



**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Biostatistics and Epidemiology**

MEMORANDUM

Date: May 20, 2013

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Through: Christopher Jankosky, MD, MPH
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Subject: Pharmacovigilance plan review for initial licensure

Applicant: Baxter Healthcare Corporation

Product: Coagulation Factor IX (Recombinant), BAX326, Rixubis

Proposed Indication: Control and prevention of bleeding episodes in hemophilia B including perioperative management and routine prophylaxis. Indication is for patients b(4) years of age and older with hemophilia B.

Submission Type: BLA 125446

PVP Submission Date: August 30, 2012

Action Due Date: June 30, 2013

1. INTRODUCTION

a. Product Description

Coagulation factor IX (Recombinant), also referred to in the BLA application as BAX326, --b(4)-----, or Rixubis is a glycoprotein secreted by genetically engineered mammalian cells derived from a Chinese hamster ovary (CHO) cell line. BAX326 consists of b(4) amino acids and has structural and functional characteristics similar to those of endogenous factor IX (FIX). Coagulation factor IX (Recombinant) is formulated as a lyophilized powder and is intended for intravenous (IV) injection.

b. Regulatory History

This submission is the initial application for licensure of BAX326, Coagulation factor IX (Recombinant) in the U.S.

c. Objectives

This memorandum is in response to a request from the Office of Blood Research and Review (OBRR) to the Office of Biostatistics and Epidemiology (OBE) to review the risk management plan submitted by Baxter Healthcare Corporation with the BLA 125446 submitted on August 30, 2012. The BLA is seeking initial licensing of the product BAX326, coagulation factor IX (Recombinant), for the indications of control and prevention of bleeding episodes in patients with hemophilia B, including perioperative management in patients with hemophilia B and routine prophylaxis. The indications are for patients b(4) years of age and older with hemophilia B.

Please note that text in italics is verbatim from the BLA.

2. MATERIALS REVIEWED

Source	Subtype	Document Reviewed
Baxter	BLA 125446	Pharmacovigilance Plan (U.S.), Version 1.0, July 16, 2012
Baxter	BLA 125446/0.4	Full Clinical Study Report for Study 250901, Sep. 11, 2012
Baxter	BLA 125446/0.4	Integrated Safety Summary, Nov. 8, 2012
Baxter	BLA 125446/0.13	Efficacy Information Amendment
Baxter	BLA125446/0.13	--b(4)----- Anti-FIX Antibody
Baxter	BLA 125446/0.13	--b(4)----- anti-Furin Antibody
Wyeth	Package insert	BeneFIX Package Insert
FDA	Annual Surveillance Report	OBE Annual Surveillance Report for BeneFIX for 2/12/11 to 2/11/12
Other	Publication	Bolton-Maggs PH, Pasi KJ. Haemophilias A and B. Lancet 2003; 361: 1801-9.
Other	Publication	Martinowitz U, Shapiro A, Quon DV, et al. Pharmacokinetic properties of IB1001, an investigational recombinant factor IX, in patients with haemophilia B: repeat pharmacokinetic evaluation

Source	Subtype	Document Reviewed
		and sialylation analysis. <i>Haemophilia</i> . 2012 Nov; 18(6):881-7.
Other	Publication	Monahan PE, Liesner R, Sullivan ST, Ramirez ME, Kelly P, Roth DA. Safety and efficacy of investigator-prescribed BeneFIX prophylaxis in children less than 6 years of age with severe haemophilia B. <i>Haemophilia</i> . 2010 May; 16:460-8.
Other	Publication	Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Treatment Guidelines Working Group on Behalf of The World Federation Of Hemophilia. Guidelines for the management of hemophilia. <i>Haemophilia</i> . 2013 Jan;19(1):e1-47, p. 61. doi: 10.1111/j.1365-2516.2012.02909.x. Epub 2012 Jul 6.
Other	Publication	Uprichard J, Adamidou D, Goddard NJ, Mann HA, Yee TT. Factor IX replacement to cover total knee replacement surgery in haemophilia B: a single-centre experience, 2000-2010. <i>Haemophilia</i> . 2012 Jan;18(1):46-9
Other	Publication	Yang R, Zhao Y, Wang X, Sun J, Jin J, Wu D, Charnigo R, O'Brien A, Zhong Z, Rendo P. Evaluation of the safety and efficacy of recombinant factor IX (nonacog alfa) in minimally treated and previously treated Chinese patients with haemophilia B. <i>Haemophilia</i> . 2012 Sep;18(5):e374-8.

3. PHARMACOVIGILANCE PLAN REVIEW

Pharmacovigilance Plan (U.S.) Version 1.0 was received on August 30, 2012. A review of the pharmacovigilance plan with supporting background clinical trial information from the BLA is included in this memorandum.

a. Clinical Safety Database

The clinical safety database for BAX326 consists of one completed study that was a combine phase 1/3 study with 73 patients. There are also three ongoing studies including one focusing on surgical procedures and one in children. Table 1 below outlines the Clinical Studies for BAX326. These studies all excluded patients with: a detectable FIX inhibitor at screening with a titer ≥ 0.6 Bethesda Units (BU) (except study 251001), patients with an acquired hemostatic defect other than hemophilia B, patients with a history of allergic reaction following exposure to FIX concentrates (except study 251001), patients with a hypersensitivity to hamster proteins or rFurin (except study 251001), patients with ongoing or recent thrombotic disease, patients with abnormal renal or hepatic function, and patients with a significant medical, psychiatric, or cognitive

illness that in the opinion of the investigator would affect the subject's safety or compliance during the study.¹

Table 1: Clinical Studies for BAX326²

Study Number (Phase)	Study Title	Number of Subjects as of Sept. 3, 2012	Status
250901 (Phase 1/3)	Prospective, controlled, multicenter study evaluating pharmacokinetics, efficacy, safety, and immunogenicity in previously treated patients with severe (FIX level <1%) or moderately severe (FIX level ≤2%) Hemophilia B	73	Interim clinical study report used by sponsor for writing of the Pharmacovigilance Plan July 2012; Final study report completed November 8, 2012
251001 (Phase 3 Continuation)	Evaluation of safety, immunogenicity, and hemostatic efficacy in previously treated patients with severe or moderately severe hemophilia B	64	Ongoing, estimated completion 2015
251002 (Phase 3)	Prospective, multicenter study evaluating efficacy and safety in previously treated patients with severe or moderately severe hemophilia B undergoing surgical or other invasive procedures	16	Ongoing, estimated completion 2015
251101 (Phase 2/3)	Prospective, uncontrolled, multicenter study evaluating pharmacokinetics, efficacy, safety, and immunogenicity in previously treated pediatric patients with severe or moderately severe hemophilia B	16	Ongoing, estimated completion late 2013

Baxter Clinical Study 250901, Phase 1/3 (Pivotal Study): *Study 250901 was a phase 1/3 study which evaluated the PK [pharmacokinetics], PK equivalence with BeneFIX, efficacy, safety, immunogenicity, and changes in health-related quality of life (HR QoL) in previously treated patients aged 12 to 65 years of age with severe (FIX level <1%) or moderately severe (FIX level ≤2%) Hemophilia B.*³ Part 1 of the study evaluated PK equivalence by studying 26 subjects in a controlled, crossover, and blinded manner. The patients received one infusion of BAX326 and 1 infusion of BeneFIX in a randomized order. Thrombotic markers were tested in addition to PK measurements. In between the two infusions and following the second infusion, subjects continued treatment as needed with a FIX concentrate other than BAX326 as determined by the investigator.

¹ BLA 125446, Pharmacovigilance Plan, p. 16.

² BLA 125444, Pharmacovigilance Plan, adapted from p. 17 and 34 with updated information from the Integrated Safety Summary, p. 9.

³ BLA 125446, Pharmacovigilance Plan, p. 17.

Part 2 of study 250901 evaluated the hemostatic efficacy, safety, immunogenicity and HR QoL of BAX326 with an open-label, uncontrolled study. The investigator and the subject decided whether the patient should receive prophylactic or on-demand treatment. Sixty subjects were enrolled for the prophylactic cohort and 15 were enrolled for on-demand treatment. The prophylactic regimen was 50 IU/kg BAX326 twice weekly for 6 months or for at least 50 exposure days (EDs). The dose and frequency could be adjusted by the investigator based on the individual's PK profile.

Part 3 of study 250901 re-evaluated the PK parameters for BAX326 with an open-label, uncontrolled study after a period of 6 months of treatment. All of the 27 patients who participated in Part 1 of study 250901 entered Part 3 after 6 months in Part 2 of the study. Part 3 consisted of a single infusion of BAX326 and the PK parameters and thrombotic markers were then compared to the same subject's data from Part 1.

The safety endpoints for this pivotal study were:

- Development of inhibitory and total binding antibodies to factor IX
- Development of antibodies to Chinese hamster ovary (CHO) proteins and recombinant furin (rFurin)
- Occurrence of severe allergic reactions, eg. anaphylaxis
- Occurrence of thrombotic events and clinically significant changes in thrombogenic markers during the PK parts of the study: prothrombin fragment 1.2 (F 1.2), thrombin-antithrombin III (TAT), D-dimer
- Investigational product (IP)-related AEs
- Clinically significant changes in routine laboratory parameters (hematology and clinical chemistry), and vital signs

Baxter Clinical Study 251001, Phase 3 (Continuation): Study 251001 is a prospective, open-label, uncontrolled continuation study following study 250901. The objective is to evaluate the safety, immunogenicity, and efficacy of BAX326 in previously treated patients with severe (FIX level <1%) or moderately severe (FIX level ≤2%) hemophilia B. The study is to provide BAX326 to subjects until the product is licensed in the subject's country or until the patient has at least 100 exposure days (EDs). The subjects will be monitored for adverse events possibly or probably related to BAX326. The goal is to include 100 adult and pediatric subjects.

Baxter Clinical Study 251002, Phase 3 (Surgery): Study 251002 is a prospective, open-label, uncontrolled trial to evaluate the safety and efficacy of BAX326 in patients with severe or moderate hemophilia B undergoing major or minor elective or emergency surgical, dental, or other invasive procedures. The enrollment goal is to have 30 patients with at least 10 major surgeries in 10 unique subjects. The study duration is 3 years and each subject's period of participation varies depending on the nature of the invasive procedure. The study started in December 2011.

Baxter Clinical Study 251101, Phase 2/3 (Pediatric): Study 251101 is a prospective, uncontrolled study in pediatric patients <12 years of age. The study is to evaluate the safety, immunogenicity, PK parameters, and changes in HR QoL over 6 months with

twice weekly prophylactic infusions for at least 50 EDs. The study was started in December 2011. The study goal is to have 24 patients enrolled in two equal cohorts of <6 years old and 6 to <12 years old.⁴

Integrated Safety Summary (ISS): Following the submission of the Pharmacovigilance Plan, the sponsor submitted an Integrated Safety Summary dated Nov. 8, 2012 which included updated information on the completed study 250901 and ongoing studies 251001, 251002, and 251101. At the time of the data lock point of Sep. 3, 2012, ninety-one patients had been treated with at least one infusion during the BAX326 clinical program. These 91 unique subjects were 86.8% White, 5.5% Japanese, 3.3% Native Latin American, 2.2% Mestizo, 1.1% Black or African American, and 1.1% Arabic. Of the 91 subjects, 6 (6.6%) were <6 years old, 10 (11%) were 6 to <12 years old, 3 (3.3%) were 12 to <16 years old, and 72 (79.1%) were adults (≥16 years old). A total of 7353 infusions of BAX326 were given in the clinical program with the majority (5716 infusions) being used for prophylaxis. Exposure was a median of 83 exposure days (EDs) per subject (range of 3 – 209 EDs).⁵

There was a total of 161 AEs in 48 (52.7%) of the 91 subjects who received BAX326 in the clinical program. Of these AEs, 6 AEs in 5 patients were considered serious. All 6 of the serious adverse events (SAEs) were considered by the investigator to be unrelated to BAX326. Table 2 lists the six serious adverse events from the BAX326 clinical trials. Further discussion of these SAEs is provided after the table.

Table 2: Serious Adverse Events from BAX326 Clinical Trials⁶

Preferred Term	Study	Severity	Relatedness to BAX326
Duodenal ulcer hemorrhage	251001	Severe	Not related
Intestinal obstruction	250901	Severe	Not related
Cervical vertebral fracture	250901	Severe	Same patient for both AEs. Not related – motor vehicle accident
Traumatic hematoma	250901	Severe	
Convulsion	250901	Moderate	Not related
Hepatitis B core antibody positive	250901	Mild	Not related

The patient with the duodenal ulcer had a gastrointestinal bleed 1 day after treatment with BAX326. He was treated with an additional dose of BAX326 and the bleeding was controlled. He continued on prophylactic BAX326.

The patient with the intestinal obstruction was found on laparotomy to have a foreign body (impacted vegetable fibers). Thus, this AE was determined to be unrelated to BAX326.

⁴ BLA 125446, Pharmacovigilance Plan, p. 22.

⁵ BLA 125446/0.4, Integrated Safety Summary, p. 38.

⁶ BLA 125446/0.4, Integrated Safety Summary, adapted from p. 30-31.

The subject with the cervical vertebral fracture and the traumatic hematoma sustained the injuries as a pedestrian hit by a motor vehicle. He received emergency treatment with BeneFIX and was thus withdrawn from the study due to receipt of a non-investigational product.

The patient with the convulsion had a history of seizures diagnosed 4 years prior to study participation. The patient typically had 1-2 seizures per year. He had a seizure several hours following BAX326 administration. The study investigator felt his seizure was due to his pre-existing seizure disorder.⁷

The patient who tested positive for Hepatitis B core antibodies had a history of chronic persistent hepatitis B. Nine years prior to participation in the study, the patient was diagnosed with chronic persistent hepatitis and was hepatitis Bs antigen positive. At enrollment in the study, the patient tested negative for hepatitis B core antibodies. At completion of the study, the patient tested positive for hepatitis B core antibodies, but the investigator felt this positive test was the result of the patient's chronic persistent hepatitis B.⁸

There were 155 non-serious AEs in the clinical program. Table 3 below lists the non-serious adverse events that occurred in at least 2 subjects during the clinical program.

Table 3: Non-serious Adverse Events in ≥ 2 Subjects for BAX326 Clinical Trials⁹

Preferred Term	Number of AEs	Number of Subjects with AEs	Relatedness
Diarrhea	6	3	Not related
Dyspepsia	2	2	Not related
Toothache	2	2	Not related
Pyrexia	5	4	Not related
Bronchitis	3	3	Not related
Gastroenteritis	3	2	Not related
Influenza	2	2	Not related
Nasopharyngitis	14	8	Not related
Pharyngitis	5	5	Not related
Pneumonia	2	2	Not related
Rhinitis	2	2	Not related
Upper Respiratory Tract Infection	4	2	Not related
Contusion	3	2	Not related
Procedural pain	3	2	Not related
Immunology test abnormal	23	17	Not related
Arthralgia	9	4	Not related

⁷ BLA 125446/0.4, Full Clinical Study Report for Study 250901, p. 236.

⁸ BLA 125446/0.4, Full Clinical Study Report for Study 250901, p. 231-232.

⁹ BLA 125446/0.4, Integrated Safety Summary, adapted from p. 32-33.

Preferred Term	Number of AEs	Number of Subjects with AEs	Relatedness
Pain in extremity	3	2	1 with unknown causality, considered possibly related
Headache	3	3	Not related
Cough	5	3	Not related

The sponsor states that *the majority of the non-serious AEs appear to have been related to mild infections or gastrointestinal disease, abnormal immunology tests (antibodies of indeterminate specificity in assays for FIX or rFurin), or arthralgia, a well-described complication of hemophilia, and not related to [BAX326].*¹⁰ The preferred term “abnormal immunology results” refers to cases in which the result of the validated, in-house enzyme-linked immunosorbent assay (ELISA) for antibodies to FIX or to rFurin was a titer of 1:20 or 1:40. This low level titer is considered to be indeterminate for the assay used. The sponsor stated that the screening ELISA test used required confirmation with a competition assay. Titers of this level are too low to be confirmed with the competition assay at three titer steps lower than the ELISA result, so they are considered indeterminate.¹¹ There was one case of a positive titer (1:80) for antibodies to rFurin which is discussed in the next paragraph.

There were four non-serious adverse events in 3 subjects that were considered by the study investigator to be related to BAX326. The first case was pain in an extremity that occurred 1 day after receiving BAX326. The cause was not known, so it was considered as possibly related. There were two AEs of dysgeusia in 1 subject. The fourth related AE was a subject who initially had an indeterminate result for antibodies for rFurin. After treatment, the patient had a confirmed titer of 1:80 for antibodies for rFurin. The patient subsequently had an indeterminate titer of 1:20. The transient rise in titer was considered treatment-related since it was a >2 fold increase.¹²

There were no deaths reported during the study. There were also no severe allergic reactions or thrombotic events. Elevated pre- and post-infusion values for thrombogenic markers in some subjects did not reveal any pattern indicative of clinically relevant thrombogenicity.¹³ No subjects developed inhibitors to FIX and no subjects developed treatment-related binding antibodies to FIX. There were 13 of 91 patients (14.3%) that expressed signals for antibodies against FIX at one or more time points of blood samples, but all had titer levels that were below the lower limit of detection for specific antibodies against FIX. Two of the 13 patients expressed signals for antibodies at screening, prior to receiving BAX326. No sample of any patient at any time point expressed a positive signal that reached the lower limit of detection for specific antibodies against FIX.¹⁴

¹⁰ BLA 125446/0.4, Integrated Safety Summary, p. 33.

¹¹ BLA 125446/0.4, Integrated Safety Summary, p. 25.

¹² BLA 125446/0.4, Integrated Safety Summary, p. 38.

¹³ BLA 125446, Pharmacovigilance Plan, p. 19.

¹⁴ BLA 125446/0.13, 1.11.3 –b(4)----- anti-FIX Antibody, slide 23.

Across the four clinical studies, 15 of the total 91 subjects (16.5%) treated had signals for antibodies against Furin. Four of these 15 expressed signals prior to BAX326 treatment. An additional subject had an antibody signal after treatment with BeneFIX and prior to BAX326 treatment. Only one subject of the 15 patients had a positive signal that reached the lower limit of detection for specific antibodies against Furin (listed as the fourth non-serious AE described above). A second subject had a similar positive antibody signal after the data cut off date of Sept. 3, 2012.¹⁵

Study on Prevalence of Furin-binding Antibodies in Healthy Individuals: In the response to an information request, the sponsor provided data from an additional study that evaluated 500 healthy individuals for antibodies to Furin. Forty-one individuals in the study (8.2%) were positive. Thirty-five of the 41 (overall prevalence of 7%) had titers of 1:20 or 1:40 which is below the threshold for confirmation and were thus deemed indeterminate. The remaining 6 of 41 subjects (overall prevalence of 1.2%) had positive titers of 1:80 to 1:320 and were confirmed to be specific for rFurin. The sponsor concluded that low-level indeterminate rFurin antibodies and higher titer (1:80 to 1:320) rFurin antibodies are found in healthy individuals and do not appear to cause any pathology. The sponsor proposed that these antibodies might be part of a natural immune system mechanism to create a functional immune representation of key body molecules.¹⁶ The sponsor cited an article by Merbl et al. to support this theory of natural autoantibodies.¹⁷

b. Safety Concerns

Inhibitor Formation: Historically, inhibitors (neutralizing antibodies to factor IX) have been detected in previously treated patients receiving factor IX products. The formation of these antibodies can lead to lack of effect for the product or to hypersensitivity reactions. As stated above, 14.3% of the 91 patients in the clinical trials had low titers that did not reach the threshold to be considered positive for FIX antibodies. Therefore, none of the patients treated with BAX326 developed inhibitors during the study. Inhibitor development appears to be more associated with the person's genetic mutation rather than the factor replacement product. Inhibitor development is approximately 50% in hemophilia B patients with complete deletions or rearrangements and 20% in patients with frameshift, premature stop, or splice-site mutations. The risk of inhibitor development is almost zero in hemophilia B patients with mis-sense mutations.¹⁸ Since there were no subjects who developed inhibitors during the clinical trials of BAX326, there is no evidence that this product has a higher potential than existing products to induce inhibitor development. Inhibitor formation and monitoring are discussed in the Warnings and Precautions section of the package insert.

Lack of Effect: Due to the nature of hemophilia, patients receiving treatment and having less than expected therapeutic effect are at risk of serious bleeding episodes. Decreased

¹⁵ BLA 125446/0.13, Efficacy Information Amendment, p. 1, 5.

¹⁶ BLA 125446/0.13, Efficacy Information Amendment, p. 1-4.

¹⁷ Merbl Y, Zucker-Toledano M, Quintana FJ, Cohen IR. Newborn humans manifest autoantibodies to defined self molecules detected by antigen microarray informatics. *J Clin Invest* 2007; 117:712-718.

¹⁸ Bolton-Maggs PH, Pasi KJ. Haemophilias A and B. *Lancet* 2003; 361: 1801-9.

efficacy of any factor replacement can potentially be due to, amongst other causes, inhibitor development or lack of compliance with dosing. Instructions are given in the PI for monitoring for inhibitor development and for adjusting the dose.

Hypersensitivity (Including Anti-CHO Antibodies): Hypersensitivity reactions are a possible concern following this type of factor replacement. “Up to 50% of hemophilia B patients with inhibitors may have severe allergic reactions, including anaphylaxis, to FIX administration.”¹⁹ Hypersensitivity reactions may be due to inhibitor development or other antibody development. There were no severe allergic reaction and no antibodies to CHO detected in any subject before or after treatment in the BAX326 clinical studies. In study 250901, binding antibodies to FIX and rFurin were found in 14.3% and 16.5% of subjects, respectively (including tests both before and after treatment), but the titers were too low to further verify with a confirmatory assay. There was one patient who had a transient rise of >2 fold in the titer for antibodies to rFurin during the clinical program before the data lock point. There was a second subject who had a titer that reached the 1:80 threshold after the data lock point. Neither of these patients had any clinical AE associated with the rise in antibody titers, and they both had titers in the range of the 500 healthy individuals tested. Also, subjects with indeterminate, low titers against rFurin in BAX326 clinical program, when followed with further testing, did not appear to have increasing titers.²⁰ Contraindications in the PI include a known hypersensitivity to the active substance in BAX326, the excipients, or to hamster protein.

Thromboembolic Events: In prior studies, factor IX complex concentrates have been associated with the development of thromboembolic complications including disseminated intravascular coagulation (DIC). Factor IX given without the additional coagulation factors found in the factor IX complex concentrates should pose a lower risk of thrombosis. Also, patients with hemophilia B who receive factor IX would be expected to be at a lower risk of thrombosis than non-hemophiliac patients who receive factor IX complex concentrates for warfarin-reversal. As stated above in the ISS, there were no thrombotic events during the BAX326 clinical program.

Nephrotic Syndrome: There have been reports in the literature of nephrotic syndrome following high doses of a plasma-derived factor IX being used in immune tolerance induction (ITI, also called immune tolerance therapy or ITT). The safety and efficacy of BAX326 for ITI has not been studied. The sponsor is not currently applying for the indication for BAX326 to include use for ITI. The proposed label specifically addresses the risk of nephrotic syndrome with ITI.

Viral Transmission: BAX326 is synthesized in a genetically engineered CHO cell line which reduces the risk of transmission of infective agents such as viruses. The manufacture of BAX326 also includes two viral inactivation/reduction steps

¹⁹ Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Treatment Guidelines Working Group on Behalf of The World Federation Of Hemophilia. Guidelines for the management of hemophilia. Haemophilia. 2013 Jan;19(1):e1-47, p. 61. doi: 10.1111/j.1365-2516.2012.02909.x. Epub 2012 Jul 6.

²⁰ BLA 125446/0.13, 1.11.3 -b(4)----- anti-Furin Antibody, slides 13-26.

(solvent/detergent (S/D) treatment and nanofiltration).²¹ The one patient in the clinical trials who had an AE involving a positive hepatitis B core antibody test was known to have a history of chronic persistent hepatitis prior to being enrolled in the study.

Areas of Missing Information: There were no subjects aged 65 and over in the clinical studies. Pharmacokinetics may be different in elderly patients. The proposed package insert recommends individualizing dose selection in these patients. Additionally, children <12 years old were not included in studies 250901, 251001, and 251002. There is an ongoing study, 251101, which includes previously treated pediatric patients less than 12 years of age. The clinical studies also did not include pregnant and lactating women, patients with renal or hepatic impairment, and patients with less severe disease with FIX levels >2%.²²

c. Sponsor's Proposed Actions

The sponsor did not find any known identified risks during the clinical trials. Important potential risks are inhibitor formation, hypersensitivity reactions (including reactions/antibodies to Chinese hamster ovary (CHO) protein), lack of effect, thromboembolic events, and nephrotic syndrome following attempted immune tolerance induction. The sponsor has provided information on all of these risks in the package insert and proposes routine pharmacovigilance to monitor these potential risks.

The sponsor has identified the following areas where there is important missing information regarding BAX326: use for immune tolerance induction, pediatric patients <12 years of age, geriatric patients, use of continuous infusion during peri-operative management, and use during pregnancy, labor and delivery, lactation, or with regards to fertility. These areas of missing information are all addressed in the proposed package insert and routine pharmacovigilance is planned for these areas. In addition, there is an ongoing study, 251101, for use in pediatric patients <12 years old. Table 4 below outlines the sponsor's proposed pharmacovigilance plan for the important potential risks and missing information for BAX326.

Table 4: Summary of Safety Concerns and Planned Pharmacovigilance Actions²³

Important Potential Risks	
Inhibitor Formation	-Routine pharmacovigilance
Hypersensitivity Reactions (including reactions/antibodies to Chinese hamster ovary (CHO) protein)	-Routine pharmacovigilance
Lack of Effect	-Routine pharmacovigilance
Thromboembolic events	-Routine pharmacovigilance
Nephrotic syndrome following attempted immune tolerance induction	-Routine pharmacovigilance
Important Missing Information	
Use for immune tolerance induction	-Routine pharmacovigilance

²¹ BLA 125446, Pharmacovigilance Plan, p. 31.

²² BLA 125446, Pharmacovigilance Plan, p. 15.

²³ BLA 125446, Pharmacovigilance Plan, p. 9-10 and 34.

Pediatric patients <12 years of age	-Routine pharmacovigilance -Pediatric Study 251101
Geriatric patients	-Routine pharmacovigilance
Use of continuous infusion during peri-operative management	-Routine pharmacovigilance
Use during pregnancy, labor and delivery, lactation, or with regards to fertility	-Routine pharmacovigilance

4. OTHER INFORMATION FROM MANAGED REVIEW PROCESS

At the time of the writing of this memo, no proposed safety signals have been expressed by the review team. The review team acknowledges that inhibitor development is the current primary clinical concern regarding all hemophilia A and B treatments. The review team requested and received additional information from the sponsor regarding the potential development of antibody formation against rFurin and FIX. This additional information has been included in this report.

5. POST-LICENSURE SAFETY REVIEW

BeneFIX is the only currently approved factor IX (recombinant) product. Post-marketing adverse reactions reported in the package insert for BeneFIX are: inadequate factor IX recovery, inadequate therapeutic response, inhibitor development, anaphylaxis, angioedema, dyspnea, hypotension and thrombosis. BeneFIX is also made in Chinese hamster ovary cells and contains trace amounts of CHO proteins. The BeneFIX package insert states that patients receiving BeneFIX may develop hypersensitivity to these non-human mammalian proteins.²⁴ BeneFIX's package insert warns that the safety of BeneFIX administered by continuous infusion has not been established. Some of the post-marketing reports of thromboembolic events described the AE occurring during BeneFIX continuous infusion.²⁵

The FDA internal annual surveillance report for BeneFIX covering the time period of 2/12/11 – 2/11/12 included an annual AERS search which found 49 worldwide adverse events with 42 of those being serious. There were 5 deaths reported: 2 were unrelated to the drug use (gun shot wound, motor vehicle accident), 2 had very limited information but one of these may have involved a hemorrhage, and the fifth case was a patient who had an acute hemorrhage during a lithotripsy operation. A nephrectomy was performed, and after a prolonged period, the hemorrhage resolved. The patient developed renal failure and respiratory failure and died within 3 months of the initial procedure. For the serious cases, the most common preferred terms were factor IX inhibition, hypersensitivity, drug ineffective, hemorrhage, urticaria, anaphylactic reaction, anaphylactoid reaction, convulsion, death, and dizziness.

A literature search on BeneFIX and recombinant factor IX on Jan. 8, 2013 revealed four recent articles related to safety (PubMed search for “BeneFIX” and “safety” and

²⁴ BeneFIX package insert, section 5.2

²⁵ BeneFIX package insert, section 6.2

“recombinant factor IX” and “safety” covering the past 5 years). The first article²⁶ describes a study of safety and efficacy of BeneFIX prophylaxis in children with severe hemophilia. The article states that approximately 7000 patients worldwide have used BeneFIX. A prospective, open-label clinical study included 25 subjects, with 10 of these subjects accruing more than 50 exposure days. Only two of the subjects had adverse events felt to be related to BeneFIX. One had a mild rash and the other patient had an allergic reaction that was associated with a low-titer FIX inhibitor. The inhibitor titers spontaneously decreased and were undetectable 2 and 3 months later. The patient received premedication and did not have allergic reactions with subsequent doses. There were no reports of thrombosis in the study. Two subjects had elevated thrombogenic markers, but they had no associated clinical symptoms. In the study, factor IX inhibitor and anti-FIX antibody assessments were conducted at baseline and every 1-3 months thereafter. The one inhibitor subject was the only patient found to be anti-FIX ELISA positive. The article did not mention the potential development of anti-CHO antibodies. The authors concluded that safety was established for BeneFIX due to the low incidence of treatment-related adverse events.

A second article²⁷ describes a study of an investigational recombinant factor IX named IB1001. The study was a randomized, double-blind, non-inferiority, cross-over study in patients ≥ 12 years old with severe or moderately severe hemophilia B. The study focused on the pharmacokinetics of the investigational product and compared it to BeneFIX. There were eight adverse events in each arm of the study (IB1001 and BeneFIX). Most of the events were mild or moderate and all except two cases of headache were considered unrelated to the study drug. There was one serious AE reported, and it involved an ankle hemarthrosis after BeneFIX treatment. The authors of the study concluded that IB1001 was well tolerated and without safety concerns.

A third article was a manufacturer-sponsored study assessing the efficacy and safety of BeneFIX in China.²⁸ Thirty-five patients were treated with BeneFIX. There were 21 AEs in 13 patients, and none were felt by the investigators to be related to the study drug. One patient was found to be positive for FIX inhibitors at study entry and was subsequently withdrawn from the study. There were no cases of new FIX inhibitor development during the study. There were no new safety concerns identified in the study.

²⁶ Monahan PE, Liesner R, Sullivan ST, Ramirez ME, Kelly P, Roth DA. Safety and efficacy of investigator-prescribed BeneFIX prophylaxis in children less than 6 years of age with severe haemophilia B. *Haemophilia*. 2010 May; 16:460-8.

²⁷ Martinowitz U, Shapiro A, Quon DV, et al. Pharmacokinetic properties of IB1001, an investigational recombinant factor IX, in patients with haemophilia B: repeat pharmacokinetic evaluation and sialylation analysis. *Haemophilia*. 2012 Nov; 18(6):881-7.

²⁸ Yang R, Zhao Y, Wang X, et al. Evaluation of the safety and efficacy of recombinant factor IX (nonacog alfa) in minimally treated and previously treated Chinese patients with haemophilia B. *Haemophilia*. 2012 Sep; 18(5):e374-8.

A fourth article²⁹ describes a retrospective study that reviewed 13 knee replacement surgeries in 11 patients with hemophilia B performed by the same surgeon over a ten-year period. Ten patients received plasma-derived Factor IX and the remaining one received BeneFIX. Seven of the patients received continuous infusions of Factor IX. Across all the cases, there was no excess hemorrhage, no thrombosis and no infections.

6. INTEGRATED RISK ASSESSMENT

This review did not identify any new safety issues arising from the clinical database for BAX326. This product is similar to BeneFIX, a recombinant factor IX product made in CHO cells that has been licensed in the U.S. for over 15 years. There were no safety signals during the clinical trials that indicate that BAX326 poses a safety profile different from the existing BeneFIX. With a data lock date of Sept. 3, 2012, the BAX326 clinical program included 91 treated patients and there was no inhibitor development, CHO-antibody development, severe allergic reactions, thrombotic events, or other unexpected events. There was one study subject who developed anti-rFurin antibodies above the confirmatory threshold level. Some cases of binding antibody formation and hypersensitivity are expected. The sponsor acknowledges and documents in the package insert that there is missing safety data for use in children <12 years old, elderly patients (≥ 65 years old), pregnant and lactating women, or for use for continuous infusion for peri-operative management or immune tolerance induction.

The proposed pharmacovigilance plan which includes routine pharmacovigilance, quarterly periodic adverse event reports for three years, 15-day expedited reports for serious, unlabeled adverse events, and completion of the pediatric study 251101 is adequate to monitor the safety of BAX326. The potential risks are outlined in the package insert. The reviewed safety data do not substantiate a need for a post-marketing requirement (PMR) or REMS.

7. RECOMMENDATION

OBE recommends that Baxter proceeds with its Pharmacovigilance Plan-U.S. Version 1.0, dated 16 July 2012 as submitted with BLA 125446.

²⁹ Uprichard J, Adamidou D, Goddard NJ, Mann HA, Yee TT. Factor IX replacement to cover total knee replacement surgery in haemophilia B: a single-centre experience, 2000-2010. *Haemophilia*. 2012 Jan;18(1):46-9.