product.

The presence of the O-acetylated variant Neu5.9Ac2 is not considered as critical as it is also found in a licensed, marketed, rFIX product and plasma derived FIX. Furthermore, it was confirmed to be an acetylated variant and no O-glycosyl variants were found. O-Acetylated sialic acids are also found in human proteins and are thus considered as not critical[3].

Despite the incorrect reference list the evaluator accepted the explanation put by the sponsor.

Response to question 3

The PI, Consumer Medicine Information (CMI) document and artworks with the Rixubis trade name have been prepared.

The evaluator considered that the documents appear to be satisfactory.

III. Nonclinical findings

Introduction

Baxter Healthcare Pty Ltd has applied to register Rixubis containing nonacog gamma, a recombinant human Factor IX (rhFIX). Orphan drug designation was granted on 3 October 2012.

Proposed clinical use

The proposed indications for Rixubis:

> *Routine prophylaxis of bleeding episodes in patients 12 years and older with haemophilia B;*
>
> *Treatment and prevention of bleeding episodes in patients 12 years and older with haemophilia B (congenital factor IX deficiency);*
>
> *Peri-operative management in patients 12 years and older with haemophilia B.*

The dosage and duration of the substitution therapy depend on the severity of the FIX deficiency, the location and extent of bleeding, and the patient's clinical condition, age and pharmacokinetic (PK) parameters of FIX, such as incremental recovery (IR) and half-life.

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

Number of FIX IU required = Body weight (kg) x Desired FIX x Reciprocal of observed recovery (dL/kg)

[3] Hardwidge, E.A. et al. 1984. Validation of Filtration Processes Used for Sterilization of Liquids. Journal of Pharmaceutical Science and Technology. Vol. 38, No. 1:37-43

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

Table 3: Guide to dosing in bleeding episodes and surgery

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

The PI document states that 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) is 40 to 60 IU/kg twice weekly. A maximum of 75 IU/kg for prophylactic treatment was used in the clinical trials (Clinical Overview). The maximum human dose of Rixubis for bleeding episodes or surgical prophylaxis is anticipated to be 150 IU/kg (stated in clinical Study 250901).

Chemistry and formulation

Rixubis, nonacog gamma, is a glycoprotein consisting of 415 amino acids in a single polypeptide chain, with an approximate molecular mass of 55,000 Da. The primary amino acid sequence of Rixubis is identical to the Ala-148 allelic form of plasma-derived FIX, and is intended to have structural and functional characteristics similar to those of endogenous FIX.

Rixubis is expressed in, synthesised and secreted by genetically engineered mammalian cells derived from CHO cell line. Some post-translational modifications of Rixubis are different from those of the plasma-derived FIX molecule, but the physicochemical properties are intended to be comparable to that of a currently registered rFIX product, BeneFIX.

The manufacture of Rixubis is differentiated from the manufacture of the rFIX in BeneFIX by the inclusion of two independent viral inactivation/reduction steps, that is, solvent/detergent (S/D) treatment and nanofiltration.

Rixubis is formulated as a sterile, nonpyrogenic, lyophilised powder preparation. Rixubis is intended for intravenous (IV) injection, and is available in single-use vials containing the labelled amount of FIX activity, expressed in International Units (IU). Each vial contains nominally 250, 500, 1000, 2000, or 3000 IU of coagulation FIX (recombinant). The data submitted are intended to support all five potencies of Rixubis. There are no novel excipients.

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

Relationship to other drugs

A plasma-derived human FIX is currently registered under the trade name MonoFIX-VF and a recombinant human FIX product (nonacog alfa [rch]) is also registered under the name BeneFIX. Both MonoFIX and BeneFIX are indicated for the treatment and prevention of haemorrhagic episodes in patients with haemophilia B. Rixubis has the same polypeptide sequence to nonacog alfa in BeneFIX, and is intended to be sufficiently similar in physicochemical properties such that the safety and efficacy of the products are considered to be comparable. The manufacture of Rixubis is differentiated from the manufacture of the rFIX in BeneFIX by the inclusion of two independent viral inactivation/reduction steps, that is, solvent/detergent (S/D) treatment and nanofiltration.

According to the Nonclinical Overview, the sponsor's nonclinical testing strategy is based on the assumption that Rixubis will not differ significantly from the licensed, rFIX drug product BeneFIX regarding safety and efficacy. This is based on the comparative safety pharmacology, PK, immunogenicity and toxicology studies submitted, and in the following information from the Nonclinical Overview:

- Physicochemical characterisation studies demonstrate that the structure, identity, purity, potency, and functional integrity of Baxter's rFIX are comparable to those of a licensed, rFIX product.
- The polypeptide sequence of Baxter's rFIX is identical to that of a licensed, rFIX product and the post‑translational modifications are comparable.
- The purity and specific activity (in units of clotting activity per mg of total protein) of Baxter's rFIX are within the same range as found for a licensed, rFIX product.

Scope of nonclinical data

The data comprised studies on the pharmacodynamics (PD), PK, safety pharmacology, single and repeat-dose toxicity, local tolerance and immunogenicity of Rixubis. All studies used BeneFIX as a comparator.

Pharmacology

Primary pharmacology

Rixubis dose-dependently shortened the activated partial prothrombin time (APTT) of human, cynomolgus monkey and rat plasma, at concentrations of between 1 and 10 IU/mL.

Administration of Rixubis before the onset of bleeding caused effective haemostasis in three FIX knockout mouse models. Dose-dependent haemostatic effect was demonstrated with doses of ≥ 10 IU/kg in the thrombelastography model (decreased clotting time), ≥ 25 IU/kg in the tail-tip bleeding, and ≥ 75 IU/kg in the carotid occlusion model. The primary PD effects of Rixubis in these studies were similar to those of BeneFIX (approved rFIX) and Mononine (plasma derived FIX).

No primary pharmacology studies in which Rixubis was administered after the beginning of a bleeding episode were submitted. Therefore, only part of the clinical indications (that is, prophylaxis) is supported by the nonclinical data.

Safety pharmacology

No studies were submitted relating to the assessment of coagulation, agglutination or haemolysis in human whole blood.

Rixubis was not thrombogenic in the rabbit stasis model at a dose of 750 IU/kg (ten times the maximum dose of 75 IU/kg used in Clinical trials described in the PI document). The Wessler scores for Rixubis were similar to those obtained for Mononine (licensed, plasma derived FIX product) but lower than those of BeneFIX (licensed, rFIX product). Spiking of FIXa into Rixubis in the amounts present in BeneFIX resulted in Wessler scores similar to those obtained with Rixubis, demonstrating a correlation between the FIXa content of the products and the Wessler scores obtained.

FIXa is an impurity in the drug product and has been associated with thrombogenicity[4]. The pharmacological action of Rixubis does not seem to be affected by the lower amount of FIXa, since the PD studies in transgenic mice showed no significant differences between Rixubis and BeneFIX.

Since presumably lower amounts of FIXa did not cause significant differences in PD parameters in transgenic mice (efficacy) and did not cause an increase in toxicity in repeat dose toxicity studies in rats and monkeys at approximately three and approximately 15 times the exposure in humans respectively (safety), the lower amount of FIXa in Rixubis compared with BeneFIX is not expected to impact on the comparability of Rixubis and BeneFIX.

In monkeys, no adverse effects on the respiratory and cardiovascular systems were observed with doses up to 450 IU/kg, six times the maximum anticipated human prophylactic dose of 75 IU/kg.

Thrombus formation, cardiovascular, or respiratory effects are not expected to be a safety concern for the clinical use of Rixubis in patients treated at the maximum anticipated human prophylactic dose of 75 IU/kg.

Pharmacokinetics

In FIX deficient mice, the FIX activity assays and the Enzyme-linked immunosorbent assay (ELISA) specifically measured human FIX. In rat plasma the FIX ELISA also specifically measured the human protein whereas in cynomolgus monkey plasma both assays (activity and antigen) measured the sum of endogenous FIX and human FIX.

Following a single intravenous bolus injection of Rixubis in FIX knockout mice, normal rats and cynomolgus monkeys, the PK profiles of FIX protein and activity were assessed, and compared with recombinant (BeneFIX) and plasma derived (Mononine) FIX drug products (in the monkey comparison, only the recombinant product was used). The formulation used in the PK studies submitted was identical with the formulation used in all pharmacology and toxicology studies.

The toxicokinetic parameters of Rixubis and BeneFIX following IV administration were compared in single-dose studies in rats, monkeys and haemophilic mice, and in four-week studies in rats and monkeys. AUC values for Rixubis and BeneFIX were generally dose-proportional in all the species analysed. Terminal half-lives were longer in monkeys (10 to 12 hours) than in rats (three to four hours) and haemophilic mice (four to 11 hours), for Rixubis, BeneFIX and Mononine. The half-life was longer in humans (27 hours), for both Rixubis and BeneFIX.

[4] Kingdon et al. 1975. Thrombos. Diathes. Haemorrh. (Stuttg.) 33:617-631

The submitted studies were adequate for the characterisation of Rixubis PK parameters. A similar PK profile was observed for Rixubis and BeneFIX in the species tested with no differences between sexes in either species.

Toxicology

Acute toxicity

In single-dose toxicity studies, mice and cynomolgus monkeys showed no signs of toxicity at the highest single intravenous dose tested (no observable adverse event level (NOAEL) of 7500 IU/kg for mice and 750 IU/kg for monkeys). The single-dose 'safety margin' at the NOAEL is therefore 100 and 10 for mice and monkeys, respectively, compared with the recommended prophylactic single dose for humans (75 IU/kg). Although the observation period in the monkey study was short (six days), this is not expected to affect the ability to assess the toxicity of Rixubis (ICH M3(R2)).

Repeat-dose toxicity

Three 4-week repeat dose IV studies in rats and monkeys were conducted. These studies were GLP compliant, and used the proposed clinical route (IV). The animals used in these studies contained endogenous FIX.

The doses chosen were not high enough to reveal a minimum lethal dose. Since 7500 IU/kg had not caused drug-related mortalities in the single dose toxicity study in mice, and 750 IU/kg had not caused adverse reactions in monkeys, higher doses could have been used in the repeat dose toxicity studies. The doses did not provide direct evidence of pharmacological action (increased coagulation), or any toxic effect. The PD effects of Rixubis could be observed indirectly by the increase in coagulation times in animals which had developed neutralising antibodies against FIX, suggesting that Rixubis in fact is homologous enough to endogenous FIX to cause antibody cross-neutralisation.

Dosing in all the animal studies was every other day (approximately 3.5 times a week), whereas the proposed clinical dosing regimen is two times per week. The duration of dosing in patients will depend on a number of factors, such as the severity of the FIX deficiency, the location and extent of bleeding, the patient's clinical condition, and age. The duration of the animal studies was short but was limited by the development of antibodies.

Small findings observed in repeat-dose toxicity studies in rats and monkeys were not considered to be of toxicological relevance (including the coagulation system), as they appeared in single animals only, did not correlate with clinical pathology or pathology findings, were not consistent between species or over time, were within the range of absolute values of control treated animals, or were not dose dependent. A comparable safety profile to the licensed, rFIX product was observed for Rixubis at similar doses in the single dose toxicity studies in mice and cynomolgus monkeys, and in repeated dose toxicity studies in rats and cynomolgus monkeys.

When the animals were given repeated doses (every other day) of Rixubis and BeneFIX IV, no toxic effects were observed in rats or monkeys at exposures three to 16 times higher than those observed in humans at the maximum prophylactic clinical dose (75 IU/kg). Higher doses are possible (for example, for bleeding episodes or surgical prophylaxis), therefore for this situation, the relative exposure would be expected to be lower.

Given that the results from the rat and monkey repeated dose toxicity studies suggest some margin of safety, and given that the only observed toxicities were presumably due to the development of neutralising antibodies, and that exposures and antibody development

were comparable between Rixubis and BeneFIX, it seems reasonable to conclude that the toxicity profile of Rixubis after repeated dose administration is comparable to BeneFIX.

Relative exposure

Exposure levels (AUC-based) of Rixubis and BeneFIX in the submitted repeat dose toxicity studies were compared with exposure data for both products in patients with haemophilia B in comparative clinical trials at 75 IU/kg IV. Obviously, relative exposure ratios would be lower for higher clinical doses of Rixubis.

Exposure ratios have been calculated based on animal:human weekly exposure (this value was obtained by extrapolation from $AUC_{0\text{-}48h}$ in rats and monkeys, and $AUC_{0\text{-}72h}$ in humans). The level of exposure in the repeat-dose toxicity studies was moderate to high (three to 16-fold).

Table 4: Relative exposure in repeat-dose toxicity studies

Species	Study duration	Dose (IU/kg) IV	AUC (weekly)a (IU.h/mL)		Exposure ratio#	
			Males	Females	Males	Females
Rat (SD)	1 month	200 (rFIX)	29	25	1.5	1.2
		200	22	22	1.0	1.0
		750	77	58	3.6	2.7
Monkey (Cynomolgus)	1 month	200 (rFIX)	63	69	3.1	3.4
		200	107	63	5.0	3.0
		750	340	280	15.9	13.1
Human (non bleeding male patients with Haemophilia B)	Single infusion of Rixubis	75 IU/kg	21		–	
	Single infusion of BeneFIX	75 IU/kg	20		–	

= animal:human plasma AUC; a = since rats and monkeys were dosed every 2 days, and clinical dosing regime is twice weekly, AUCt-last in animals was converted to AUC(weekly) by multiplying the value by 3.5, and AUC0-72h in humans was converted to AUC(weekly) by multiplying the value by 2.

Genotoxicity

No genotoxicity studies were conducted. This is considered acceptable and in accordance with the relevant EMA/ICH guideline (CHMP/ICH/299/95; ICH S6 (R1)), which states that the range and type of genotoxicity studies routinely conducted for pharmaceuticals are not applicable to biotechnology-derived pharmaceuticals and therefore are not needed. Nevertheless, recombinant coagulation FIX has been shown to be nonmutagenic in the Ames assay and nonclastogenic in a chromosomal aberrations assay (PI document for BeneFIX).

Carcinogenicity

No carcinogenicity studies were conducted. This is considered acceptable and in accordance with the relevant EMA/ICH guideline (CHMP/ICH/299/95; ICH S6 (R1)), which states that standard carcinogenicity bioassays are generally inappropriate for biotechnology-derived pharmaceuticals.

Reproductive toxicity

The absence of reproductive and developmental toxicity studies is acceptable given that Rixubis is only intended for physiological replacement of normal FIX activity and that haemophilia B is an X chromosome-linked recessive disorder that occurs almost exclusively in males. Changes have been suggested in the PI document to acknowledge the lack of animal reproductive toxicity studies.

Pregnancy classification

Animal reproduction studies have not been conducted with Rixubis. Coagulation factors derived from human plasma are exempt from pregnancy categorisation. However, rFIX is classified as pregnancy category B2 drugs. The proposed B2 category is acceptable.

Local tolerance

There were no injection site reactions following IV injection in the repeat-dose toxicity studies in monkeys (at 363.5 IU/mL) and rats (at 40 to 150 IU/mL), or in a specialised local tolerance study in rabbits (at 730 IU/mL compared with the maximum clinical concentration of 600 IU/mL).

The local toxicity of Rixubis was examined following administration of a single paravenous (PV) or intra-arterial (IA) dose to rabbits, in order to investigate misdosing scenarios. IA administration of 5 mL/animal of either control buffer (0 IU), or Rixubis (3650 IU/animal; 730 IU/mL) was well-tolerated in rabbits, with no irritation for 72 hours post-dose.

Incidences of histopathology findings (inflammatory reaction and livid discoloration) were observed in rabbits treated with 0.5 mL/animal of Rixubis or BeneFIX (and not in buffer-treated animals) by the PV route. The incidence of findings was similar for Rixubis and BeneFIX. Thus, the local tolerance profile of Rixubis was similar to BeneFIX following IV or PV dosing, and local reactions following IV dosing are expected to be minimal. Paravenous administration should be avoided.

Development of antibodies

Immunogenicity was evaluated as part of the general toxicity studies in rats and monkeys and in a dedicated immunogenicity study in mice. Rixubis and BeneFIX were immunogenic with binding antibodies found in mice, rats, and monkeys, after repeated administration. Neutralising antibodies were observed in one monkey in one study (Study 1933-012), and this resulted in a transient increase of APTT and fibrinogen. Neutralising antibodies were not found in rats and were not evaluated in mice. In mice, no antibodies were detected against host cell (CHO) proteins. The serum concentration of FIX was not decreased after repeated administration of Rixubis or BeneFIX in rats or monkeys.

The development of antibodies in the nonclinical species was not different between Rixubis and BeneFIX, did not give rise to any observable immunological reactions or effects, and is not expected to compromise the safety assessment of Rixubis.

Antibody development may occur in humans, but the frequency with which this might happen can only be ascertained from clinical studies.

Excipients

No signs of toxicity which can be attributed to the excipients were observed in any of the studies at the maximum doses tested.

Comments on the safety specification of the risk management plan

Results and conclusions drawn from the nonclinical program for Rixubis detailed in the sponsor's draft Risk Management Plan (RMP) are in general concordance with those of the nonclinical evaluator.

Nonclinical summary and conclusions

- Baxter Healthcare Pty Ltd has applied to register a new biosimilar product, Rixubis, containing nonacog gamma (a recombinant human FIX (rhFIX) glycoprotein) as the active substance. The product is indicated for routine prophylaxis of bleeding episodes in patients 12 years and older with haemophilia B, treatment and prevention of bleeding episodes in patients 12 years and older with haemophilia B (congenital FIX deficiency), and peri-operative management in patients 12 years and older with haemophilia B. The indications are similar to those of BeneFIX, the reference product.
- The Sponsor has conducted generally adequate studies on the pharmacology, PK and toxicity of Rixubis, according to the relevant guidelines.
- The PD properties of Rixubis and BeneFIX were similar in mouse models of haemophilia B, treated with the agents prophylactically, at doses between 10 and 75 IU/kg. There were no significant differences in the reduction of bleeding times, time to artery occlusion and blood loss between the two products. No nonclinical studies in which Rixubis was administered after the beginning of a bleeding episode were submitted. Therefore, only part of the clinical indications (that is, prophylaxis) is supported by nonclinical data.
- The sponsor used three animal models to investigate the kinetics and toxicity of Rixubis: mice, cynomolgus monkeys and rats. There were no significant differences in the plasma kinetics between Rixubis and the approved rFIX, BeneFIX.
- In rabbits, Rixubis showed lower thrombogenic activity than BeneFIX, with no evidence of thrombi development. No adverse effects of Rixubis in behaviour, body temperature, cardiovascular or respiratory parameters were observed in safety pharmacology studies in monkeys.
- In acute toxicity studies by the IV route, no drug-related mortality was observed at up to 7500 IU/kg in mice and 750 IU/kg in monkeys. One four-week repeat dose IV study in rats and two in monkeys revealed no remarkable findings and no mortalities, at similar exposures of either Rixubis or BeneFIX. Overall, no clinically-relevant toxicities were seen.
- There was no difference in the immunogenicity of the two products, based on formation of anti-FIX antibodies in mice, rats and monkeys. No antibodies were detected against host cell (CHO) proteins in mice.
- Rixubis and BeneFIX treatment by the IV, PV, and IA routes resulted in similar toxicity profiles in rabbits.
- Secondary pharmacology, genotoxicity, carcinogenicity and reproductive toxicity studies were not conducted, which was considered acceptable for this biosimilar product.

- The similarity of Rixubis or BeneFIX has been adequately demonstrated in nonclinical studies, and there are, therefore, no nonclinical objections to the registration of Rixubis. The PI should be amended.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Clinical rationale

The submission to develop a safer and effective replacement product to treat haemophilia B is an acceptable rationale.

Contents of the clinical dossier

The clinical dosser documented a full clinical development program of pharmacology, efficacy and safety studies except for biopharmaceutical studies that were modified.

The submission contained the following clinical information:

- The PK of Factor VIII (FVIII) and FIX concentrates are generally accepted as a surrogate for haemostatic efficacy. Kinetics of Rixubis after a single dose, and after at least 30 EDs were evaluated in the completed pivotal Phase I/III Study 250901. In the ongoing Phase III surgery Study 251002, pre-surgical PK parameters were assessed only in subjects undergoing major elective surgery who did not undergo PK assessment in Study 250901.
- No population PK (PopPK) analyses were submitted.
- The pivotal study was Study 250901, a Phase I/III prospective, controlled, multicentre study evaluating PK, efficacy, safety, and immunogenicity in PTPs with severe (FIX level < 1%) or moderately severe (FIX level 1 to 2%) Haemophilia B.
- Dose-finding studies were not done. The dose was determined. The selection of dose regimens in this study is based on pre-clinical PK, PD, single and repeated dose in vivo toxicity studies, as well as the standard human clinical dose for BeneFIX, the only other rFIX in clinical use, and on regulatory agency guidelines.
- Study 251002 was a Phase III, prospective, multicentre study evaluating efficacy and safety in PTPs with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) haemophilia B undergoing surgical or other invasive procedures.
- An Integrated Analysis of Safety (ISS) for Rixubis was provided in which the safety of Rixubis was integrated across the complete and ongoing studies in terms of adverse events (AEs), and the risk of developing FIX inhibitors in PTPs assessed.

Paediatric data

The submission did not include paediatric data. The proposed indications exclude children under 12 years of age. A trial in children (Study 251101) is ongoing.

Good clinical practice

In both studies, the study protocol, informed consent form, and all amendments were reviewed and approved by the Independent Ethics Committee (IEC) of each participating

institution. The study was conducted in accordance with the Study Protocol, the International Conference on Harmonisation Guideline for Good Clinical Practice E6 (ICH GCP, April 1996), Title 21 of the US Code of Federal Regulations (US CFR), the European Clinical Trial Directive (2001/20/EC and 2005/28/EC), and applicable national and local regulatory requirements. Written informed consent was obtained from each patient and/or their legally authorised representative before entering into the study according to applicable regulatory requirements and ICH GCP.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 5 shows the studies relating to each PK topic.

Table 5: Submitted PK studies

PK topic	Subtopic		Study ID
PK in healthy adults	General PK	Single dose	NA
		Multi dose	NA
	Bioequivalence†	Single dose	NA
		Multi-dose	NA
	Food effect		NA
PK in special populations	Target population §	Single dose	Study 250901
		Single dose	Study 251002
	Hepatic impairment		NA
	Renal impairment		NA
	Neonates/infants/children < 12 years		NA
	Elderly		NA
Genetic/gender-related PK	Males versus females		NA
PK interactions			NA
Population PK analyses	Healthy subjects		
	Target population		
	Other		

* Indicates the primary aim of the study.
† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the PK studies had deficiencies that excluded their results from consideration.

Evaluator's overall conclusions on pharmacokinetics

The clinical evaluator's conclusions are that in the pivotal Study 250901:

- PK equivalence of Rixubis and the commercially available rFIX was confirmed.
- The PK parameters analysed for Rixubis and the commercial rFIX (IR, C_{max}, half-life, mean residence time (MRT), CL and volume of distribution at steady state (Vss)) were comparable.
- Repeated in vivo recovery testing for up to 26 weeks demonstrated that the mean incremental FIX recovery was consistent over time.
- Rixubis half-life remained constant in Part 3.
- The comparison of Rixubis pilot product used in Part 1 and Rixubis commercial product used in Part 3 (Part 1/Part 3 ratio) showed that higher AUC, IR and C_{max} values were observed with the commercial product. The Part 1/Part 3-ratio of MRT, half-life and CL demonstrates very similar values for both pilot and commercial products.

For Surgery Study 251002:

- Pre-surgical PK parameters ($AUC_{0\text{-}72\ h}$/dose, $AUC_{0\text{-}inf}$/dose, C_{max}, and IR at 30 minutes) calculated for seven subjects in the full analysis set (FAS), were higher than those in the pivotal study, while the values for MRT, CL, T½and Vss were lower.
- Although a comparative study that was properly powered may have shown these differences to be statistically significant, they are unlikely to be clinically significant.

Pharmacodynamics

The PD characteristics of rFIX are intrinsic to its therapeutic action and are measured by the FIX activity after administration. These measurements also form the PK and efficacy properties of the compound.

Efficacy

Prophylaxis, treatment and prevention of bleeding episodes in patients 12 years and older with haemophilia B.

Pivotal efficacy study - Study 250901

Study 250901 was a Phase I/III prospective, controlled, multicentre study evaluating the PK, efficacy, safety, and immunogenicity of rFIX (Rixubis) in PTPs with severe or moderately severe haemophilia B. The study began on 29 July 2011 and finished on 3 May 2012.

Subjects were enrolled at investigative sites in 14 countries. No adjustments for race or ethnic factors have been planned as there is no evidence that the effect of FIX products is affected by differences in race or ethnicity.

The study was in three parts each of which had a different design.

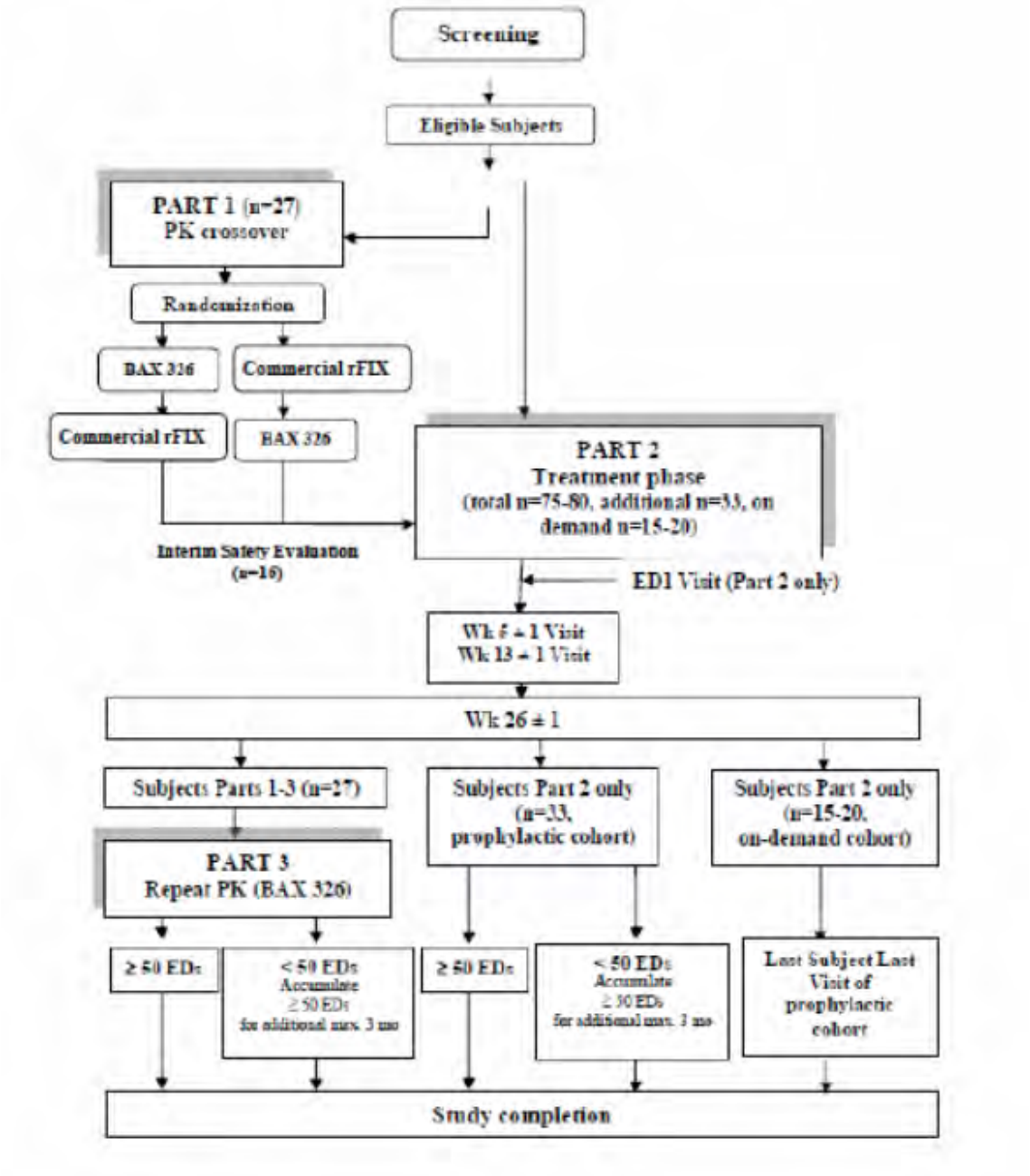
- Part 1 was a PK study.
- Part 2 was an open-label, uncontrolled study of the haemostatic efficacy, safety, immunogenicity and Health Related Quality of Life (HR QoL) of Rixubis over six

months with twice weekly prophylactic infusions with Rixubis or at least 50 exposure days (EDs) to Rixubis, whichever occurred last, in 60 subjects in order to have 50 evaluable subjects (prophylactic cohort).

- Part 3 was an open-label, uncontrolled repeat PK study with Rixubis (single dose of 75 ± 5 IU/kg) in the subjects who participated in Part 1 and had been treated for 26 ± one weeks in Part 2, having accumulated at least 30 EDs to Rixubis. Thrombotic markers were also assessed at specified time points.

The three parts are, however, connected as shown in Figure 2.

Figure 2: Design of Pivotal Study 250901



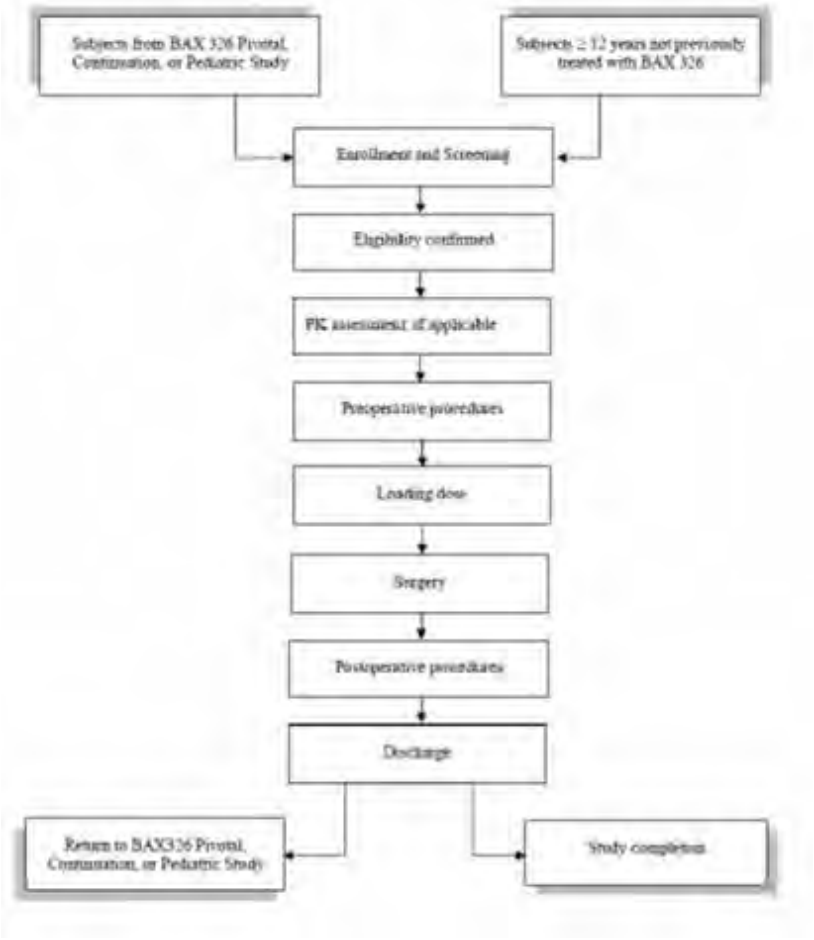
Surgery study 251002

Study 251002 was a Phase III, prospective, open-label, uncontrolled, multicentre study designed to evaluate the haemostatic efficacy and safety of Rixubis in approximately 30 subjects with severe or moderately severe haemophilia B undergoing major and minor

surgical, dental or other invasive procedures. The overall study design is illustrated in Figure 3.

The objectives of the study were to evaluate the haemostatic efficacy and safety of Rixubis in the peri- and postoperative setting. The study was carried out at five centres, began on 19 December, 2011 and is ongoing (anticipated duration three years). This interim analysis was based on the complete data of 14 subjects. Data cut-off was performed after 13 surgeries, of which ten were major surgeries, had been completed per protocol.

Figure 3: Design of Study 251002



Evaluator's summary and overall conclusions on efficacy

Pivotal study 250901

The pivotal study of prophylactic and on-demand treatment with Rixubis showed the median annualised bleeding rate (ABR) per patient was 27 in the on-demand group, and two in the prophylactic group, although no direct comparison could be made. Nevertheless the efficacy of prophylactic treatment in reducing the ABR compared to treatment on-demand was demonstrated. The efficacy was similar to that reported in the PI of a commercially available rFIX (BeneFIX) in Australia.

In the prophylaxis group, 30% of bleeding events (BEs) required more than three infusions, compared to only 1.5% of BEs in the on-demand group. The data showed the total dose per bleed in the prophylaxis group was twice that in the on-demand group. This was also shown for the total consumption of Rixubis/kg/month. Higher doses than the overall mean were needed for non-joint bleeds and for bleeds caused by injury. Dosage of FIX was increased more for major bleeds than for minor bleeds.

It follows that Rixubis is effective as prophylactic treatment to reduce the frequency of BEs, and to treat them when they occur. Prophylactic treatment required twice the amount of Rixubis to achieve this result. No conclusions could be drawn from the QoL assessments that were underpowered. Patients were not asked in QoL assessments whether they preferred prophylactic to on-demand treatment.

Surgical study 251002

The study showed that for major surgery in six of 11 patients treated with Rixubis, the treatment was effective in reducing intraoperative blood loss to an amount predicted for the average blood loss of a healthy matched individual. In two cases the loss was less and in two cases equal to the maximum predicted.

However in four of seven subjects, who all had major surgery with a drain placed, postoperative blood loss exceeded the maximum predicted blood loss. In these cases, the patients' FIX levels were suboptimal (34% to 81%) after FIX treatment.

Ratings for homeostatic efficacy were done by the operating surgeons, and so had the problem of potential bias. All intraoperative assessments were 'excellent' as were 50% of those at drain removal. At hospital discharge, in the FAS, 78.6% (11 of 14) of ratings were 'excellent'.

The difficulty in recruiting for and conducting this type of study is acknowledged as well as the fact that the number of subjects and surgical procedures complied with the requirements of the CPMP Guidelines (at least five patients undergoing ten surgical procedures). However problems with the study were as follows:

1. The numbers of patients who had major surgery (n=11) and minor surgery (n=5) were small, given the intention had been to recruit a total of 30 subjects. This report is an interim analysis, but no clear reason is given for not waiting to complete the study.
2. The PK properties of Rixubis in seven patients studied differed from those in other patients in the pivotal study and no statistical comparison could be done. This may relate to the failure to obtain adequate FIX levels in patients in the post-operative period although a specified protocol was followed.
3. The postoperative blood loss at drain removal exceeded the maximum predicted in four of seven subjects who had major surgery.
4. The surgery called 'major' included two cases of abdominal surgery, each for herniorraphy. This abdominal surgery does not compare to abdominal surgery such as liver transplantation or splenectomy for risk of blood loss, the latter two having been part of the assessment of a commercial rFIX product (BeneFIX) and reported in the PI for that product. As well one case of dental extraction was classed as major surgery and two other cases as minor.
5. All assessments of homeostatic efficacy were by the operating surgeon, so that bias was possible, although again this was according to recommendations of the CPMP Guidelines.

The clinical evaluator concluded that the efficacy results of the interim analysis of the surgical study need to be treated with caution and that the study should be completed and final results analysed to confirm those of the interim analysis.

Safety

Because the clinical studies were similar in terms of Rixubis product, dosage and safety assessments, the safety data provided is combined and evaluated from the ISS, with reference to the individual study reports where indicated. The patient population is homogeneous except for the one paediatric study, and the requested indication does not

include this paediatric population. A safety issue that would occur in this population and not in the adult population seems unlikely so the safety assessments have been combined.

Studies providing evaluable safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies 250901 and 251002

In the pivotal efficacy studies, the following safety data were collected:

- general AEs were assessed by the investigator for seriousness, severity and causal relationship to investigational product (IP) exposure as defined in the protocol. For each AE, the outcome (that is, recovering/resolving, recovered/resolved, recovered/resolved with sequelae, not recovered/not resolved, fatal) and action taken (that is, dose increased, dose not changed, dose reduced, drug interrupted, drug withdrawn) was also to be recorded on the AE electronic case report form (eCRF).

Recovering/resolving AEs were to be followed until resolution, medically stabilised, or 30 days after the study completion/termination visit, whichever came first.

Pivotal studies that assessed safety as a primary outcome

Not applicable.

Dose-response and non-pivotal efficacy studies

Not applicable.

Other studies evaluable for safety only

Continuation Study 251001: This ongoing continuation study was a prospective, open-label, multicentre, uncontrolled, Phase III study in up to 100 PTPs with severe (FIX level < 1%) or moderately severe (FIX level 1-2%) haemophilia B, who had completed the Pivotal Study 250901 or the Paediatric Study 251101. Sixty four (64) subjects who completed the Pivotal Study 250901 were available for safety assessment only.

Pivotal studies that assessed safety as a primary outcome

Not applicable.

Patient exposure

In estimating drug exposure, one exposure day was defined as a calendar day (12:00 am to 11:59 pm) during which a subject received IP, regardless of the number of infusions or amount of product given during the day.

The number of subjects infused, number of infusions, total units administered, and total EDs according to study event (prophylaxis, treatment of bleeding episodes, PK assessments, prophylaxis, peri- and postoperative homeostatic management, or other, and all study events) were calculated overall and for each age group. The median, minimum, and maximum per-subject values were determined for each of these parameters.

Subjects participated in the Rixubis clinical program for a median of 13.11 months (range: 1.31 to 25.23 months). Subjects were treated with Rixubis for a median of 83 EDs (range: 3 to 209 EDs), with a median number of infusions of 85 (range: 3 to 212 infusions), and median consumption of Rixubis of 4653.0 IU/kg (range: 169 to 13496 IU/kg).

The 91 treated subjects received a total of 27,836,871 IU of Rixubis in 7353 infusions, including:

- 20,813,743 IU administered in 5716 infusions for prophylaxis
- 3,238,856 IU administered in 882 infusions for bleeding episodes
- 2,260,888 IU administered in 440 infusions for PK analysis
- 200,294 IU administered in 30 infusions for peri- and post-operative homeostatic management
- 1,323,090 IU administered in 285 infusions for 'other' reasons.

The median EDs of 83 and the median number of infusions (85) are small compared to those that would be received in a lifetime of treatment, and very small in the paediatric group. It should be remembered therefore that any AEs events detected in these studies would be those occurring in the short term. Longer term monitoring is recommended.

Deaths and other serious adverse events

There were no deaths. Two subjects were withdrawn due to an unrelated SAE requiring emergency treatment with another FIX product rendering them ineligible for continuation of the Rixubis study.

While eight SAEs are described in narratives in the Pivotal 250901 CSR, only the five SAEs, which occurred in four subjects during or after exposure to IP and within the cut-off date, were included in this integrated analysis. An additional SAE occurred in one subject in Continuation Study 251001, resulting in a total of six SAEs reported in five (5.5%) subjects. The six SAEs were as follows:

- Duodenal ulcer haemorrhage: one SAE in one subject (severe)
- Intestinal Obstruction: one SAE in one subject (severe)
- Cervical vertebral fracture: one SAE in one subject (severe)
- Traumatic haematoma: one SAE in one subject (severe)
- Convulsion: one SAE in one subject (moderate)
- Hepatitis B core antibody positive: one SAE in one subject (mild)

Four SAEs in three (3.3%) subjects were severe. One moderate SAE was reported in one (1.1%) subject and one mild SAE was reported in one (1.1%) subject. No SAEs were judged by the investigator or the sponsor to be possibly or probably related to Rixubis.

One SAE of convulsion, considered unrelated to IP, was also categorised as a temporally-associated AE (see comments, below).

Comment: The SAEs reported in all studies require further evaluation.

Evaluator's overall conclusions on clinical safety

1. The safety of the pilot material and the commercial preparation were not assessed separately.
2. The number of patients assessed for safety was 91. The median number of EDs, 83 days, and the median number of infusions per patient in the program, 85 days, are small compared to those that would be received in a life-time of treatment, and very small in the paediatric group. It should be remembered therefore that any AEs detected in these studies would be those occurring in the short term. Longer term monitoring is recommended.

3. One hundred and sixty one (161) AEs occurred in 52.7% of patients, of which 155 were non-serious, and 117 of mild severity. Four non-serious AEs in three patients were related to Rixubis – dysgeusia (two events in one patient); pain in an extremity; and the development of rFurin antibodies.
4. Sixty-five (65) temporally-associated AEs (beginning during or within 24 hours of infusion regardless of causality) that occurred in 29 subjects (0.88%) included diarrhoea, pyrexia, gastroenteritis, nasopharyngitis, pharyngitis, procedural pain, abnormal immunological tests and headache.
5. No inhibitors to FIX, no treatment-related binding antibodies to FIX, and no antibodies to CHO proteins were detected in treated subjects. One subject developed a positive assay for rFurin (confirmed titre 1:80), considered to be not of clinical significance.
6. No thrombotic events or severe allergic reactions were reported in any subject in the integrated analysis.
7. There were no deaths. Eight SAEs were reported in all studies, of which six were relevant to the studies. Two SAEs (car accident, and suicide) were appropriately excluded. The six SAEs were considered not related to Rixubis treatment, and were a bleeding duodenal ulcer (severe); intestinal obstruction (severe); cervical vertebral fracture (severe); traumatic haematoma (severe); convulsion (moderate); and conversion to HepBcAb positive (mild).
8. A majority of patients had past infections with Hepatitis B or C or both and a large number had chronic hepatitis with one or both viruses. One clinically significant event of an abnormal alanine aminotransaminase occurred in a patient with chronic hepatitis B and C.
9. The product has not been marketed in any country so no PMR was available.

   Conclusion: The clinical evaluator agreed with the conclusion of the ISS that 'Taken together, the safety assessments utilised in this integrated analysis demonstrate safety and tolerability in subjects with severe or moderately severe haemophilia B', with the addition that safety data from longer term treatment with Rixubis should be provided when available.

First round benefit-risk assessment

First round assessment of benefits

- The first benefit of Rixubis is that it is effective treatment in reducing the frequency of spontaneous and injury-related bleeding when administered as routine prophylaxis in patients 12 years and in treating and preventing bleeding episodes in patients 12 years and older with severe or moderately severe haemophilia B (congenital FIX deficiency).
- A second benefit is that Rixubis is a recombinant product and so does not have the potential safety risks of viral transmission associated with plasma derived products.

A benefit of Rixubis in the peri-operative management of patients 12 years and older with severe or moderately severe haemophilia B seems likely, but the data provided in the interim analysis of the relevant study require confirmation from the results of the completed study before this benefit can be claimed with confidence.

First round assessment of risks

The risks of Rixubis in the proposed usage are those associated with FIX products:

- Thrombotic events - patients potentially at risk are those with signs of fibrinolysis, disseminated intravascular coagulation (DIC) or liver disease, and patients postoperatively or who are otherwise at risk of a thrombotic event or DIC.
- FIX Inhibitor Formation – FIX containing products have been associated with the development of activity-neutralising antibodies (inhibitors) in 1.5 to 3.0% of PTP with severe haemophilia B. As a consequence of FIX inhibitor development, minor and major bleeding cannot always be prevented or treated effectively, potentially resulting in increased morbidity and diminished quality of life.
- Allergic-type hypersensitivity reactions, including anaphylaxis, have been reported for all FIX products.

A correlation has been reported between the occurrence of a FIX inhibitor and allergic reactions. Fifty-one (58%) of the 88 FIX inhibitors reported to the international haemophilia B database in 2005 were associated with an allergic manifestation. There seems to be no difference in the frequency of allergic reactions or inhibitor development in individuals receiving rFIX compared with those receiving plasma derived FIX. A relationship may exist between the presence of major deletion mutations in a patient's FIX gene and an increased risk of inhibitor formation and of acute hypersensitivity reactions. Patients known to have major deletion mutations of the FIX gene should be observed closely for signs and symptoms of acute hypersensitivity reactions, particularly during the early phases of initial exposure to FIX products.

None of the above risks, thrombotic events, inhibitor formation, and hypersensitivity reactions, were observed in the studies submitted, nor were any significant product-related AEs reported.

Note**:** This risk assessment is based on the assumption that the sponsor's answers to questions and requests regarding the large number of major and minor protocol deviations are answered satisfactorily and do no indicate serious breaches of ethics, GCP and guidelines for patient safety (see Clinical Questions).

A remaining risk factor is that the above safety data are derived from relatively short term treatment, compared to a life-time of treatment in such patients. Therefore longer term safety data on the use of Rixubis is necessary.

First round assessment of benefit-risk balance

The benefit-risk balance of Rixubis for routine prophylaxis of bleeding episodes in patients 12 years and older with haemophilia B, and for the treatment and prevention of bleeding episodes in patients 12 years and older with haemophilia B (congenital FIX deficiency) is favourable.

The benefit-risk balance of Rixubis for peri-operative management in patients 12 years and older with haemophilia B is unfavourable, but would become favourable if the Surgical Study 251002 were completed and the data supports that of the interim analysis.

First round recommendation regarding authorisation

Subject to an acceptable response to the Clinical Questions put to the sponsor the clinical evaluator recommends that Rixubis be approved for:

- Routine prophylaxis of bleeding episodes in patients 12 years and older with haemophilia B and
- Treatment and prevention of bleeding episodes in patients 12 years and older with haemophilia B (congenital FIX deficiency)

The clinical evaluator does not recommend approval of Rixubis for peri-operative management of patients 12 years and older with haemophilia B until the Surgical Study 251002 is completed and the results evaluated and confirm those of the interim analysis.

List of questions

Protocol deviations

The large numbers and types of major and minor protocol deviations in the pivotal study have resulted in a number of questions and requests to the sponsor and will require an acceptable response before any approval of the requested indications can be made.

Safety

Does the presence of FIX antigen in a subject's blood interfere with the measurement of FIX activity or on the detection of inhibitor antibodies to FIX?

Second round evaluation of clinical data submitted in response to questions

Protocol deviations

The large numbers and types of major and minor protocol deviations in the pivotal study resulted in a number of questions and requests to the sponsor. The questions and the clinical evaluator's assessment of the sponsor's response follow.

Question 1

General

1. Please explain and justify the large number of minor and major protocol deviations that occurred in the pivotal trial.

Sponsor's Response: The sponsor described the Protocol Deviation Plan (PDP) used in the pivotal study and the oversight of the protocol deviations twice a year by an independent Data Management Committee (DMC). Documentation was provided of the DMC's meetings and decision to continue the study without change.

> Comment: The PDP described and defined major and minor deviations in detail but did not include procedures to manage these if the number seemed excessive in number or severity (major). This decision was left presumably to the DMC. This body only met twice a year and was provided at each meeting with the list of protocol deviations to that date. In all cases, no action was taken in relation to the large number of protocol deviations reported, especially in the early stages of the study. The conclusion then is that the PDP and the DMC failed to raise concerns about the large number of protocol deviations that were occurring.

To explain and justify the large number of protocol deviations, the sponsor made three points:

- Baxter's approach to report protocol deviations at the subject level, not at the site level, leading to a higher number of protocol deviations.

> Comment: The point made is not clear to this evaluator. If 10 protocol deviations were reported from one site, was that less worrying than 10 individual subject reports from that site?

- Baxter's approach to list several protocol deviations separately although they relate to the same event: for example, when a site infused a wrong (out of range) dose for PK or IR and used two different lots, two separate protocol deviations were reported, although it affected a single event/infusion only. This has also contributed to the higher number of protocol deviations.

  Comment: The effect of such double reporting on the number of protocol deviations cannot be assessed without knowing the number of such cases. This information was not provided.

- Limited number of subjects per site, thus the experience of the investigator is limited and this contributes to the higher number of reported protocol deviations that would not be otherwise observed, if the investigator could gain experience with many more subjects available.

  Comment: This reason was supported by later data such as the higher occurrence rate of protocol deviations early in the study and by the drop in reported protocol deviations after adequate instructions and training. While explaining the high numbers of protocol deviations, this does not excuse that number and the apparent lack of adequate training and preparation of the investigators before the trial began. The use of ill-prepared facilities for patient treatment, many in foreign countries from the USA, raises substantial ethical issues.

2. Given that the protocol clearly and correctly sets out the schedule and procedures for the trial, and states the method of recording, notifying and reporting protocol deviations, please explain whether the problem was with the investigators or the trial monitoring or both.

Sponsor's response: The sponsor noted the complexity of the treatment, the high number of laboratory assessments and subjects' assessments that contributed to the number of protocol deviations in the early period of the study. As well, the study design was that the patients self-administered the IP at home in the time between the study visits. During this home treatment phase, protocol deviations accumulated, before the site identified the protocol deviations and retrained the subject during the next interval study visit.

Comment: The reasons are acceptable as explanations of the high number of protocol deviations seen.

Question 2

Definitions of major and minor deviations:

This question related to two cases of apparent inconsistencies in classifying major and minor deviations.

Sponsor's response: In the first case, significant under-dosing occurred from the required IR dose, so this was a major protocol deviation whereas on the second occasion in the same patient the dose was recommended and not required and the administered dose only slightly lower and so classified a minor protocol deviation as defined. In the second case two major protocol deviations were reported for the same patient during the one infusion due to under-dosing and to the use of the wrong strength IP, each reported as a major protocol deviation.

Comment: The explanation is acceptable.

A related question was to review all deviations and identify similar contradictions and inconsistencies, for example where the events listed appear to be similar but have been classified differently.

Sponsor's response: Baxter reviewed data and found the following inconsistency:

· Subject under-dosing for prophylactic dosing erroneously classified as major deviation

No other inconsistencies were identified.

Question 3

Repeated major deviations:

Ten patients each had two or more major deviations, representing 14% of the total patient population, and 56% of all major deviations. Administration errors (major deviations) occurred repeatedly in some patients. Two patients had one error; eight had two errors each; one had three errors; and two had five errors each, all major deviations. It is disturbing that the same drug administration error occurred in the same patient repeatedly in some of these cases, and at the same study center in different patients (for example Site 06). Please explain how such repeated mistakes occurred and how these are compatible with compliance with GCP.

Sponsor's response (abridged): The sponsor responded that the majority of the repeated major deviations occurred at three sites, namely Site 06, Site 15, and Site 21. A summary of the occurrence of protocol deviations at each of the three sites was then given, with the subsequent action of the site monitor, who acted to correct the problem.

At Site 06, seven major protocol deviations occurred. At Site 15, seven major protocol deviations occurred. At Site 21, five major protocol deviations occurred. Three of them were related to the first three in-clinic infusions. For all other sites with patients with two or one major protocol deviations regarding IP administration, the CRAs identified the deviations and re-trained the sites accordingly. As a consequence no further IP administration deviations occurred after the Week 5 visits, except for a small number of patients where the protocol deviations occurred at the last study infusion due to sites not following protocol defined procedures and IP dose calculations.

At the three sites listed, the major protocol deviations occurred in most cases prior to the first visit of the site monitor on the fifth week of the trial. The sponsor's response states the 'Clinical Research Associate (CRA) re-trained the site on IP administration and from then on no major protocol deviations related to IP infusion occurred'.

> Comment: The response explains how multiple major protocol deviations occurred in the same patients at several sites. Appropriate GCP was followed after the problem was identified. However the criticism made above applies here, that prevention by adequate site training should have taken place instead of action post hoc. Prior assessment of the expertise and quality of care provided at these and other sites were initially inadequate and this may be regarded as a breach of GCP.

Question 4

Deviations that may have affected patient safety

In the following cases, the protocol deviation listed may have compromised patient safety even though the deviation has been listed in some cases as minor. Please provide for each case below the clinical state of the patient at the time of the deviation; the detailed description of that deviation; and why patient safety was not compromised.

There followed in this question a series of 16 patients, identified by number, with the information as given in the listing of protocol deviations in the report of the pivotal study. The issues involved can be grouped and summarised as follows:

Under-dosing and safety

In seven cases, the subjects were under-dosed because they were given the prophylactic dose of 40-60 IU/kg instead of the IR dose of 70-80 IU/kg required by the study design. As the prophylactic dose was still a safe dose, patient safety was not compromised.

In two cases at Site 18, under-dosing occurred because the study drug was not available for prophylactic treatment at that site from 16 until 25 January 2012. The former subject had one bleed during this time and was appropriately treated with Rixubis, but the source of this material was not stated. The second subject did not have any bleeding. This situation potentially compromised safety, as it is unclear how Rixubis could be available to treat bleeds if they occurred and yet not be available to the site, as stated.

In two cases, under-dosing occurred because of lack of subject compliance. In the first case, no bleeding occurred during the period of under-dosing. In the second case, the subject bled at a rate greater than expected for the prophylaxis group. However the prophylactic dose was only increased towards the end of the study (after 12 bleeding episodes) from initially approximately 49 IU/kg to 67 IU/kg with an average dose over the study of 52.8 IU/kg. In this case the subject's safety was compromised by the failure of adequate supervision and subsequent increase in treatment dosage.

In one case, the subject self-administered study drug every second day for eight days, contrary to protocol without adverse effects.

Mistakes in reporting and monitoring

One case of protocol deviation was reported in error and some mistakes were made in classification of minor protocol deviations as major. A case of misreporting by a site monitor was more serious and resulted in a delay in reporting that the study drug had been stored at a too high temperature. While potentially compromising safety, no AEs were reported.

Mistakes in obtaining informed patient consent

These two mistakes were satisfactorily explained by the sponsor.

> Summary and Comment: The only adverse safety outcome that resulted from the protocol deviations recorded was for one subject who suffered increased frequency of bleeds from inadequate prophylactic dosing associated with a delay in increasing the administered dose for prophylaxis. However a number of other subjects were put at risk of bleeding in such situations as lack of supply of the study drug, and under-dosing due to poor compliance that was not acted upon until late in the study. While the under-dosing because of mistakes in the IR and prophylactic dosing did not constitute a demonstrated safety risk, it does raise questions about adequate pre-trial assessment of the competence and experience of these sites in following a complex clinical trial protocol, and so gives a signal for more care in complying with GCP.

Question 5

Deviations that may have affected PK analyses

In two cases, the protocol deviation was misreported. In one case, different lot numbers of the study drug were used contrary to protocol, but no safety issue was involved. In a third case, less than the required five day washout period was used, and the data included in the PK analysis. However after this shorter period, the pre-infusion concentration was only 2.3% (presumably of the C_{max} or AUC) so this was acceptable.

Question 6

Monitoring of trial sites for compliance

1. The study report of the pivotal trial states that Baxter performed five site compliance audits out of 29 trial centres participating in the pivotal trial. Please respond to the following questions and requests.

   Only three audit closure certificates (for Sites 18, 45 and 52) were included in the study report. Please provide the certificates from the other two Sites, 01 and 26. Also it is noted that the certificate for Site 45 was not signed by the Lead Auditor but by another person on his behalf. Please explain the role of this person in the audit process.

   Comment: The sponsor supplied copies of the missing certificates and satisfactorily explained the role of the signatory.

2. Please explain why only five sites were audited out of the 29 in the study and why these sites were chosen. It is noted that although Sites 01, 18 and 26 entered most patients –10, eight and eight respectively. The total number of patients entered from the five sites was 30, less than half the 72 patients entered in total. These five sites listed only three major protocol deviations compared to 33 major deviations listed by the other 24 sites. Please explain why the sites with the most deviations were not audited.

   Comment: The sponsor's response required an extended evaluation. The clinical evaluator concluded that Baxter's process followed to select sites to be monitored for compliance failed to identify and monitor the sites with the highest total number of major protocol deviations, and the highest number of protocol deviations per subject. It did select and monitor three of the five sites with the highest number of major and minor protocol deviations in total and per subject. It failed to select and monitor the sites with the highest number of discontinuations before treatment. The fact that a procedure was in place to select sites for monitoring is not acceptable when that procedure does not identify those sites that potentially place subjects at risk. The failure is also of concern with respect to compliance with GCP.

3. Site 52 was audited. This site entered one patient who was reported as having two major and 20 minor protocol deviations. It is noted that doctor conducting the trial had only participated in one clinical trial previously, and although described as specialised in haemophilia as well as HIV/AIDs and Infection Immunity, his/her main publications shown are all in virology. Nevertheless the study report stated that 'No critical observations were cited'.

   Please explain why no criticism was made by the auditor of Site 52.

   Comment: Again Baxter justified this situation because certain procedures were followed and definitions used, even though the outcome potentially compromised patient safety, as with site monitoring. In this case only one patient was enrolled and that one patient experienced two major and 20 minor protocol deviations. The clinical evaluator's assessment of the treatment received by this patient was that 'I regard the patient's safety to have been compromised in this case due to a failure of monitoring to increase the prophylactic dose of Rixubis appropriately.'). My further assessment is that in this case Baxter's response that 'observations were cited' was inadequate.

4. Data Management Procedures in the report of the pivotal study, states 'The handling of data by INC Research, including data quality assurance, was to comply with regulatory guidelines (for example, ICH GCP) and the standard operating procedures of the CRO'.

Please describe how INC Research handled the reporting of protocol deviations and relate these procedures to the potential failures in safety and GCP based on the questions asked above.

Comment: Baxter again argues that because the Protocol Deviation Plan was followed, no action needed to be taken about site deficiencies except retraining. This and other cases show that Baxter waits for a protocol deviation to occur then begins retraining after the patient had been put at potential risk. If the site had been better assessed before patient treatment began, the protocol deviations seen in this trial would have been reduced and the patients placed at less risk.

Actions of the data monitoring committee with respect to protocol deviations

The report of the pivotal study describes the oversight of the trial data by the independent Data Monitoring Committee (DMC). These sections only describe monitoring related to safety results from the trial based on available data.

Did the DMC review protocol deviations at any time? If so, please provide the details of such reviews on each occasion they were done**.**

Comment: The submitted documents confirm the oversight described. After every meeting, the DMC gave a 'GO' decision. Presumably this was because the DMC followed set guidelines in its decisions. Again, following company guidelines did not produce the desired outcome for patient safety since the DMC did not express any concern about the frequency of protocol deviations and the quality of the sites in the trial.

Safety question relating to assay of FIX

This question arose because a number of patients have inactive FIX (FIX antigen) circulation in their blood.

Does the presence of (endogenous) FIX antigen in a subject's blood interfere with the measurement of FIX activity or on the detection of inhibitor antibodies to FIX?

Comment: The first half of the sponsor's response reviewed the ELISA assay for neutralising antibodies. In this assay, endogenous FIX antigen does interfere with the measurement of inhibitors to FIX and cannot be avoided. The presence of inhibitors is assumed when no FIX-specific antibodies are detected in the ELISA assay, as was the case in the pivotal trial. FIX activity is measured by its biological activity. The sponsor claims that FIX antigen does not result in false positive results, shown by the fact that patients with detectable FIX antigen levels had no or very low FIX activities. In addition, the assay is designed to provide all reagents in excess thus FIX antigen does not compete with active FIX. PCE may wish to comment.

Response from sponsor concerning evaluation of surgical study 251002

The response was to issues identified in the evaluator's conclusions on clinical efficacy for two indications. The issues and responses were as follows:

1. The numbers of patients who had major surgery (n=11) and minor surgery (n=5) were small, given the intention had been to recruit a total of 30 subjects. This report is an interim analysis, but no clear reason is given for not waiting to complete the study.

The response explained that the 30 subjects were chosen to allow participants in the continuing section of the pivotal trial to have necessary surgery and still receive Rixubis to ensure treatment continuity. The sponsor stated 'Since the data provided in the interim analysis meet the requirements of the EMA guidelines as well as the FDA requirements, the interim report should rather be considered as a final analysis'.

Comment: It was acknowledged that the number of patients (n=5) met the CPMP guidelines, but five patients remain a small number to support a new indication. Meeting the requirement for numbers does not mean that any resulting outcome is acceptable. As requested, the clinical evaluator considered the trial report as final.

2. The PK properties of Rixubis in seven patients studied differed from those in other patients in the pivotal study and no statistical comparison could be done. This may relate to the failure to obtain adequate FIX levels in patients in the post-operative period although a specified protocol was followed.

The sponsor responded by referring to the marked inter-individual variability in both studies, that is, in the pivotal and the surgery study, that although median and mean values differ for both studies, the ranges (minimum and maximum values) either overlap or are contained within the range of the pivotal study (in case of MRT), and that no comparison was intended. Baxter believed that patients were treated according to their standard of care instead of following the protocol specific treatment guidance. Once in-depth re-training was performed, the postoperative pre-infusion FIX levels were higher.

Comment: The PK parameters do differ in the surgical patient population, and many of these do not depend on following protocol. The difficulty in following this treatment protocol is noted.

3. The postoperative blood loss at drain removal exceeded the maximum predicted in four of seven subjects who had major surgery.

The response given to this issue was lengthy. The main arguments related to explanations for the failure of the pre and postoperative FIX concentrations to equal those required by the trial protocol, and whether this failure contributed to the unexpected blood loss in four patients.

The guidance provided in the study protocol recommended that pre-infusion levels of 30 to 60% for minor surgery and 80 to 100% for major surgery be maintained until adequate wound healing followed by 30 to 60% for the subsequent seven days. The mean pre-infusion FIX levels on the first two postoperative days were approximately 55% and the minimum FIX levels were 34.1 and 27.1%, respectively. On postoperative Day 3, the mean pre-infusion level was slightly higher with 59.33 ± 23.69%, with a range of 28.5 to 88.2%. Since the mean and in particular the minimum FIX levels are considerably lower than the recommended 80 to 100%, and also lower than the dose recommended by the World Federation of Haemophilia, Baxter concluded that it seemed the majority of investigators adhered to their standard of care regimen rather than to the guidance recommended in the study protocol.

The sponsor then presented details of the four patients with postoperative blood loss greater than expected, making the following points.

In the first case, the excessive blood loss was small (10 ml), the use of a tourniquet made the measurements of blood loss difficult, and the postoperative FIX levels were satisfactory (89.5%).

Comment: The clinical evaluator accepted that the 'excessive' blood loss in this case is doubtful and of clinical significance.

In two cases the post-operative FIX levels were 34 to 40%, and 40 to 56% respectively and the blood loss 30% and 27% greater than predicted.

In the third case, the postoperative FIX level fell on one occasion to 55%.

Comment: In three cases of seven in the study, treatment with Rixubis did not prevent excessive blood loss. The sponsor agrees that 'the low pre-infusion FIX levels in two surgeries in the early postoperative phase and a drop in FIX activity on postoperative

Day 2 to 55% in one surgery may explain the higher actual than predicted maximum blood loss'.

4. The surgery called 'major' included two cases of abdominal surgery, each for herniorraphy. This abdominal surgery does not compare to abdominal surgery such as liver transplantation or splenectomy for risk of blood loss, the latter two having been part of the assessment of a commercial rFIX product (BeneFIX) and reported in the PI for that product. As well, one case of dental extraction was classed as major surgery and two other cases as minor.

The sponsor provided definitions and criteria used as a guidance for major and minor surgery based on two sets of guidelines, one from the American College of Surgeons, and the other from the Australian Haemophilia Centre Directors' Organisation. The classification in the trial was consistent with those definitions.

Comment: While major and minor surgery was correctly defined in the trial, the sponsor agreed "that there is a difference between herniorrhaphy and liver transplantation or splenectomy" (with respect to potential blood loss).

5. All assessments of haemostatic efficacy were by the operating surgeon, so that bias was possible, although again this was according to recommendations of the CPMP Guidelines.

The sponsor responded that the surgeon was responsible for the intra- and postoperative efficacy assessment whereas the principal investigator who was the haemophilia expert was responsible for the haemostatic efficacy assessment on the day of discharge.

Comment: The principal investigator could hardly be regarded as independent for the purpose of independent assessments.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of Rixubis in the proposed usage are unchanged for the first indication. For the second indication, use in surgical patients, the associated recommendation has been changed to read as follows:

The interim analysis of Surgical Study 251002 is now to be regarded as final at the sponsor's request. Although a benefit of Rixubis in the peri-operative management of patients 12 years and older with severe or moderately severe haemophilia B seems likely, the data provided from seven patients who had major surgery is not sufficiently convincing on its own to justify a new indication.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of Rixubis in the proposed usage are unchanged from those previously identified.

Second round assessment of benefit-risk balance

The benefit-risk balance of Rixubis, given the proposed usage for routine prophylaxis of bleeding episodes in patients 12 years and older with hemophilia B, and for the treatment and prevention of bleeding episodes in patients 12 years and older with hemophilia B (congenital FIX deficiency) is favourable.

The benefit-risk balance of Rixubis for peri-operative management in patients 12 years and older with haemophilia B is unfavourable, but may become favourable if further studies provide more convincing evidence of efficacy.

Second round recommendation regarding authorisation

The clinical evaluator recommended that Rixubis be approved for:

- Routine prophylaxis of bleeding episodes in patients 12 years and older with haemophilia B and
- Treatment and prevention of bleeding episodes in patients 12 years and older with haemophilia B (congenital FIX deficiency).

The clinical evaluator does not recommend approval of Rixubis for peri-operative management of patients 12 years and older with haemophilia B.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

RMP for Australian/New Zealand, Version 1, dated 27 December 2012.

Safety specification

Subject to the evaluation of the non-clinical aspects of the Safety Specification (SS) by the Toxicology area of the Office of Scientific Evaluation (OSE) and the clinical aspects of the SS by the Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor is as follows (Table 6):

Table 6: Summary of ongoing safety concerns

Risks	Safety Concern
Important Identified Risks	None
Important Potential Risks	Inhibitor formation
	Hypersensitivity reactions (including reactions / antibodies to CHO protein
	Lack of effect
	Thromboembolic events (for example, DIC and fibrinolysis)
	Nephrotic syndrome following attempted ITI in haemophilia B patients with FIX inhibitors and a history of allergic reactions.
Important Missing	No clinical data on use of Rixubis for ITI

Risks	Safety Concern
Information	Insufficient clinical data on the use of Rixubis in paediatric patients younger than 12 years of age
	No clinical data on the use of Rixubis in geriatric patients
	No data on the use of Rixubis for continuous infusion during peri-operative management
	No data on the use of Rixubis during pregnancy, labour and delivery, lactation, or with regards to fertility

OPR reviewer comment:

Notwithstanding the evaluation of the non-clinical and clinical aspects of the SS, it is recommended that the table of ongoing safety concerns is not acceptable.

As this product may be injected intravenously by patients at home there is the possibility of pain and bleeding at the injection side, due to sub-optimal injection techniques. Pain and bleeding at the injection side should be considered as a potential risk and therefore, an addition to the RMP to address these risks is suggested. This is of particular importance in the light that these patients are deficient in clotting FIX, and consequently these symptoms may be severe.

The important potential risk of Hypersensitivity/Allergic reactions requires further emphasis. The product will be administered by patients at home, without supervision of healthcare professionals and therefore, measures have to be taken to manage anaphylactic reactions at home. Consequently, an amendment to the PI and CMI is recommended.

The following patient populations were excluded from the clinical development program for the product:

1. Patients with high risk gene mutations 12-17,
2. HIV positive patients with a viral load > 2 00 particles/µL and immuno-compromised patients as evidenced by a CD4 count ≤ 2 00 cells/mm^3,
3. Patients with renal disease as defined by a serum creatinine level > 1.5 times the upper limit of normal,
4. Patients with hepatic disease (Definition criteria for liver disease varied between trials).

It is recommended that the sponsor adds the unknown safety and efficacy for patients with high risk gene mutations, patients who are HIV positive and patients with renal and hepatic disease as missing information in the table of ongoing safety concerns. Risk minimisation and pharmacovigilance activities to address this missing information should be assigned as appropriate. Specifically, it is recommended that:

1. High risk gene mutations,
2. HIV positive,
3. Kidney disease and
4. Liver disease

is added to the dot-points in the CMI in section 'What should I tell my doctor before using Rixubis?' In addition, it is recommended that the sponsor includes a statement in the PI in

section 'Precautions' explaining that the safety of the product for these patient populations has not been established.

Pharmacovigilance plan

Proposed pharmacovigilance activities

Routine and additional pharmacovigilance activities are proposed by the sponsor. An additional pharmacovigilance activity includes a paediatric study.

To address the important missing information about the safety and efficacy of the product in patients < 12 years one paediatric study is ongoing (Study 251101). The sample size is based on the requirements of the EMA 'Guideline on clinical investigation of recombinant and human plasma-derived FIX products'. Ten subjects aged six to < 12 years and 10 subjects aged more than six years are required. To account for a potential drop out, a total of 24 subjects consisting of 12 subjects per age cohort will be enrolled. Recruitment for the trial was stopped when 23 patients were enrolled. Submission of final data was expected for the third quarter of 2013.

Two more studies are ongoing at the time of this evaluation:

Study 251001 - Submission of final data is expected for the second quarter of 2015.

Study 251002 - Submission of final data is expected for the third quarter of 2015.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

The proposed PP is considered acceptable at this time. This product is not yet registered in any country and therefore, there is no post-marketing data available to prompt any further activities.

The milestones for submission of final data obtained from the clinical trials are considered acceptable by the RMP evaluator. It is recommended that the sponsor submits final or interim study reports, resulting from the ongoing clinical trials, to the TGA at the same time as reports are submitted to other regulatory agencies.

Class effects including embolic/thrombolic events and nephrotic syndrome during immune tolerance induction (ITI) have been considered and are included in the risk management plan.

Risk minimisation activities

Sponsor's conclusion in regard to the need for risk minimisation activities

The sponsor concluded that there is no need for additional risk minimisation activities at this time.

The sponsor stated: 'Any new risk or increase in the frequency or severity of an existing risk that might be identified during routine or additional pharmacovigilance monitoring would lead to re-evaluation of routine risk minimisation activities, need for additional risk minimisation activities, and need for an update of this RMP and/or the CCDS/PI.

OPR reviewer comment:

As with similar products off-label use for ITI is likely to occur. A high percentage of this will occur in paediatric patients. The sponsor has discussed that safety and efficacy of this product has not been established for ITI. This is included as missing information in the table of ongoing safety concerns in the RMP and in section 'Inhibitors-Nephrotic syndrome' in the proposed Australian PI. This is considered acceptable.

The justification of the sponsor to undertake only routine risk minimisation activities is considered generally acceptable. Suggestions for minor amendments to the CMI and PI were made.

Potential for medication errors

The sponsor stated: 'The potential for medication errors in Australia are not expected to differ from the potential for medication errors in the rest of the world.

During the PK cross-over portion of pivotal Study 250901, one patient received a dose of 150 IU/kg of Rixubis instead of 75 IU/kg of BeneFIX. This error in dosage and drug is considered a human error and not directly related to the Rixubis itself. No other medication errors were reported during the clinical development program.

Instructions for proper dosage and administration of Rixubis are provided in the Australian PI. The outer product packaging and vial labelling clearly indicate the concentration of Rixubis. In addition, each product concentration is assigned a unique colour which is displayed on the outer carton and the vial, and differentiates it from other product concentrations. Instructions for reconstitution, use of the Baxject II device, and syringe are provided in the Australian PI.

Instructions to administer Rixubis as a bolus infusion are clearly stated in the Australian PI.

OPR reviewer comment:

As this product will be used by specialised patient populations and treatment will be initiated by specialised physicians, the risk for medication error is considered to be low. The actions taken by the sponsor in order to minimise medication errors, are considered generally acceptable. Suggestions for minor amendments to the CMI, to ensure safe and correct administration of the product by patients were made.

Risk minimisation plan

Planned actions

The sponsor states that an RMP is not deemed necessary at this time.

The risks described in this RMP do not require additional risk minimisation activities. Information regarding these potential risks and missing information have been included in the Rixubis Australian PI. Therefore, routine risk minimisation activities will be exercised for Rixubis. No additional risk minimisation activities are recommended at this time.

OPR reviewer comment:

It is considered that at this time the justification from the sponsor not to implement any additional risk minimisation activities is acceptable.

In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft PI document be revised.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application; the implementation of the submitted AU/NZ RMP satisfactory to the TGA is imposed as a condition of registration; and the draft PI and CMI documents should NOT be revised until the Delegates Overview has been received.

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated TGA request for further information. It is important to ensure that the information provided in response to these includes a consideration of the relevance for

the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

1. It is recommended that RMP for Australia/New Zealand, Version 1, dated 27 December 2012, and any future updates are implemented as a condition of registration.
2. Pain and bleeding at the injection side should be considered as a potential risk and therefore, an addition to the RMP to address these risks is recommended. This should also be addressed in the PI and CMI as appropriate.
3. It is recommended that the sponsor adds the unknown safety and efficacy for patients with high risk gene mutations, to the table of ongoing safety concerns as missing information. Risk minimisation and pharmacovigilance activities to address this missing information should be assigned as appropriate, and as specified by the RMP evaluator.
4. HIV positive patients with a viral load > 200 particles/µL and immuno-compromised patients as evidenced by a CD4 count ≤ 200 cells/mm^3 should be included in the table of ongoing safety concerns as missing information. Risk minimisation and pharmacovigilance activities to address this missing information should be assigned as appropriate, and as specified by the RMP evaluator.
5. It is recommended that the sponsor adds the unknown safety and efficacy for patients with liver disease as missing information. Risk minimisation and pharmacovigilance activities to address this missing information should be assigned as appropriate, and as specified by the RMP evaluator.
6. It is recommended that the sponsor adds the unknown safety and efficacy for patients with renal disease as missing information. Risk minimisation and pharmacovigilance activities to address this missing information should be assigned as appropriate, and as specified by the RMP evaluator.
7. It is recommended that the sponsor submits final or interim study reports, resulting from the ongoing clinical trials, to the TGA at the same time as reports are submitted to other regulatory agencies.
8. Changes are recommended to the proposed PI and CMI.

Second round evaluation

Table 7 seeks to reconcile issues identified in the RMP evaluation report for the above submission with consideration of the following documents:

1. RMP for Australian/New Zealand, Version 1, dated 27 December 2012
2. Sponsor's response to the TGA request for further information, dated 29 August 2013
3. OMA Clinical Evaluation Report for rFIX, Rixubis, dated May 2013 (first round) and October 2013 (second round)
4. OSE, Non-clinical Evaluation Report (NCER) for Nonocog gamma (Rixubis) dated 28 August 2013.

It is considered that the sponsor's response to the TGA's request for further information has not adequately addressed all of the issues identified in the RMP evaluation report.

Table 7: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
It is recommended that RMP for Australia/New Zealand, Version 1, dated 27-Dec-2012, and any future updates are implemented as a condition of registration.	Baxter confirms that the RMP and any future updates will be implemented upon registration. Please note that an updated RMP, dated 26 August 2013 was included in this response.	The sponsor has not submitted a summary of changes to outline the differences between the two RMPs. It is recommended that the sponsor submits a summary outlining the differences between the two RMP versions, and the rational for any changes to the RMP.
Pain and bleeding at the injection site should be considered as a potential risk and therefore, an addition to the RMP to address these risks is recommended. This should also be addressed in the PI and CMI as appropriate.	The proposed potential risk (pain and bleeding at the injection site) is not specific to the active ingredients or excipients in Rixubis, the syringe or Baxject II device used with Rixubis; rather, these risks apply to any intravenous administration procedure. These risks represent procedural complications of intravenous administration. Therefore, Baxter proposes not to include pain and bleeding at the injection site as a potential risk within the RMP.	This is considered acceptable.
It is recommended that the sponsor adds the unknown safety and efficacy for patients with high risk gene mutations, to the table of ongoing safety concerns as missing information. Risk minimisation and pharmacovigilance activities to address this missing information should be assigned as appropriate, and as specified by the RMP	PTPs with high risk gene mutations (such as nonsense mutations) were included in clinical studies with Rixubis. While there is an increased risk of inhibitor development and hypersensitivity reactions in this population, high risk gene mutations are considered rare in haemophilia B patients. The risk of hypersensitivity reactions is highest in the early phases of initial exposure. In Australia, Rixubis is indicated in	To address the possibility of inhibitor development and to ensure the safety of patients with high risk mutations, the sponsor makes the following recommendation: *At the time of receiving Rixubis, patients should have high risk gene mutations determined. Furthermore, during the first 20 EDs, it is recommended that the patient be monitored in a treatment facility.* It is noted that this

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
evaluator.	patients 12 years and older with haemophilia B. At the time of receiving Rixubis, patients should have high risk gene mutations determined. Furthermore, during the first 20 EDs, it is recommended that the patient be monitored in a treatment facility. Patients with high risk gene mutations are discussed within the context of Hypersensitivity Reactions in the Australian PI. Therefore, Baxter proposes not to include the safety and efficacy in patients with high risk gene mutations as important missing information within the RMP.	recommendation has not been included in the proposed Australian PI. However, the sponsor has agreed to add the below statement to the Australian PI in response to recommendations made in the round 1 RMP report. The following statement is now included in the PI (underlined has been added in response to section 31 questions*): Initiate treatment under the supervision of a physician experienced in the treatment of haemophilia and continue treatment under supervision for a period of time.* This statement in conjunction with the warnings regarding inhibitor development and hypersensitivity reactions in PRECAUTIONS and DOSAGE AND ADMINISTRATION appears to be an acceptable risk mitigation strategy to address the risk for patients with high risk gene mutations. Nevertheless, the RMP evaluator maintains the opinion that this patient population should be included as missing information in the table of ongoing safety concerns of the RMP. Reporting of safety related events in this patient population should occur in every PSUR.
HIV positive patients with a viral load >200 particles/µL and immuno-compromised patients as evidenced by a CD4 count ≤200 cells/mm^3 should be	Patients who are HIV positive (with a viral load >200 particles/µL) or immunocompromised (as evidenced by a CD4 count ≤200 cells/mm^3) were excluded from clinical trial	It is noted that a statement is included in the Clinical Trials section of the PI stating that this patient population has been excluded from participation in clinical trials. It is

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
included in the table of ongoing safety concerns as missing information. Risk minimisation and pharmacovigilance activities to address this missing information should be assigned as appropriate, and as specified by the RMP evaluator.	populations as it may be difficult to adequately determine the immunogenicity of Rixubis in immunocompromised patients. Efficacy and safety of Rixubis in these patients is not expected to differ from other patients. Therefore, Baxter proposes not to include safety and efficacy in patients who are HIV positive or immunocompromised as important missing information within the RMP.	understood that Baxter does not believe that there is a safety concern with this patient population using the product. There is a high incidence of HIV in the target population. The sponsor states in the RMP that up to 10% of haemophilia patients are HIV positive. The RMP evaluator maintains the opinion that this patient population should be included as missing information in the table of ongoing safety concerns of the RMP. Reporting of safety related events in this patient population should occur in every PSUR.
It is recommended that the sponsor adds the unknown safety and efficacy for patients with liver disease as missing information. Risk minimisation and pharmacovigilance activities to address this missing information should be assigned as appropriate, and as specified by the RMP evaluator.	Patients with hepatic disease were included in clinical studies with Rixubis. Patients with a medical history of hepatitis (excluding those with active disease) were included in clinical studies. Patients with a medical history of hepatitis or active hepatitis with ALT and/or AST not exceeding five times the upper limit of normal were included in clinical studies. In pivotal Study 250901, 63/73 subjects (86%) who received IP had a medical history of hepatitis (A and/or B and/or C). Of which, 38 had increased liver parameters (ALT and/or AST and/or ALP) at screening or at any time point during study participation. Patients with active hepatitis would need to be monitored more closely than other	It is noted that a statement is included in the Clinical Trials section of the PI stating that this patient population has been excluded from participation in clinical trials. It is understood that Baxter does not believe that there is a safety concern with this patient population using the product. However, the RMP evaluator maintains the opinion that this patient population should be included as missing information in the table of ongoing safety concerns of the RMP. Reporting of safety related events in this patient population should occur in every PSUR.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	patients. The Australian PI reflects that patients with severe chronic liver disease (as evidenced by an INR > 1.4) were excluded from pivotal Study 250901. In addition, patients with hepatic disease are discussed within the context of thromboembolic events in the Australian PI. Therefore, Baxter proposes not to include safety and efficacy in patients with hepatic disease as important missing information within the RMP.	
It is recommended that the sponsor adds the unknown safety and efficacy for patients with renal disease as missing information. Risk minimisation and pharmacovigilance activities to address this missing information should be assigned as appropriate, and as specified by the RMP evaluator.	Patients with renal disease were excluded from clinical trial populations for Rixubis and are routinely excluded from clinical trial populations. Baxter does not believe this constitutes Important Missing Information for inclusion in the RMP. As the haemophilia B population ages, there may be an increased incidence of renal disease. However, it is not currently considered a leading co-morbidity in this population. Therefore, Baxter proposes not to include the safety and efficacy in patients with renal disease as important missing information within the RMP.	It is noted that a statement is included in the Clinical Trials section of the PI stating that this patient population has been excluded from participation in clinical trials. It is understood that Baxter does not believe that there is a safety concern with this patient population using the product. However, the RMP evaluator maintains the opinion that this patient population should be included as missing information in the table of ongoing safety concerns of the RMP. Reporting of safety related events in this patient population should occur in every PSUR.
It is recommended that the sponsor submits final or interim study reports, resulting from the ongoing clinical trials, to the TGA at the same time as reports	Baxter will endeavour to submit final or interim study reports (resulting from the ongoing clinical trials) to the TGA. However, as there is no existing process in TGA that allows sponsors to submit	The sponsor should note that relevant study results from studies, referenced in the RMP, can be submitted to the RMP coordinator. Such a submission should include a cover letter

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
are submitted to other regulatory agencies.	study reports independently of a major variation, the timing of these submissions may not be in sync with that of other regulatory agencies.	summarising the study results and any impact the results may have on the RMP. Please submit to the RMP coordinator e-mail address: rmp.coordinator@tga.gov.au

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There were no objections to registration from the Quality evaluators. Shelf-life of 24 months is proposed by the sponsor but the quality evaluator supports a maximum of 18 months on the basis of data reviewed.

Nonclinical

There were no objections raised on non-clinical grounds. Non-clinical efficacy data only supported use in prophylaxis.

Clinical

Evaluator's recommendations

The clinical evaluator recommended approval but with a restricted indication as follows:

> *Routine prophylaxis of bleeding episodes in patients 12 years and older with haemophilia B and*
>
> *Treatment and prevention of bleeding episodes in patients 12 years and older with haemophilia B (congenital factor IX deficiency)*

The clinical evaluator did not recommend approval of Rixubis for:

> *Peri-operative management of patients 12 years and older with haemophilia B.*

Overview of data

The pivotal study was Study 250901, in patients with severe or moderately severe haemophilia B. This study included subjects given twice weekly prophylaxis and other subjects treated on-demand. The study included PK assessment (see below).

Supportive Study 251002 is an ongoing study of use at the time of surgery.

There were no paediatric efficacy data. A trial in children (Study 251101) is ongoing and some safety data were incorporated from that trial.

Pharmacokinetics

Study 250901, Parts 1 and 3, provided most PK data. In the single dose cross-over Part 1, bioequivalence of Rixubis and BeneFIX was established in a PTP adult population based on $AUC_{0\text{-}72hr}$/dose; other parameters also suggested bioequivalence. 500 IU potency vials from one lot were used.

Exposure after initial use of Rixubis (n=28) was compared with exposure after six months of treatment (n=25) in Study 250901, Part 1 versus Part 3. Mean exposure rose after six months by approximately 6 to 8% (with a trend for increasing IR at Day 1, Week 5, Week 13 and Week 26), and there was no evidence of any dramatic decline in recovery in any particular patient.

Assessment of IR was made during the PK study. This included comparison of IR in Part 1 of the study (that is, after one dose) with BeneFIX. Point estimates indicated a modest difference in IR at C_{max}, although statistical significance of the difference between the two products was not tested, and ranges observed were broadly overlapping.

Formulation: The clinical evaluator accepted that the change from pilot to commercial production did not bias the pivotal study's results, but noted efficacy analysis suggested the 'commercial' material was more active and effective at least in treatment of bleeds (based on a somewhat limited analysis).

Limited PK data were obtained in surgical Study 251002, from seven subjects. Results could not be compared formally across studies. IR at 30 minutes was calculated to be 1.06.

Efficacy

Study 250901 – pivotal

Parts 1 and 3 (PK) of this study are discussed above; Part 2 was open-labelled and uncontrolled and examined twice-weekly prophylaxis or, in a separate group, on-demand use.

Subjects had severe (FIX level < 1%) or moderately severe (FIX level 1-2%) haemophilia B and were PTPs (minimum 150 EDs). Study sites were predominantly in Russia, Poland, Bulgaria, Ukraine and Romania (raising the possibility of different historical standards of care compared to Australia). Subjects in the on-demand cohort needed 12 plus bleeding episodes in 12 months before enrolment. Choice of cohort was at the discretion of investigator and subject.

56 subjects were studied in the prophylaxis cohort (another three had treatment for < three months) and 14 subjects in the on-demand cohort. The evaluator explored in some detail a high incidence of major protocol deviations. Prophylaxis patients received twice weekly injections; mean number of EDs was 58.3 (minimum 50).

Patients were 12 to 65 years of age. Median age was 33 years; there were three children (12, 13 and 15 years). FIX activity at baseline was < 1% in 53.4% of subjects, and 1 to 2% in 46.6% of subjects. 85% were Caucasian. Arthropathy was common (48/56).

In prophylaxis, patients received 50 IU/kg twice weekly (40-60 IU/kg, at the discretion of the investigator), which could increase to 75 IU/kg twice weekly. On-demand use to treat bleeds followed instructions for dosing of BeneFIX in the EU SmPC. Rixubis was used to treat bleeds in the prophylaxis arm.

The mean ABR episodes in the prophylaxis cohort (n=56) was 4.26 and the median was 1.99, suggesting a skewed distribution of events (43% of subjects had no bleeds during the period). The evaluator compares these results with analogous ones reported in the BeneFIX PI. The sponsor assessed the medical literature for on-demand outcomes to conduct a historical comparison, concluding that twice weekly prophylaxis with Rixubis

produced a lower ABR than historical ABR values with on-demand treatment. There was no head-to-head comparison with BeneFIX in prophylaxis.

In the on-demand cohort (n=14), mean ABR was 33.9 and median 27.0 (range 12.9 to 73.1), higher than historical outcomes.

15.3% of bleeds required ≥ three infusions. AHCDO guidelines refer to a study showing that > 90% of bleeding episodes were controlled by one to two infusions of other rFIX, however confounders such as severity of bleeding may impact on this historical comparison. Interestingly, bleeds in the on-demand group in Study 250901 generally required fewer infusions and a lower total dose, though this analysis was not stratified by severity of bleed.

No pattern of increased consumption indicative of inhibitor formation was reported.

Study 251002 – supportive

This is an ongoing, open label, uncontrolled study in patients with severe/moderately severe Haemophilia B undergoing surgical/dental/other invasive procedures. Study sites were in Russia, Poland, Bulgaria and Ukraine.

Dose was tailored to raise FIX concentrations to 80 to 100% of normal for major surgery and 30 to 60% of normal for minor surgery. Dose frequency was per local guidelines, which led to low FIX concentrations in some subjects. Replacement was by bolus infusion; continuous infusion was not assessed.

The 14 subjects ranged in age from 19 to 54 years. 11/14 had severe haemophilia B and three had moderately severe deficiency. 11/14 had 'major' surgery (seven orthopaedic, two hernia repairs, one dental and one excision of neurofibroma).

There were intra-operative, post-operative and day of discharge ratings of haemostatic efficacy (excellent/good/fair/none), based on variation from expected blood loss. No primary efficacy outcome was clearly defined.

Intraoperative blood loss matched expected blood loss. Postoperative blood loss from drains (in seven major surgery patients) was often higher than predicted. Ratings of haemostatic efficacy by surgeons were 'excellent' in 14/14 subjects intraoperatively, and either excellent or good subsequently; the evaluator saw the potential for observer bias to influence this assessment. Blood product use did not seem excessive.

Safety

An ISS involved 91 unique patients (73 from Study 250901, two from Study 251002 and 16 paediatric patients from Study 251101, some of these also in continuation Study 251101). There was a median of 83 EDs (range, three to 209) and 78% of infusions were for prophylaxis. Exposure was relatively short-term.

Immunogenicity was assessed by assaying total binding and inhibitory antibodies to FIX and other product-related proteins. Low levels of binding anti-FIX antibodies (1:20, 1:40) could not be confirmed so were not reported as positive.

No subject developed an inhibitory antibody to FIX with titre ≥ 6 Bethesda units. No subject had confirmed treatment-related binding antibodies to FIX, although 11 subjects developed 'indeterminate titres' of antibodies to FIX (that is, low titre and not confirmable).

Eleven subjects developed indeterminate titres of anti-Furin antibodies. In three this was prior to Rixubis exposure. One subject had transient, low-level (1:80) confirmed antibodies to rFurin; AEs were not reported; follow-up titre was 1:20 (indeterminate).

The FDA Clinical Review of Rixubis notes regarding the potential clinical significance of these antibodies:

Baxter provided data from 500 healthy subjects from five different geographies in Austria who were screened for the prevalence of rFurin antibodies using the same assay in the pivotal study. Forty-one healthy subjects were found to be reactive (8.2%) without prior exposure to the IP. Of these, 7% had titres of 1:20 or 1:40 and 1.2% had higher titres ranging from 1:80 to 1:320. A review of the literature was also provided describing the historical knowledge of self-reactive rFurin antibodies that are of unclear origin but of no associated pathology.

No thrombotic AEs were reported. No severe allergic reactions were reported, however anaphylaxis may occur years after initial exposure. There were no deaths. One subject haemorrhaged from a duodenal ulcer; it is unclear if the patient was on prophylaxis (but bleeding would be captured by efficacy evaluation).

Risk management plan

The proposed RMP was broadly acceptable to the TGA's OPR. The Round 2 RMP evaluation identified unresolved procedural and content-related issues:

1. It is recommended that the sponsor submits a comprehensive summary outlining any differences between RMP (version 1.0, dated 26 August 2013) and RMP (version 1.0, dated 27 December 2012.), and outlines the rationale behind any change. This summary should be reviewed and approved by the RMP section prior to market approval.
2. It is recommended that the following patient populations be included as missing information in the table of ongoing safety concerns of the RMP.
    a. Patients with high risk gene mutations
    b. HIV positive and immunocompromised
    c. Patients with liver disease, and
    d. Patients with kidney disease

    Reporting of safety related events in these patient populations should occur in every PSUR.

The latest RMP version submitted to the TGA was version 1.0, dated 26 August 2013.

The sponsor should aim to resolve these outstanding issues with the RMP Evaluation Section prior to market launch of the product.

If by inclusion of these groups in the table of ongoing safety concerns in the RMP close scrutiny of efficacy and safety in these groups is encouraged in the post-market setting, the RMP evaluator's position seems reasonable.

Delegate considerations

Efficacy

In pivotal Study 250901, clinical efficacy was not compared for Rixubis and BeneFIX. Comparison was made with historical on-demand outcomes. Evidence that prophylaxis with Rixubis reduces ABR compared to on-demand use of other agents is an insensitive measure of Rixubis' comparative efficacy. Product-specific differences are confounded by effect of schedule (prophylaxis versus on-demand). If a cross-study comparison of ABR outcomes for Rixubis versus BeneFIX in the prophylaxis setting is attempted, no sign of any alarming decline in efficacy is seen, but such comparisons are subject to major biases.

The TGA-adopted EU guideline states that PK data (IR, half-life, AUC, MRT, CL) 'are the most important (surrogate) endpoints for efficacy of a new factor VIII/IX product'. Therefore, efficacy can also be inferred from assaying the increase in FIX upon infusion of Rixubis. The sponsor's single dose cross-over study showed the mean IR was 0.87 for Rixubis, 0.77 for BeneFIX. (The guideline also refers to assessment of 'clinical efficacy' (for example, response as rated by physicians for treatment of bleeds; consumption of FIX) but there is no requirement for randomised comparison.)

For peri-operative use, the guideline requires assessment of haemostatic efficacy, blood loss and transfusion requirements. The sponsor's study examined these endpoints.

Dosing guidelines

Reported difference in IR between Rixubis and BeneFIX might have implications for dosing guidelines; although differences are not major and probably need validation (for example, other studies indicate different IR for BeneFIX).

Inhibitors

No subjects developed clearly positive titres of inhibitory antibodies or allergic AEs/inefficacy/increased consumption tied to rising antibody titres.

The significance of low titre non-neutralising antibodies to FIX/Furan was unclear. The assay to detect antibodies induced by Rixubis appeared non-specific (that is, it detected 'normally occurring' or cross-reacting antibodies, at least for rFurin).

The generally uncontrolled study design in the Rixubis clinical programme does not allow detection of, for example, a higher incidence of inhibitor development than is seen with BeneFIX.

Given the historical incidence of inhibitors in haemophilia B (1 to 6% overall; but 9 to 23% in severe disease), the programme's sample size (n=91 with at least moderately severe disease) may provide sufficient power to rule out a high incidence of inhibitors, to the extent that patients were followed up (inhibitors commonly develop after 10 to 20 EDs[5]).

Indication – peri-operative use

The clinical evaluator recommended excluding use in the peri-operative setting. The Delegate agreed with the clinical evaluator that few subjects undergoing major surgery were evaluated (noting that few subjects are required in this setting according to regulatory guidelines), and that evidence of clinical efficacy was difficult to interpret.

Given understanding about the mechanism of action of FIX replacement in haemophilia B and endorsement of the use of surrogate PK endpoints by TGA-adopted EU guidelines, there is latitude to bridge evidence of efficacy across from the on-demand component of Study 250901 and from PK information in that study and the surgical study.

In the Delegate's opinion, this provides a sufficient basis to allow use in the peri-operative setting.

Indication – use in children

The US PI restricts use to adults. The Delegate agreed with this approach, given the scant evidence for efficacy and safety in children 12 plus years of age, availability of BeneFIX in children and the expectation of paediatric data for Rixubis.

[5] DiMichele D. 2007. Inhibitor development in haemophilia B: an orphan disease in need of attention. British Journal of Haematology, 138, 305–315

Overall benefit-risk

A key benefit of rFIX is reduced risk of transmitting viral infection/prion disease. Given the history of replacement therapy in haemophilia B, this is a real issue for patients. Rixubis appears to offer this benefit.

Development of inhibitory antibodies is a key concern with clotting factor replacement (although this occurs less in haemophilia B than haemophilia A). Rixubis is not likely to induce inhibitory antibodies in the tested population to any unusual degree.

Nomenclature

Nonacog gamma has been accepted as an Australian Approved Biological Name by the TGA's naming committee. It might suggest lack of interchangeability with nonacog alfa. There is some evidence of bioequivalence between Rixubis and BeneFIX, although IR was slightly different across products.

Proposed action

The Delegate considered that there is a positive benefit-risk balance for Rixubis in the population defined as follows:

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

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Is there sufficient evidence for use in peri-operative management of haemophilia B?
2. Is there sufficient evidence for use in children 12 plus years of age?
3. Is risk of inhibitor development acceptably low?
4. In what patient population is there a positive benefit-risk balance for this product?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Baxter overall concurs with the Delegate's recommendations, in particular with the recommendation to approve the following indications for Rixubis:

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

However, Baxter wishes to provide additional information on the following points:

1. Evidence for use in peri-operative management of Haemophilia B
2. Risk of inhibitor development
3. RMP: request for summary outlining differences
4. RMP: rationale for not including specific patient groups as missing information

Evidence for use in peri-operative management of Haemophilia B

The Delegate commented that 'The clinical evaluator recommends excluding use in the perioperative setting….. Given the understanding about the mechanism of action of FIX replacement in haemophilia B and endorsement of the use of surrogate PK endpoints by TGA-adopted EU guidelines, there is latitude to bridge evidence of efficacy across from the on-demand component of Study 250901 and from PK information in that study and surgical study. In my opinion, this provides sufficient basis to allow use in the peri-operative setting.'

Baxter concurs with the Delegate's intention to recommend registration of Rixubis for use in the peri-operative setting.

The haemostatic efficacy data obtained so far demonstrate that Rixubis is efficacious, however; they also show the generic difficulties to objectively evaluate a FIX concentrate in the surgical setting where many variables influence intra and postoperative blood loss. This also includes different surgical techniques and postoperative standard of care observed in a multicentre and multinational study. However, since these data were also regularly reviewed and evaluated by an independent Data Safety Monitoring Board (DSMB) consisting of haemophilia experts who did not at any time express any concerns regarding haemostatic efficacy and safety of Rixubis, Baxter believes that the benefit/risk ratio of Rixubis in the peri and postoperative setting is favourable.

Risk of inhibitor development

Baxter believes that there is an acceptably low risk of inhibitor development in patients treated with Rixubis.

The Delegate commented that 'The significance of low titre non-neutralising antibodies to FIX/Furan was unclear. The assay to detect antibodies induced by Rixubis appeared nonspecific…. The generally uncontrolled study design in the Rixubis clinical programme does not allow detection of, for example, a higher incidence of inhibitor development than is seen with BeneFIX. Given the historical incidence of inhibitors in haemophilia B….the programme's sample size….may provide sufficient power to rule out a high incidence of inhibitors….."

The development of antibodies to FIX, rFurin, and CHO protein is a safety endpoint in pivotal Study 250901, continuation Study 251001, and paediatric Study 251101 (Studies 251001 and 251101 have not been submitted to the TGA). The presence of binding antibodies to FIX, to recombinant human furin proteins, and to CHO protein was determined by validated highly sensitive and specific in-house ELISA employing polyclonal anti-human Ig antibodies (IgG, IgM and IgA) as detection antibodies. The assay strategy includes a multi-tiered approach as suggested by regulatory guidelines published by FDA and EMA (EMEA/CHMP/BMWP/14327/2006 "Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins", FDA Draft Guidance for Industry 2009 'Assay Development for Immunogenicity Testing of Therapeutic Proteins'). This strategy includes a highly sensitive screening assay to differentiate positive and negative antibody signals and subsequently a confirmatory assay to prove specificity of the detected antibody.

None of the subjects in these studies developed treatment-related positive binding antibodies to FIX or to CHO protein.

Two subjects developed transiently positive antibodies, which reached the lower limit of detection for specific antibodies (1:80) against rFurin, at one time point in the continuation study but were negative at the time of the data cut-off date. The presence of low titre (1:80) antibodies against rFurin which were confirmed for specificity had no impact on safety or efficacy of Rixubis. There was no temporal association with AEs or abnormal laboratory parameters. Also, there was no impact on PK or the efficacy of

Rixubis to prevent bleeding episodes. Furthermore, the presence of binding antibodies to rFurin was considered not clinically significant by the investigators. In addition, a literature review did not reveal any reports suggesting a clinical impact of antibodies against rFurin. Similar low titres (1:80 to 1:320) of antibodies against rFurin were found in some healthy individuals, which were observed when we studied a cohort of 500 healthy blood donors. The biological relevance of these low-titre self-reactive antibodies against rFurin is not clear. However, they are not associated with any pathology. Recently, it was shown that low-titre self-reactive antibodies have a crucial influence on protecting the body against waste products[6]. They bind apoptotic cells and thereby facilitate uptake by dendritic cells, preventing the activation of the adaptive immune system by molecules released upon apoptosis[7]. These findings provide evidence that low titre self-reactive antibodies fulfil an important role in the homeostasis of the immune system.

In addition, the inhibitor response of Rixubis (assessed in pivotal Study 250901 and paediatric Study 251101) remained constant over time, which suggests no indication of subclinical inhibitors.

Finally, the structure, identity, purity, potency and functional integrity of rFIX in Rixubis are comparable to the commercially available rFIX in BeneFIX. As such, we would expect the inhibitor profile in both products to be similar. This is reflected in the clinical trial results where the inhibitor profile of BeneFIX in clinical trials is: one low titre transient inhibitor in 65 PTPs and two high titre inhibitors in 63 Previously Untreated Patients (PUPs).[8]

RMP: request for summary outlining differences

Please note that the request to provide a comprehensive summary outlining any differences between the previous and latest versions of the RMP have already been addressed.

RMP: rationale for not including specific patient groups as missing information

The RMP evaluator recommended that following four patient groups be included as missing information in the RMP with the intent that the safety-related events for these groups would be included in every PSUR. Baxter would like to reassure the TGA that a safety related issue does not have to be important missing information in order to be discussed in the PSUR. Any safety related issue would be included in the PSUR, regardless of medical history/comorbidity.

1. Patients with high risk gene mutations

PTPs with high risk gene mutations (such as nonsense mutations) were included in clinical studies with Rixubis.

While there is an increased risk of inhibitor development and hypersensitivity reactions in this population, high risk gene mutations are not very common in haemophilia B patients. The risk of hypersensitivity reactions is highest in the early phases of initial exposure. About 30 to 45% of the haemophilia B subjects have severe form of the disease (< 1% FIX activity) and in these subjects the disease is detected early in life much before 12 years. The remaining 55% of the haemophilia B patients have the moderate (1 to 5% FIX activity) and mild forms of the disease (> 5% FIX activity). For a French haemophilia cohort it was reported that the median age at diagnosis was 7.7 months, with significant

[6] Chou MY, Fogelstrand L, Hartvigsen K, Hansen LF, Woelkers D, Shaw PX, Choi J, Perkmann T, Bäckhed F, Miller YI, Hörkkö S, Corr M, Witztum JL, Binder CJ. 2009. Oxidation-specific epitopes are dominant targets of innate natural antibodies in mice and humans. J Clin Invest.119:1335-1349

[7] Elluru SR, Vani J, Delignat S, Bloch MF, Lacroix-Desmazes S, Kazatchkine MD, Kaveri SV, Bayry J. 2008. Modulation of human dendritic cell maturation and function by natural IgG antibodies. Autoimmun Rev. 7:487-490

[8] Australian BeneFIX PI (15 Aug 2013)

differences among subgroups: 5.8 months in severe haemophilia, 9.0 months in moderate forms, 28.6 months in mild forms[9]. At the time of receiving Rixubis, patients should have high risk gene mutations determined. Furthermore, during the first 20 EDs, it is recommended that the patient be monitored in a treatment facility. Moreover, inhibitor development and allergic reactions are considered rare in mild and moderate haemophiliacs due to the presence of circulating FIX molecules.

All 73 subjects participating in Rixubis studies were included in the inhibitor assessment. There were no inhibitors in the study. Therefore, the upper 95% confidence limit is 5.15%. The sample size for the study was adequate to detect the development of inhibitors. All subjects had at least 150 EDs before study entry and subjects were treated for a minimum of 50 EDs in clinical studies with Rixubis.

The study included 54 (73.9%) subjects with mutations and of these 14 subjects (19.2%) had nonsense mutations and one subject (1.4%) had a deletion mutation. These 15 subjects experienced a total of three unrelated SAEs and 10 unrelated non-SAEs. Thus, the safety profile of subjects with mutations in this study is comparable to subjects without mutations.

Patients with high risk gene mutations are discussed within the context of Hypersensitivity Reactions in the Australian PI.

Therefore, Baxter believes that patients with high risk gene mutations do not need to be included as missing information in the table of ongoing safety concerns of the RMP.

2. HIV positive and immunocompromised patients

Patients who are HIV positive (with a viral load > 200 particles/μL) or immunocompromised (as evidenced by a CD4 count ≤ 200 cells/mm^3) were excluded from clinical trial populations as it may be difficult to adequately determine the immunogenicity of Rixubis in immunocompromised patients.

Efficacy and safety of Rixubis in these patients is not expected to differ from other patients as the intent is to treat bleeding episodes in this patient population. The fact that these subjects have HIV infection does not change the mode of action of factor concentrates or influence the therapy choice for treating bleeding episodes in these patients. HIV patients with advanced disease stage are normally excluded from clinical trials due to the high frequency of signs and symptoms attributable to the infection, severely limiting the evaluation of safety in such trials. There were three HIV positive subjects out of the 73 total subjects in the study. These three subjects experienced nine unrelated non-SAEs and did not experience any SAEs. Hence the safety and efficacy profile of these subjects is comparable to the rest of the subjects in the study.

Therefore, Baxter believes that patients who are HIV positive and immunocompromised do not need to be included as missing information in the table of ongoing safety concerns of the RMP.

3. Patients with hepatic disease

In clinical studies with Rixubis, the following groups were included:

- patients with hepatic disease
- patients with a medical history of hepatitis (excluding those with active disease)
- patients with a medical history of hepatitis or active hepatitis with ALT and/or AST not exceeding five times the upper limit of normal.

[9] Chambost H et al. 2002. What factors influence the age at diagnosis of hemophilia? Results of the French hemophilia cohort. The Journal of Pediatrics 141: 548-552.

In pivotal Study 250901, 63/73 subjects (86%) who received treatment had a medical history of hepatitis (A and/or B and/or C). Of which, 38 had increased liver parameters (ALT and/or AST and/or ALP) at screening or at any time point during study participation.

Northcott et al. (2013)[10] evaluated the prevalence of transfusion acquired hepatitis C in Australian patients with bleeding disorders. Demographic data, virological data and liver disease status from 700 patients with inherited bleeding disorders were analysed. Of these 700 patients, 424 (61%) had been tested for chronic hepatitis C (CHC) infection and 219 (52%) were hepatitis C antibody positive, with the prevalence approaching 100% in patients with severe bleeding disorders. Therefore, the subjects studied in Rixubis clinical studies are reflective of the target population. It is important to note that not all patients with hepatic disease were excluded. Rather, only those subjects with hepatic disease that may alter the assessment of efficacy of Rixubis were excluded. This is consistent with exclusion criteria used in clinical studies for other factor products.

As the information has already been included in the study population, Baxter believes that patients with liver disease do not need to be included as missing information in the table of ongoing safety concerns of the RMP.

4. Patients with kidney disease

Patients with renal disease were excluded from clinical trial populations for Rixubis and are routinely excluded from clinical trial populations, as they can present with signs and symptoms attributable to these diseases which may severely limit the evaluation of safety in such trials.

As the haemophilia B population ages, there may be an increased incidence of renal disease: A data collection from the medical records of 3422 males with haemophilia showed that the rate of acute renal disease discharges ranged from 2.4 to 4.8 per 1000 patients per year and averaged 3.4 over the studied six year period. This rate was higher than the estimated rate of 1.9 per 1000 males for the general population. In addition, age-specific rates of acute renal disease in persons with haemophilia (PWH) were higher in nearly every age group than among US males. Likewise, the corresponding average rate of 4.7 chronic renal disease discharges per 1000 PWH was higher than the rate of 2.9 per 1000 for US males. Chronic renal disease rates were markedly higher in every age group for PWH compared with males in renal disease rates were markedly higher in every age group for PWH compared with males in the general population. Multivariate analyses showed that several characteristics were strongly associated with acute renal disease among PWH. PWH diagnosed with acute renal disease were nine times more likely to be HIV infected, five times more likely to have hypertension and three times more likely to have an inhibitor than those without the diagnosis[11]. These findings were challenged by later studies, for example, a review of medical records of Slovenian haemophiliacs resulted in only one case of mild reduction of renal function of unknown cause, and these authors concluded that haematuria per se did not cause renal disease in none of the 29 PWH studied[12].

However, FIX concentrates do not undergo metabolisation in the kidneys, and the mode of action and choice of therapy in haemophiliacs will not be influenced by this co-morbidity.

In summary, while representing an important comorbidity from a clinical perspective, Baxter does not believe that renal disorders in haemophilia constitute Important Missing Information for inclusion in the RMP.

[10] Northcott et al. 2013. Prevalence of transfusion acquired hepatitis C in an Australian bleeding disorder population. Haemophilia 19: 847-852.
[11] Kulkarni R et al. 2003. Renal disease among males with haemophilia. Haemophilia 9(6): 703-710.
[12] Benedik-Dolincar M and Benedik M. 2007. Haematuria in patients with haemophilia and its influence on renal function and proteinuria. Haemophilia 13(5), 489-492.

Conclusion

Baxter concurs with the Delegate's comments, in particular with the recommendation to approve the following indications for Rixubis:

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

Baxter has provided further rationale to not include the following as missing information in the RMP and would kindly ask for further consideration on these points:

- Patients with high risk gene mutations
- HIV positive and immunocompromised patients
- Patients with hepatic disease
- Patients with renal disease

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered Rixubis powder for injection containing 250, 500, 1000, 2000 and 3000 IU of nonacog gamma to have an overall positive benefit–risk profile for the amended indication;

> *Routine prophylaxis of bleeding episodes in adults with haemophilia B.*
>
> *Treatment and prevention of bleeding episodes in adults with haemophilia B (congenital factor IX deficiency).*

The ACPM concluded that the evidence provided in the sponsor's submission did not satisfactorily establish the safety and efficacy of Rixubis powder for injection containing 250, 500, 1000, 2000 and 3000 IU of nonacog gamma for the following indication:

> *Peri-operative management in adults with haemophilia B.*

Specific advice:

The ACPM provided the following specifically requested advice:

1. Is there sufficient evidence for use in peri-operative management of Haemophilia B?

The supportive study was small and uncontrolled. The definition of 'major' surgery was considered inaccurate. Only 11 patients had 'major' surgery; this included two hernia repairs and seven had orthopaedic procedures. There was no major intra-abdominal surgery. The small size of the surgery study and the paucity of major surgery mean that this contingency has been inadequately assessed. This could be reassessed when more data from supportive Study 251002 is available. There are alternative products which can be used peri-operatively.

2. Is there sufficient evidence for use in children 12 plus years of age?

The ACPM advised there was insufficient evidence to support use in this population. There were only three teenagers in the pivotal study. Children have access to other products. The ACPM await publication of the on-going paediatric trial with interest.

3. Is risk of inhibitor development acceptably low?

The large amounts of clotting factors sometimes needed in trauma or surgery are considered to be a risk factor for the development of inhibitors; however, the risk of inhibitor development is considered much lower in Haemophilia B compared to Haemophilia A. The limited evidence available suggests high level inhibitor formation seems unlikely. Longer term follow-up is needed to be absolutely certain.

4. In what patient population is there a positive benefit-risk balance for this product?

The ACPM advised there was sufficient evidence to support a positive benefit-risk balance in the indications recommended here, namely:

- Routine prophylaxis of bleeding episodes in adults with haemophilia B.
- Treatment and prevention of bleeding episodes in adults with haemophilia B (congenital factor IX deficiency).

Proposed conditions of registration:

The ACPM agreed with the delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Subject to satisfactory implementation of the Risk Management Plan most recently negotiated by the TGA,
- Negotiation of Product Information and Consumer Medicines Information to the satisfaction of the TGA.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Rixubis for lyophilised powder for intravenous injection vial, diluent vial and Baxject II Transfer device containing nonacog gamma 250, 500, 1000, 2000 and 3000 IU, indicated for:

Routine prophylaxis of bleeding episodes in adults with haemophilia B

Treatment and prevention of bleeding episodes in adults with haemophilia B (congenital factor IX deficiency)

Peri-operative management in adults with haemophilia B

Specific conditions of registration applying to these goods

- Implement the Rixibus RMP version 1.0, dated 26 August 2013, with Australian specific annex (version 1.0) and any future updates as a condition of registration.

- It is a condition of registration that, as a minimum, the first five independent batches of Rixubis nonacog gamma 250 IU, 500 IU, 1000 IU, 2000 IU and 3000 IU imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Office of Laboratories and Scientific Services (OLSS)

Attachment 1:.Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2:.Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
http://www.tga.gov.au