Application Type	Efficacy Supplement Application
STN	125446/31
CBER Received Date	November 13, 2013
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Division / Office	DHCR /OBRR
Priority Review	No
Reviewer Name(s)	Stephanie O. Omokaro, MD
Review Completion Date / Stamped Date	
Supervisory Concurrence	
Applicant	Baxter Healthcare Corporation
Established Name	Coagulation Factor IX (Recombinant)
(Proposed) Trade Name	RIXUBIS
Pharmacologic Class	Coagulation factor
Formulation(s), including Adjuvants, etc	Intravenous injection
Dosage Form(s) and Route(s) of Administration	Lyophilized Powder for Injectable Solution, Intravenous
Dosing Regimen	Calculated by body weight. Available in 250, 500, 1000, 2000, 3000 IU single use vials
Indication(s) and Intended Population(s)	Control and prevention of bleeding episodes, routine prophylaxis to prevent or reduce the frequency of bleeding episodes and perioperative management in children with hemophilia B

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Glossary

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ABR	Annualized bleeding rate
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
aPTT	Activated partial thromboplastin time
AUC	Area under the plasma concentration versus time curve
$AUC_{0-\infty}$ or AUC_{0-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
CIC	Circulating immune complexes
CL	Clearance
CRM	Cross-reacting material
DIC	Disseminated intravascular coagulation
DMC	Data Monitoring Committee
DVT	Deep vein thrombosis
eCRF	Electronic case report form
EC	Ethics committee
ED	Exposure day
EDCS	Electronic data capture system
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
ER	Emergency room
FAS	Full analysis set
FDP	Finished Drug Product
FFP	Fresh frozen plasma
FIX	Factor IX

Abbreviation	Definition
GCP	Good clinical practice
HAV	Hepatitis A virus
anti-HBs	Antibody to hepatitis B surface antigen
anti-HBc	Antibody to hepatitis B core antigen
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
h(r)	hour
HR QoL	Health-related quality of life
hs-CRP	High-sensitive C-reactive protein
ICF	Informed consent form
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
INR	International normalized ratio
IP	Investigational product
IR	Incremental recovery
ITI	Immune tolerance induction
IU	International units
MRI	Magnetic resonance imaging
MRT	Mean residence time
NOAEL	No observable adverse event level
PE	Pulmonary embolism
PI	Principal investigator
PK	Pharmacokinetic
PRBC	Packed red blood cells
PTP	Previously treated patient
PUP	Previously untreated patient
SAE	Serious adverse event
SAER	Serious adverse event report

Abbreviation	Definition
SIC	Subject identification code
SPC	Summary of product characteristics
STD	Standard deviation
SWFI	Sterile water for injection
TAT	Thrombin-antithrombin
$T_{1/2}$	Elimination phase half-life
VAS	Visual analog scale
V_{ss}	Volume of distribution at steady state
WFH	World Federation of Hemophilia

Page numbers: All page numbers in this document refer to the electronic page number from the digital documents as numbered by Adobe Acrobat.

1. Executive Summary

RIXUBIS is a recombinant human coagulation Factor IX (rFIX) that is secreted by genetically engineered mammalian cells derived from a Chinese Hamster Ovary (CHO) cell line. RIXUBIS is licensed in the US since June 2013. RIXUBIS is a lyophilized preparation indicated as intravenous replacement therapy for control and prevention of bleeding episodes, routine prophylaxis and perioperative management in adults with hemophilia B.

The supplemental Biologics License Application (sBLA) from Baxter is seeking a label expansion to include control and prevention of bleeding episodes, routine prophylaxis and perioperative management in children with hemophilia B. The sBLA contains data from a single phase 2/3 prospective, open-label, uncontrolled, multicenter study evaluating the hemostatic efficacy, safety, immunogenicity and health-related quality of life (HR QoL) of RIXUBIS in previously treated patients (PTPs) <12 years of age. RIXUBIS has received orphan designation and exclusivity for the routine prophylaxis indication.

A total of 23 subjects were enrolled in the pediatric study and all of these subjects were used for analysis of safety and efficacy in the treatment phase. RIXUBIS is effective in preventing bleeding in pediatric hemophilia B subjects on a twice weekly prophylaxis dose. The subjects were dosed with 40-60 IU/kg twice weekly with a mean annualized bleeding rate (ABR) of 2.7 compared to a historical mean ABR prior to enrollment of 6.8. A 22% lower recovery and a 36-66% higher clearance [36% (6-12 years) and 66% (<6 years) per kg body weight] than adult subjects treated with RIXUBIS was observed in pediatric subjects. The starting dose of 60 IU/kg was recommended for children <12 years based on a 40% difference in exposure (AUC) of RIXUBIS in children <6years of age. Dose adjustment of RIXUBIS is needed in pediatric subjects.

FIX inhibitor formation was not observed. Non-neutralizing FIX antibodies of indeterminate-titer were seen in 6 subjects and indeterminate-titer anti-rFurin antibodies were seen in 2 subjects. FIX and rFurin antibodies were considered of indeterminate specificity because they were below the threshold pre-specified for positivity and within the limits of assay variability. A risk analysis assessment addressing potential safety concerns was performed for similar findings during the pivotal study. The risk assessment analysis showed no associated clinical findings including no adverse events, lack of therapeutic effect or alterations in pharmacokinetics in study subjects that developed indeterminate or low-titer antibodies. Healthy subject data using the same assay was provided at the time of initial licensure and demonstrated similar reactivity without exposure to the investigational product.

The benefit to risk profile for RIXUBIS in children remains favorable despite indeterminate-titer non-inhibitory binding antibodies to FIX and rFurin as there was no observed clinical significance.

Recommendation:
An approval is recommended.

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Hemophilia B (Christmas disease) is a rare hereditary blood disorder caused by deficiency or dysfunction of factor IX resulting in bleeding secondary to abnormal clot formation. The hemophilia B gene is located on the X chromosome with an X-linked recessive inheritance pattern, affecting 1 in 100,000 male births and rare females.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Treatments for hemophilia B require replacement with a form of factor IX. Factor IX therapy includes human plasma products such as fresh-frozen plasma or prothrombin complex concentrates. Monoclonally purified, recombinant factor IX preparations are now available and are the mainstay of therapy.

2.3 Safety and Efficacy of Pharmacologically Related Products

FDA-approved recombinant factor IX products include BeneFIX, which was approved in 1997, RIXUBIS approved in 2013 and ALPROLIX approved in 2014. There are two plasma derived factor IX products approved: Alphanine and Mononine.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

RIXUBIS was approved for adults with hemophilia B in 2013.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The evidence for safety and efficacy for this product was collected under IND 14488, BLA 125446/0 and sBLA 125446/31.

3. Significant Efficacy/Safety Issues Related to Other Review Disciplines

3.1 Chemistry, Manufacturing, and Controls

Please refer to RIXUBIS' original BLA for details on CMC. No manufacturing changes have been made since the licensure in US. A brief summary of the product and its manufacturing process are provided below.

RIXUBIS is a purified protein that has –b(4)- amino acids in –b(4)- chain. It has a–b(4)-amino acid sequence that is comparable to the Ala148 allelic form of plasma–derived factor IX with ---b(4)---------- RIXUBIS is secreted by genetically engineered mammalian cells derived from a CHO cell line. No human or animal materials are employed during the manufacturing process of RIXUBIS.

The purification process includes two validated viral inactivation/reduction steps: solvent/detergent virus inactivation and nanofiltration. The potency (in international units, IU) is determined using an *in vitro* one-stage clotting assay against the World Health Organization International Standard for factor IX concentrate. Factor IX potency results for RIXUBIS can be affected by the type of aPTT reagent and reference standard used in the assay; differences of up to 40% have been observed.

The final product is a sterile, nonpyrogenic, preservative-free, lyophilized preparation for intravenous injection.

4. Sources of Clinical Data and Other Information Considered in the Review

4.1 BLA/IND Documents that Serve as the Basis for the Clinical Review

Documents pertinent to the review of this submission were provided in this BLA 125446/31.

4.2 Table of Studies/Clinical Trials

The clinical trial is summarized in the Table below.

Table 1
Listing of Clinical Studies in the BAX326 Clinical Development Program

Study Number	Type of Study	Study Status	Subjects in ISS[a]	Criteria	Dose Range and Frequency
251101	Pediatric Phase 2/3	Completed	1	PTP < 12 y	Prophylactic treatment: 50 IU/kg twice weekly, (range: 40 to 80 IU/kg) Acute bleeding episodes: to be treated with BAX326

[Adapted from BLA 125446/0 Full Clinical Study Report]

4.3 Consultations

No consultations were requested by the clinical team.

4.4 Advisory Committee Meeting (if applicable)

N/A

4.5 External Consults/Collaborations

N/A

5. Applicable Literature

Montgomery RR, Gill JC, Scott JP. Hemophilia and von Willebrand's Disease (2003). In: Nathan and Oski's Hematology of Infancy and Childhood, 6th, Nathan DG, Orkin SH, Ginsberg D, Look AT (Eds), WB Saunders, Philadelphia.

European Medicines Agency. (2011, July 21). Guideline on clinical investigation of recombinant and human plasma-derived factor IX products (EMA/CHMP/BPWP/144552/2009). Retrieved from http://www.ema.europa.eu

Xue, L., Johnson, R., & Gorovits, B. (2010). Prevalence and isotypic complexity of the anti-chinese hamster ovary host cell protein antibodies in normal human serum. *The AAPS Journal, 12*(1), 98-106.

Guidelines for the Management of Hemohilia (2005). *World Federation of Hemophilia, www.wfh.org.*

Bullinger, M., Globe, D., Wasserman, J., Young, N.L., & von Mackensen, S. (2009). Challenges of Patient-Reported Outcome Assessment in Hemophilia care- a State of the Art Review. *Value In Health*, 12(5), 808-820.

Johnson, K.A. & Zhou, Z-Y. Cost of care in Hemophilia and Possible Implications of Health Care Reform. ASH Education Book (2011), 413-418. *American Society of Hematology, http://asheducationbook.hematologylibrary.org/content/2011/1/413.full.pdf*

Bourne, G.L. & Grainger, D.J. (2011). Development and characterization of an assay for furin activity. *Journal of Immunological Methods*, 364, 101-108.

Wasley, L.C. et al. (1993). PACE/Furin can process the vitamin K-dependent pro-factor IX precursor within the secretory pathway. The *Journal of Biological Chemistry*, 268(12), 8458-8465.

Ornatowski, W. et al. (2007). Elevated furin levels in human cystic fibrosis cells result in hypersusceptibility to exotoxin A-induced cytotoxicity. The *Journal of Clinical Investigation*, 117(11), 3489-3497.

Saenko, E.L. et al. (2002). The future of recombinant coagulation factors. *Journal of Thrombosis and Haemostasis*, 1, 922-930.

6. Discussion of Individual Studies/Clinical Trials

The pediatric trial was initiated on December 20, 2011 and completed on May 14, 2013. The final clinical study report was submitted on November 13, 2013.

6.1 Trial #1

Pharmacokinetics, Safety and Efficacy of RIXUBIS in Pediatric Subjects with Hemophilia B

The pharmacokinetic (PK) results are covered in the review conducted by clinical pharmacology.

6.1.1 Objectives (Primary, Secondary, etc)

The objective of the trial was to evaluate the safety and efficacy of RIXUBIS in pediatric subjects with hemophilia B. Safety assessments included acute infusion reactions and inhibitor formation, while efficacy was determined by breakthrough bleeding during prophylaxis and efficacy ratings at bleed resolution.

The detailed objectives of the trial were as follows:

Primary Objective:
To evaluate all adverse events (AEs) possibly or probably related to RIXUBIS.

Secondary Objective(s):
• To evaluate the PK parameters of RIXUBIS in PTPs <12 years of age

• To monitor incremental recovery (IR) of RIXUBIS over time

• To evaluate the hemostatic efficacy of RIXUBIS in the management and prevention of acute bleeding episodes for a period of 6 months

• To evaluate safety in terms of immunogenicity for a minimum of 50 exposure days (EDs), the occurrence of thrombotic events, as well as clinically significant changes in routine laboratory parameters (hematology/clinical chemistry) and vital signs

• To evaluate changes in HR QoL and health resource use.

6.1.2 Design Overview

The study was designed as a phase 2/3 prospective, open-label, uncontrolled, multicenter trial to evaluate the hemostatic efficacy, safety, immunogenicity and health-related quality of life (HR QoL) in PTPs <12 years of age with twice weekly prophylactic infusions over the duration of 6 months or at least 50 exposure days (EDs), whichever occurred last.

Prior to the start of the 6 month prophylactic treatment period, a PK evaluation was performed. There were 2 cohorts, based on the age of the subjects: <6 years (N=11) and 6

to < 12 years (N=12). Non-linear mixed model (population PK) was used to estimate the pharmacokinetic parameters from factor IX activity measurements in 4 blood samples obtained up to 60 hours following the infusion in each subject.

Factor IX levels and history of inhibitor development were gathered prior to RIXUBIS infusion. Clinical and laboratory assessments were conducted as safety evaluation. These included thrombotic markers (D-dimer, F1+2, and TAT) that were evaluated pre-infusion and at multiple times post infusion.

6.1.3 Population

Requirements for this study included severe (FIX activity <1%) or moderately severe (FIX activity 1-2%) deficiency. Subjects also had at least 150 prior EDs with a FIX product or previous enrollment in IMMUNINE study.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects in a non-bleeding state were to receive an initial infusion with RIXUBIS at a dose of 75 ± 5 IU/kg for PK assessment. The maximum infusion rate for the PK infusion was 4 mL/minute. A minimum wash-out period of 5 days, preferably 7 days, had to be observed prior to the PK infusion. A dose of 75 ± 5 IU/kg RIXUBIS was administered at each of the study visits for the PK portion to assess FIX IR.

A dose of 50 IU/kg RIXUBIS, ranging from 40-80 IU/kg, was given twice weekly for a period of 6 months or for at least 50 EDs. The first two prophylactic RIXUBIS infusions following the PK assessment were administered at the study site (ED 2 and 3) and the subject was monitored for vital signs and the occurrence of AEs over a period of 2 hours.

The prophylaxis dose and frequency could be adjusted at the discretion of the investigator according to the individual IR and the half-life of the subject, the age, the number of breakthrough bleeds, and/or the subject's physical activity. However, the frequency of RIXUBIS administration could not be less than twice weekly.

6.1.5 Directions for Use

No special instructions were used.

6.1.6 Sites and Centers

The trial was a multi-investigator, multicenter, international study. Sites from Europe (Bulgaria, Czech Republic, Germany, Poland, Romania, Spain, Sweden, UK, Ukraine), Russia, South America (Argentina, Brazil, Chile, Colombia) and Japan were included.

6.1.7 Surveillance/Monitoring

The safety of this study was reviewed by an independent data and safety monitoring board (DSMB), composed of 5 experts in the field of hemophilia clinical care and research as well as an independent biostatistician who met at least annually at specified time points for data review. Screening assessments were provided in Table 21.3 (see

below) in amendment 7 of the protocol document. Physical examinations, medical histories, and concomitant medications were assessed. Adverse events and vital signs were recorded at each PK time point. The total duration for PK assessment was 72 hours, with evaluation of thrombogenicity pre- and post-infusion.

21.3 Schedule of Study Procedures and Assessments

Table 21.3-21.3-1
Schedule of Study Procedures and Assessments

Procedures/ Assessments	Screening Visit	Baseline[a]	Part 1 for Infusions 1 and 2 (Duration 2-4 Weeks)			Part 2 Study Visits (Duration 26 ± 1 Weeks)[b]				Part 3 (Duration ~ 1 Week)			Study Completion/ Termination Visit[f]
			Pre-Infusion	In-fusion	Post-Infusion	ED 1[c]	Week 5 ± 1 EDs 10-15[d]	Week 13 ± 1	Week 26 ± 1[e]	Pre-Infusion	In-fusion	Post-Infusion	
Informed consent[g]	x												
Eligibility criteria	x												
Medical history	x												
Medications and non-drug therapies	x	x	x	x	x	x	x	X	x	x	x	x	x
Physical examination	x[h]		x			x	x	X	x	x[h]			x
Adverse events	x	x	x	x	x	x	x	X	x	x	x	x	x
Laboratories[i]	x	x	x		x	x	x	X	x	x		x	x
Vital signs[j]	x	x	x		x	x	x	X	x	x		x	x
Randomization		x[k]											
IP treatment[l]		(x)		x[m]		x	x	X	x		x		x
Hand out subject diary	x				x	x	x	X	x[n]			x[n]	
Review subject diary		x	x		x	x	x	X	x	x		x	x
HR QoL					x[o]	x[c]			x			x[o]	

[Source: BLA 125446/31 Pediatric Study Protocol]

6.1.8 Endpoints and Criteria for Study Success

The pharmacokinetic trial was conducted in pediatric subjects. The primary pharmacokinetic endpoint was to monitor IR over time. Additional PK endpoints were area under the plasma concentration vs. time from 0 to 72 hours, total AUC/dose, MRT, CL, IR, elimination phase half-life and Vss.

Clinical safety assessments included AEs and the following laboratory studies: immunology (total binding and inhibitory antibodies to FIX, antibodies to CHO proteins and rFurin), hematology, clinical chemistry, viral serology and urinalysis.

Hemostatic efficacy was assessed by the subjects and treating physicians using a predefined 4-point rating scale (See Table 9.5-2).

Table 9.5-2
Rating Scale for Treatment of Bleeding Episodes

Excellent	Full relief of pain and cessation of objective signs of bleeding (e.g. swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution.
None	No improvement or condition worsens.

[Source: BLA 125446/31 Full Clinical Study Report]

In subjects 2 to 7 years of age, the PedsQL (Parent-proxy versions for ages 2-4 and 5-7) and health resource utilization scales were measured. Subjects between 8 and 11 years of Age were assessed with the Haemo-QOL (short version), PedsQL (child version) scales and health resource utilization were measured

6.1.9 Statistical Considerations & Statistical Analysis Plan

There were no formal sample size considerations. The sample size was based on EMA requirements that there be at least 10 subjects aged 6 to 12 years and 10 subjects < 6 years. A total of 24 subjects were enrolled to account for potential drop-outs.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Inclusion criteria included:

1. Severe or moderately severe hemophilia B (factor IX activity ≤1-2%)
2. Previously treated subjects with a minimum of 150 exposure days to a factor IX preparation
3. Subject age at time of screening: <12

Exclusion criteria included:

1. History of factor IX inhibitor ≥0.6 Bethesda units
2. Existence of another coagulation disorder
3. Known hypersensitivity to hamster proteins or rFurin

6.1.10.1.1 Demographics
The mean subject age was 7 years; age range was 1.8-11.8 years. All subjects were Caucasian with the exception of one of Indian descent. All were male.

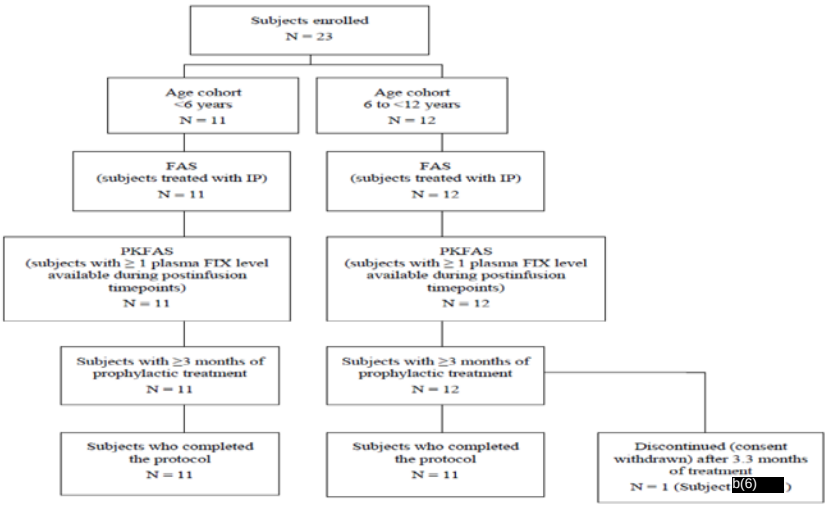
6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
The two age groups (age <6 years and 6 to 12 years) had similar average baseline levels of factor IX. The mean annualized bleeding rate (ABR) was 6.8 prior to enrollment for

both age groups. The study excluded subjects with significant concurrent illnesses and subjects receiving drugs such as chemotherapy, aspirin, or other anticoagulants.

6.1.10.1.3 Subject Disposition

Twenty three subjects were enrolled. All were treated with RIXUBIS and completed the PK assessment. Eleven were <6 years and 12 were 6 - <12 years of age. Twenty-two subjects completed the protocol and one subject discontinued after 3 months of treatment due to efficacy concerns.

Figure 10.1-1
Flowchart for Study 251101



[Source: BLA 125446/31 Full Clinical Study Report]

6.1.11 Efficacy Analyses

Please refer to the clinical pharmacology memo for PK data and assessment. Of note, a 22% lower recovery and a 36-66% higher clearance [36% (6-12 years) and 66% (<6 years) per kg body weight] than adult subjects treated with RIXUBIS was observed in pediatric subjects. The starting dose of 60 IU/kg was recommended for children <12 years based on a 40% difference in exposure (AUC) of RIXUBIS in children <6years of age. Dose adjustment of RIXUBIS is needed in pediatric subjects.

All subjects (N=23) received prophylaxis at a mean dose of 56.25 IU/kg twice weekly (ranging from 40-80 IU/kg) for a mean treatment duration of 6 months. The mean ABR of 2.7 (See Table 10) was 40% lower than the mean historical rate of 6.8. The mean ABR was higher in the older age cohort (6 to <12 years) at 3.4 compared to 1.9 in subjects < 6 years of age. This difference may be attributed to increased activity as well as number of target joints in the older age cohort but accurate conclusions are limited by the small sample size. Nonetheless, the results remain consistent with improvement and reduction in the bleeding frequency with prophylactic treatment. RIXUBIS is effective in reducing bleeding when administered as routine prophylaxis in pediatric subjects 12 years or younger with hemophilia B.

Table 10 **Efficacy of Prophylaxis of RIXUBIS in 23 PTPs <12 Years of Age**	
Total annualized bleeding rate (ABR) Mean ± SD Median (range)	 2.7 ± 3.14 2.0 (0.0–10.8)
ABR for joint bleeds Mean ± SD Median (range)	 0.8 ± 1.76 0.0 (0.0–7.2)
ABR for spontaneous bleeds Mean ± SD Median (range)	 0.2 ± 0.66 0.0 (0.0–2.0)
Subjects with zero bleeds % (n)	 39.1.% (9)

* The prophylactic regimen consisted of 40 to 80 IU/kg. RIXUBIS twice weekly However the data support a dose of 60-80IU/kg.
. The historical mean ABR prior to enrollment was 6.8.

[Source: RIXUBIS Package Insert]

There were a total of 26 bleeds recorded during the study in 14 subjects. The remaining 39% of subjects had no bleeding during prophylaxis with RIXUBIS. The majority of bleeding episodes were injury related (88%). By site and causality for all bleeds, 27% were joint bleeds, 73% were muscle or soft-tissue bleeds, 8% were spontaneous and 4% were of unknown cause. Fifty-eight percent of all bleeds required one infusion, 31% were treated with 2 infusions and 12% required more than 3 infusions.

For each bleeding episode, subjects or their caretaker were asked to rate the efficacy of RIXUBIS on a four point scale of excellent to poor. An excellent rating was defined as full relief of pain and cessation of objective signs of bleeding after a single infusion with no additional infusion required; Good: definite pain relief and/or improvement in signs of bleeding after a single infusion; possibly requires more than one infusion for complete resolution; Fair: probable and/or slight relief of pain and/or slight improvement in signs of bleeding after a single infusion; possibly requires more than one infusion for complete resolution; None: no improvement or condition worsens. Hemostatic efficacy at bleed resolution was rated as excellent or good in 96% of total bleeds. Fifty percent of the bleeding episodes were rated as excellent, 46% as good, and 4% as fair. The mean total dose per bleed was 94.4 ± 52.41 IU/kg (median: 71.4 IU/kg, range: 36-255 IU/kg). There was one subject who required 4 infusions totaling 255 IU/kg appropriate for an injury related bleed in the occipital area. The high dose corresponds to the type of bleed and severity and did not reveal safety concerns.

No meaningful conclusions could be drawn from HR QoL measurements as the assessments were considered underpowered and exploratory.

The efficacy of perioperative management in children with hemophilia B >12 years of age was evaluated during the pivotal study in adults and can be extrapolated to children <12 years of age.

6.1.11.1 Dropouts and/or Discontinuations

One subject discontinued from the study after three months of treatment due to the guardian's doubts regarding efficacy of RIXUBIS prophylaxis. The subject experienced 3 injury related bleeds and only one required treatment. The one treated joint bleed was rated as fair and required 2 RIXUBIS infusions at a dose of 77 IU/kg per dose to achieve hemostasis. No subject discontinued treatment secondary to adverse events.

6.1.12 Safety Analyses

6.1.12.1 Methods

Safety of study subjects was monitored in terms of AEs, immunogenicity, history and physical examination, laboratory measurements, and bleeding assessments. Although bleeding was monitored and considered an efficacy outcome, subjects were monitored for development of inhibitors that might predispose to bleeding. Immunogenicity testing by ELISA included total binding antibodies to FIX, inhibitory antibodies to FIX, antibodies to CHO protein and rFurin. The protocol included pre-specified definitions of adverse reactions including severity, seriousness, and relatedness. A DSMB monitored the study.

Preinfusion baseline levels of factor IX, inhibitory, and non-inhibitory antibodies were also assessed.

6.1.12.2 Overview of Adverse Events

Overall, there were 48 AEs that occurred in 17 subjects. There were no deaths as well as no cases of nephrotic syndrome, inhibitors, or anaphylaxis.

There were no patterns of increased consumption or other patterns suggestive of inhibitor formation. Formation of binding antibodies against FIX (non-neutralizing) and rFurin proteins is discussed in section 6.1.12.5.

There were no treatment-emergent adverse events observed within 24 hours after RIXUBIS infusion. The most frequently occurring events were indeterminate-titer binding antibodies to FIX and /or rFurin (26%), rhinitis (9%), nasopharyngitis (9%), headache (9%) and abdominal pain (9%).

There were 4 serious AEs observed (subcutaneous hemorrhage, humerus fracture, device related infection and hemarthrosis) that are considered unrelated to RIXUBIS based on clinical review of case reports.

6.1.12.3 Deaths

There were no deaths in subjects who received RIXUBIS.

6.1.12.4 Nonfatal Serious Adverse Events

Of the 4 SAEs reported, none were considered related to treatment. There were no patterns suggestive of inhibitor formation. The SAEs included subcutaneous

hemorrhage, humerus fracture, device related infection and hemarthrosis and are unlikely to be caused by RIXUBIS.

6.1.12.5 Adverse Events of Special Interest (AESI)

Inhibitor formation was monitored using the –b(4)----------of the Bethesda assay titer > 0.6 BU or total binding antibodies with a positive titer of 1:80. Events of special interest included thrombosis, hemolysis, transmitted infections, and immunogenicity. No case of confirmed inhibitor, thrombosis or hemolysis was detected.

A validated screening and confirmatory ELISA assay was used to detect antibodies against CHO, FIX and rFurin. No anti-CHO antibodies were detected during the study. Eight subjects developed binding antibodies against FIX (N=6) and/or rFurin (N=2) of indeterminate specificity (1:20 and 1:40 titers). These 8 subjects were antibody negative for the confirmatory assay since the titers were too low for the assay to be done. No clinically relevant abnormalities were reported in any of these subjects. Baxter performed a comprehensive risk assessment analysis for similar results obtained during the pivotal and continuation studies in both adult and pediatric subjects and determined no clinical consequences.

The conclusion that indeterminate antibodies (1:20 and 1:40) had no impact on safety and efficacy, no temporal association with adverse events and no impact on pharmacokinetic parameters is well supported by review of the data.

6.1.12.6 Clinical Test Results

None of the subjects developed thrombosis, anaphylactic reactions or inhibitor antibodies to RIXUBIS.

Aside from the antibodies of indeterminate specificity to FIX and/or rFurin, there were no patterns of clinically significant laboratory abnormalities that could be ascribed to RIXUBIS. Similarly, no patterns of abnormal vital signs or physical examination findings were noted.

6.1.12.7 Dropouts and/or Discontinuations

One subject discontinued from the study after three months of treatment due to the guardian's doubts regarding efficacy of RIXUBIS prophylaxis. The subject experienced 3 injury related bleeds and only one required treatment. The one treated joint bleed was rated as fair and required 2 infusions of RIXUBIS at a dose of 77 IU/kg per dose to achieve hemostasis. No subject discontinued treatment secondary to adverse events.

The number of discontinued subjects is within acceptable limits.

8.4.4 Common Adverse Events

The summary table of adverse reactions below is adapted from the RIXUBIS package insert.

Summary Table of Adverse Reactions

System Organ Class	Adverse Reactions (AR)	Number of ARs (N)	Number of Subjects (N=99) n (%)	Percent per Infusion (N=14,018)
Nervous System Disorders	Dysgeusia	2	1 (1.01%)	0.014%
Musculoskeletal and Connective Tissue Disorders	Pain in extremity	1	1 (1.01%)	0.007%

System Organ Class	Adverse Reactions (AR)	Number of ARs (N)	Number of Subjects (N=99) n (%)	Percent per Infusion (N=14,018)
Investigations	Positive furin antibody test[a]	2	2 (2.02%)	0.014%

8.4.5 Clinical Test Results

No safety signals were seen in the routine laboratory results, physical examinations, or vital signs. The results of immunogenicity studies are provided in section 8.5.

8.4.6 Adverse Events of Special Interest

Events of special interest included thrombosis, hemolysis, transmitted infections, and immunogenicity. No episodes of thrombosis, hemolysis, or product-transmitted infection occurred during the study.

8.5 Additional Safety Evaluations

8.5.1 Immunogenicity (Safety)

There was no pattern of increased consumption of product, the absence of which is evidence against clinically significant immunogenicity mediated by neutralizing antibody against the therapeutic protein.

Although formation of FIX inhibitors was not observed, non-neutralizing FIX antibodies of indeterminate-titer were seen in 6 subjects and similarly development of indeterminate -titer anti-rFurin antibodies was seen in 2 subjects (N=23). FIX or rFurin antibodies were considered indeterminate specificity because they were below the threshold pre-specified for positivity and within the limits of assay variability. None of these subjects reached the threshold for positivity at a titer of 1:80 and there were no associated adverse events in any of the subjects.

The potential clinical significance of binding antibodies to FIX and/or rFurin was evaluated at the time of initial licensure through a risk analysis assessment addressing potential safety concerns. Baxter provided data from 500 healthy subjects from 5 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 investigational product. Of these, 7% had titers of 1:20 or 1:40 and 1.2% had higher titers 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. The theorized mechanism is the creation of an immunological homunculus that maintains immune homeostasis as well as binds apoptotic cells thereby facilitating uptake and clearance by dendritic cells.

The risk assessment analysis showed no associated clinical findings in study subjects with low-titer or indeterminate titer binding antibodies during the development program for RIXUBIS including no adverse events, lack of therapeutic effect or alterations in pharmacokinetics.

8.6 Safety Conclusions

Six subjects out of 23 developed indeterminate -titer non-neutralizing antibodies to FIX (26%) and 2 subjects had indeterminate -titer binding antibodies to rFurin (9%) host cell proteins. None of the subjects reached the true limit of detection for rFurin antibody or FIX antibody. No clinically significant adverse reactions could be ascribed to these antibodies, though the long-term consequences are unknown.

9. Additional Clinical Issues

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Not studied.

9.1.2 Use During Lactation

Not studied.

9.1.3 Pediatric Use and PREA Considerations

RIXUBIS is recommended for approval for pediatric use in control and prevention of bleeding, routine prophylaxis and perioperative management. Routine prophylaxis in children is an orphan designated indication with exclusivity. A 22% lower recovery and a 36-66% higher clearance [36% (6-12 years) and 66% (<6 years)] than adult subjects treated with RIXUBIS was observed in pediatric subjects (<12 years, n=23). The starting dose of 60 IU/kg was recommended for children <12 years based on a 40% difference in exposure (AUC) of RIXUBIS in children <6years of age. Dose adjustment of RIXUBIS is needed in pediatric subjects.

9.1.4 Immunocompromised Patients

Not studied.

9.1.5 Geriatric Use

Not applicable because of younger age of this population.

10. Conclusions

RIXUBIS is effective in control and prevention of bleeding, routine prophylaxis and perioperative prophylaxis in adults and children with hemophilia B. Baxter's calculations were reproduced and confirmed by both the clinical, pharmacology and statistical reviewers. In 23 pediatric subjects, development of inhibitory antibodies against the product was not observed.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hemophilia B is a rare condition with variable deficiency of coagulation factor IX. • Hemophilia is accompanied by bleeding into tissues and joints which can be spontaneous, post-traumatic, or perioperative. • Bleeding can be acutely devastating, such as intracranial bleeding, or chronically destructive such as hemophilic arthropathy.	• Hemophilia B is a serious, progressive, life-threatening disease. • The bleeding associated with hemophilia can cause clinically significant complications. • Current treatment is expensive and carries risks of infection or adverse reactions.
Unmet Medical Need	• There are two other recombinant factor IX products licensed for use by FDA. • Numerous other plasma-derived factor IX products exist, but carry the same risks as other human plasma products, such as infection with known or unknown agents, acute hypersensitivity reactions, or immunogenicity with resistance.	• Although alternative recombinant therapy exists for Hemophilia B, it is expensive with the average on-demand treatment ranging from ~$130,000-300,000/year and even higher costs for those on prophylactic therapy. Increasing the number of available licensed products could have a positive impact and allow options for hemophilia patients who remain untreated due to high costs.
Clinical Benefit	• RIXUBIS was shown to be effective for treatment of, and prevention against spontaneous or traumatic bleeding by both prophylactic or on-demand regiments • RIXUBIS was shown to be effective in the perioperative setting for reduction of bleeding during surgery.	• RIXUBIS is similarly effective to the currently licensed recombinant product.
Risk	• Six subjects out of 23 developed indeterminate-titer non-neutralizing antibodies to FIX and 2 subjects had indeterminate-titer binding antibodies rFurin host cell proteins. • No associated clinical sequelae were noted. • The long term consequences of indeterminate or low-titer binding FIX and/or rFurin antibodies are unknown though cross-reactivity with innate proteins is possible.	• The risks of long-term exposure to immunogenic proteins with RIXUBIS are largely unknown but increasing or very high titers could theoretically result in allergic reactions, anaphylaxis, serum sickness, autoimmunity, and immunogenicity.
Risk Management	• An approval is recommended.	• An adequately designed PMC cohort event safety and efficacy monitoring study would help to better understand potential aspects of the process of immunogenicity development was implemented at the time of initial licensure. • Recipients would need to be routinely evaluated in order to monitor for reactivity and complications, many of which are unknown at this point requiring broad surveillance.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Summary and Assessment

A risk assessment analysis was performed and showed no associated clinical findings in study subjects with indeterminate or low-titer binding antibody formation to FIX and/or rFurin during the development program for RIXUBIS including no adverse events, lack of therapeutic effect or alterations in pharmacokinetics.

Due to the effective hemostasis in control and prevention of bleeding episodes, routine prophylaxis and perioperative prophylaxis in adults and children with hemophilia B, the benefits are considered to outweigh the risks of this product.

No new risks were identified in the pediatric trial. No new pharmacovigilance plan or post-marketing risk mitigation management activities were provided nor requested. Overall the benefit/risk profile is favorable.

11.2 Discussion of Regulatory Options

The regulatory option discussed was approval of the indications of control and prevention of bleeding, routine prophylaxis and perioperative prophylaxis in children with hemophilia B.

11.3 Recommendations on Regulatory Actions

An approval is recommended.

11.4 Labeling Review and Recommendations

In conjunction with the Advertising & Promotional Labeling Branch (APLB), Clinical Pharmacology Branch and Nonclinical Branch, a labeling review with recommendations was sent to Baxter and negotiated from August 7-23, 2014. The amended draft package insert submitted on August 28, 2014 is acceptable.