Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

To:	Craig Zinderman, MD, MPH Associate Director for Product Safety, Division of Epidemiology (DE), Office of Biostatistics and Epidemiology (OBE), Center for Biologics Evaluation and Research (CBER)
Through:	Meghna Alimchandani, MD Chief, Pharmacovigilance Branch (PVB), DE, OBE, CBER
From:	Bethany Baer, MD Medical Officer, PVB, DE, OBE, CBER
Subject:	Rixubis Safety and Utilization Review for the Pediatric Advisory Committee
Sponsor:	Baxalta
Product:	Rixubis [Coagulation Factor IX (Recombinant)]
STN:	125446/233
Indication:	An antihemophilic factor indicated in adults and children with hemophilia B for control and prevention of bleeding episodes, perioperative management, and routine prophylaxis.
Meeting Date:	Pediatric Advisory Committee Meeting, March 2017

Contents

1 INTRODUCTION

1.1 Objective

The objective of this memorandum for the Pediatric Advisory Committee (PAC) is to present a comprehensive review of the postmarketing pediatric safety covering a period including 18 months following the approval of an expanded age range in accordance with Section 505B (i) (1) of the Food and Drug Cosmetic Act [21 U.S.C. §355c]. The trigger for this pediatric postmarketing safety review was the approval for use of Rixubis in children on Sep. 12, 2014.

An abbreviated presentation of this review to the PAC is planned for this product as it does not meet the criteria that would necessitate a full oral presentation or a justified abbreviated presentation. Specifically, no new safety signals were identified. During the surveillance period, there were no reports of deaths following Rixubis. The product does not have a requirement for a postmarketing safety study or Risk Evaluation and Mitigation Strategy (REMS), and there have been no label changes regarding safety since the PAC trigger. Although the PAC presentation is abbreviated, the analysis of the safety data is comprehensive, and this memorandum documents FDA's complete evaluation, including review of adverse event reports in passive surveillance data, periodic safety reports from the manufacturer, data mining, and a review of the published literature.

1.2 Product Description

Rixubis is a coagulation factor IX (recombinant) antihemophilic factor which was referred to as BAX326 during development. It is a glycoprotein secreted by genetically engineered mammalian cells derived from a Chinese hamster ovary (CHO) cell line. Rixubis consists of 415 amino acids and has structural and functional characteristics similar to those of endogenous factor IX (FIX). Rixubis is formulated as a lyophilized powder and is intended for intravenous (IV) injection.

1.3 Regulatory History

Rixubis was first approved in the United States for use in adults on June 26, 2013. This approval was also its international birth date. On Sep. 12, 2014, the indication was expanded to include use in children.

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
    - FAERS reports for Rixubis for dates Jun. 26, 2013 – Oct. 13, 2016
- Manufacturer's Submissions
    - Rixubis U.S. package insert, dated Sep. 2014
    - Letter regarding dose distribution data, received Nov. 17, 2016
    - Pharmacovigilance Plan (U.S), Version 2, dated Oct. 25, 2013

    - Status of Postmarketing Study Commitments and Requirements for Reporting Period: 2015 July 1 – 2016 June 30
    - Final Clinical Study Report 251002, dated Oct. 14, 2014
- FDA Documents
    - Rixubis Approval Letter, dated Jun. 26, 2013
    - Rixubis Supplement Revised Approval Letter, dated Oct. 17, 2014
    - Rixubis Pharmacovigilance Plan Review for Initial Licensure, dated May 20, 2013
    - Rixubis Pharmacovigilance Plan, Version 2, Review for Pediatric Supplement, dated Aug. 1, 2014
- Publications (see Literature Search in section 8)
- Other Sources
    - www.clinicaltrials.gov for BAX326 study 251001 and 251002

3 LABEL CHANGES IN REVIEW PERIOD

The label was updated for use in children on Sep. 12, 2014. At the same time, the Postmarketing Experience (section 6.2) of the label was updated to include the following terms as adverse reactions reported since licensure: hypersensitivity reactions, urticaria, and rash. There have been no label changes related to safety concerns for Rixubis since the PAC trigger on Sep. 12, 2014.

4 PRODUCT UTILIZATION DATA

Baxalta provided distribution data for the U.S. and worldwide for Oct. 1, 2013 (marketing start) – Sep. 30, 2016:

U.S.: (b) (4)

Worldwide: (b) (4)

The distribution for use in different patient age ranges was not available.

Estimate of number of patients treated:

U.S.: between (b) (4) patients

Worldwide: between (b) (4) patients

Method for estimating patients treated: (b) (4)

(b) (4)

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

Rixubis' current Pharmacovigilance Plan (U.S.) is Version 2.0, dated Oct. 25, 2013. There are no identified risks for Rixubis. Important potential risks for Rixubis are: inhibitor formation, lack of effect, hypersensitivity reactions, thromboembolic events, and nephrotic syndrome. These events are risks for all factor IX replacement products in general. Rixubis did not have any subjects develop inhibitors in the clinical trials, but other factor IX products have historically had inhibitors develop in a low percentage of treated patients. Inhibitor formation can be associated with lack of effect of the product. Lack of effect may also be the result of inadequate dosing. Although the sponsor includes "lack of effect" as a potential risk in the pharmacovigilance plan, lack of effect in the absence of inhibitors would generally be considered an issue of efficacy and not safety, and would apply to any factor replacement product. The Rixubis package insert includes instructions for monitoring for inhibitor development and for adjusting the dose if there is less than expected therapeutic effect.

Hypersensitivity reactions may be due to inhibitor development or other antibody development. During the Rixubis clinical studies, there were no patients who developed severe allergic reactions or inhibitors to factor IX. The Rixubis package insert lists contraindications to Rixubis which include a known hypersensitivity to the active substance in Rixubis, the excipients, or to hamster protein.

Thromboembolic events are possible with any factor that involves the clotting cascade. Patients with hemophilia B who receive factor IX are expected to be at a lower risk of thrombosis than non-hemophilic patients who receive factor IX. There were no thrombotic events during the Rixubis clinical trial program.

Nephrotic syndrome is a potential risk for factor IX products as 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. Of note, the safety and efficacy of Rixubis for immune tolerance induction has not been studied, and Rixubis is not approved for use for immune tolerance induction.

A summary of the identified potential risks and areas of missing information is included in Table 1 below.

Table 1: Rixubis Safety Concerns and Planned Pharmacovigilance Actions[1]

Identified Risks – None	
Potential Risks	**Planned Pharmacovigilance Actions**
Inhibitor Formation	Routine pharmacovigilance Continuation study (251001) extension Surgery study (251002) extension
Hypersensitivity Reactions (including reactions/antibodies to Chinese hamster ovary (CHO) protein)	Routine pharmacovigilance Continuation study (251001) extension Surgery study (251002) extension
Lack of Effect	Routine pharmacovigilance
Thromboembolic events	Routine pharmacovigilance Continuation study (251001) extension Surgery study (251002) extension
Nephrotic syndrome following attempted immune tolerance induction in hemophilia B patients with FIX inhibitors and a history of allergic reactions	Routine pharmacovigilance
Missing Information	**Planned Pharmacovigilance Actions**
Use for immune tolerance induction	Routine pharmacovigilance
Geriatric patients	Routine pharmacovigilance
Use of continuous infusion	Routine pharmacovigilance
Effects on fertility	Routine pharmacovigilance

5.2 Postmarketing Studies

5.2.1 Continuation Study[2]

The continuation study was included in the initial 2013 approval letter as a postmarketing commitment. The study is an evaluation of long-term efficacy and safety of Rixubis in 100 patients of all age groups with hemophilia B, of which at least 25 are subjects naïve to Rixubis. This study is a Phase 3, open, prospective, uncontrolled, multicenter study in multiple countries. It includes patients who completed the pivotal study or the pediatric study or were newly recruited. The patients will be followed until the accumulation of up to 100 Rixubis exposure days (EDs) or until Rixubis is licensed in the subjects' country, whichever occurs last. As of June 30, 2016, a total of 84 patients previously exposed to Rixubis and 30 Rixubis-naïve patients have received treatment in the study. The study is scheduled to be completed by June 30, 2017, and the final report is to be submitted by Dec. 31, 2017.

[1] Rixubis Pharmacovigilance Plan, Version 2.
[2] Baxter, Status of Post Postmarketing Study Commitments and Requirements for Reporting Period: 2015 July 1 – 2016 June 30.

5.2.2 Surgery Extension Study[3]

This study was not a postmarketing commitment but was part of the sponsor's pharmacovigilance plan for Rixubis. It was the extension of the phase 3, prospective, open-label, uncontrolled surgical study conducted for licensure. The study was completed in May 2014 and included 30 unique patients who underwent 38 surgeries (including 21 major surgeries). The investigators found only one possibly related adverse event. The event was hemorrhagic anemia which resolved. There were no cases of thrombotic events, no severe allergic reactions, and no development of factor IX inhibitory antibodies or factor IX total binding antibodies observed during the study.

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following use of Rixubis between Jun. 26, 2013, and Oct. 13, 2016. FAERS stores postmarketing adverse events and medication errors submitted to FDA for all approved drug and therapeutic biologic products. These reports originate from a variety of sources, including healthcare providers, consumers, and manufacturers. Spontaneous surveillance systems such as FAERS are subject to many limitations, including variable report quality and accuracy, inadequate data regarding the numbers of doses administered, and lack of direct and unbiased comparison groups. Reports in FAERS may not be medically confirmed and are not verified by FDA. FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Also, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven.

6.2 Results

The results of the FAERS search of adverse event reports for Rixubis during the review period are listed in Table 2 below.

Table 2: FAERS Reports for Rixubis (Jun. 26, 2013 through Oct. 13, 2016)

Age	Serious* US	Serious Non-US	Deaths US	Deaths Non-US	Non-Serious US	Non-Serious Non-US	Total US	Total Non-US
<18 years	7	2	0	0	3	0	10	2
≥18 years	12	1	0	0	2	0	14	1
Unknown	3	3	0	0	3	0	6	3
Total	22	6	0	0	8	0	30	6

*Serious adverse events (including Otherwise Medically Important Conditions (OMIC)) are defined in 21CFR600.80

[3] Baxter, Final Clinical Study Report 251002, dated Oct. 14, 2014.

6.2.1 Deaths

There were no deaths following Rixubis reported to FAERS during this surveillance period.

6.2.2 Serious Non-fatal Reports

During the reporting period, there were 28 serious non-fatal reports. Of these, 7 were in patients <18 years of age in the United States. These 7 cases were individually reviewed. All 7 of the cases were reports of hemorrhage, likely related to the patient's underlying condition and indication for using Rixubis. Three of the reports were solicited reports through the sponsor's market research program and included several episodes of bleeding over the past year in the each of the three patients. One of the reports specifically mentioned that there was trauma before the bleed in a patient that was on Rixubis for bleeding prophylaxis. The second report involved a patient who was receiving Rixubis on an on demand schedule that included preventative doses prior to sports. The third report did not include information on the treatment schedule.

The four remaining reports were submitted spontaneously by a single provider and listed the event as a "breakthrough bleed." No information was provided on the treatment regimen being used for these four patients.

None of the seven reports mentioned a concern for inhibitor development in the patient.

6.2.3 Non-serious Reports

During the reporting period, there were 8 non-serious reports, with 3 of those involving U.S. patients <18 years old. Table 3 lists the principal adverse event for these reports.

Table 3. Principal adverse event for non-serious FAERS reports (Jun. 26, 2013-Oct. 13, 2016; <18 years of age, U.S.)

Principal Adverse Event*	No. of Reports	Label Status
Hypersensitivity Reaction	1	Labeled
Diluent/reconstitution error	1	Unlabeled
Vascular access complication	1	Unlabeled

*Based on review of the reported signs, symptoms, and diagnoses, the predominant clinical entity was determined to be the principal adverse event.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of Rixubis were disproportionally reported compared to other products in the FAERS database. Data mining covers the entire postmarketing period for this product, from initial licensure through the data lock point of Oct. 3, 2016. Disproportionality alerts do not, by themselves, demonstrate causal associations; rather, they may serve as a signal for further investigation. A query of Empirica Signal using the Trade (S) run identified two preferred terms (PTs) with a disproportional reporting alert for Rixubis.

(Disproportional reporting alert is defined as an EB05>2; the EB05 refers to the lower bound of the 90% confidence interval around the Empiric Bayes Geometric Mean). The two PTs were:

- *Haemorrhage* (14 reports, EB05=36.9): These cases are reports of hemorrhage due to trauma or to breakthrough bleeds (confounded by indication/underlying condition).
- *Claustrophobia* (3 reports, EB05=2.74): These three reports all refer to a single case of a 61-year-old man with hemophilia B who was receiving Rixubis as well as lithium for other medical problems. He had a hypersensitivity reaction following Rixubis. He was also found to have other neurological symptoms including tremor and hallucinations that were associated with an elevated lithium level.

6.4 Periodic Adverse Event Reports (PAERs)

The manufacturer's postmarketing periodic safety reports for Rixubis covering the surveillance period were reviewed. There were between 0 and 8 initial reports received by the sponsor in each quarter. The adverse events reported were consistent with those seen in FAERS. No additional safety issues were identified and no actions were taken by the sponsor for safety reasons.

7 LITERATURE REVIEW

A search of the US National Library of Medicine's PubMed.gov database on Oct. 18, 2016, for peer-reviewed literature published between Jun. 26, 2013, and Oct. 13, 2016, with the search term "Rixubis" or "BAX326" and "safety" retrieved 8 articles on human safety. The articles were reviewed, and the safety conclusions are listed in the table below. No new safety issues for Rixubis were identified in these articles.

Article	Safety Conclusion
Windyga J, Lissitchkov T, Stasyshyn O, et al. Pharmacokinetics, efficacy and safety of BAX326, a novel recombinant factor IX: a prospective, controlled, multicenter phase I/III study in previously treated patients with severe (FIX level <1%) or moderately severe (FIX level ≤2%) haemophilia B. Haemophilia. 2014 Jan;20(1):15-24.	This article describing one of the pre-licensure clinical trials concluded that Rixubis is safe for treating hemorrhages and for routine prophylaxis in hemophilia B patients ≥12 years of age.
Valentino LA. The role of Rixubis in the treatment of hemophilia B. Immunotherapy. 2014 Apr;6(4):381-94.	A review of the clinical trial data for Rixubis. The author concluded that long-term post-authorization surveillance studies are necessary to fully elucidate the safety profile

Article	Safety Conclusion
Windyga J, Abbuehl BE, Hafeman AE. BAX326 (recombinant coagulation factor IX) for the treatment and prophylaxis of hemophilia B. Expert Rev Hematol. 2014 Jun;7(3):333-42.	A report of the phase III studies for Rixubis. The authors concluded that Rixubis was safe and well-tolerated in the 73 treated subjects. No study subjects developed inhibitory or treatment-related antibodies to FIX, CHO protein or rFurin.
Windyga J, Lissitchkov T, Stasyshyn O, et al. Efficacy and safety of a recombinant factor IX (Bax326) in previously treated patients with severe or moderately severe haemophilia B undergoing surgical or other invasive procedures: a prospective, open-label, uncontrolled, multicentre, phase III study. Haemophilia. 2014 Sep;20(5):651-8.	A report of the phase III study of Rixubis use in hemophilia B patients undergoing surgery. The authors concluded that Rixubis (BAX326) was safe and effective for peri-operative management of the 14 patients in the study.
Solano Trujillo MH, Stasyshyn O, Rusen L, et al. Safe switching from a pdFIX (Immunine®) to a rFIX (Bax326). Haemophilia. 2014 Sep;20(5):674-81.	A prospective study of patients transitioning from a plasma-derived FIX product to Rixubis. None of the 44 patients developed inhibitors or specific binding anti-FIX antibodies during the study. There were no severe allergic reactions, thrombotic events, or related SAEs with Rixubis. The authors concluded that there is direct evidence of a safe and effective transition from a plasma-derived FIX to Rixubis.
Windyga J, Solano Trujillo MH, Hafeman AE. BAX326 (RIXUBIS): a novel recombinant factor IX for the control and prevention of bleeding episodes in adults and children with hemophilia B. Ther Adv Hematol. 2014 Oct;5(5):168-80.	The authors of this article concluded that "overall, the safety profile of BAX326 in clinical trials has been strong, with no inhibitor or specific antibody formation, thrombosis, or treatment-related serious adverse events or anaphylaxis."
Turecek PL, Abbuhl B, Tangada SD, et al. Nonacog gamma, a novel recombinant factor IX with low factor IXa content for treatment and prophylaxis of bleeding episodes. Expert Rev Clin Pharmacol. 2015 Mar;8(2):163-77	A review of the development and clinical trials of Rixubis. The authors concluded that Rixubis is safe and well tolerated and had a low incidence of adverse drug reactions.

Article	Safety Conclusion
Urasinski T, Stasyshyn O, Andreeva T, et al. Recombinant factor IX (BAX326) in previously treated paediatric patients with haemophilia B: a prospective clinical trial. Haemophilia. 2015 Mar;21(2):196-203.	This article described the pediatric study with Rixubis used as prophylaxis and on-demand treatment for bleeds. There were no treatment-related severe adverse events, thrombotic events, or inhibitory or specific binding antibodies against rFurin or CHO protein seen in the study.

8 CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for Rixubis does not indicate any new safety concerns. This PAC review was initiated due to the expansion of use to include children. In general, very few adverse events were reported in the pediatric age group (<18 years) during the review period. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern. There were no reports of death. The adverse events in children are similar to those seen in adults and are consistent with the known safety profile for Rixubis.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of Rixubis. The results of the postmarketing extension study will be reviewed when the study is complete.

10 APPENDIX

FAERS cases of U.S. pediatric serious non-fatal reports reviewed: 10591434, 11795172, 11798358, 12291779, 12291781, 12295834, 12295838.

FAERS cases of U.S. pediatric non-serious reports reviewed: 10482199, 12359287, 9786877.

FAERS cases for data mining finding of haemorrhage: 10593142, 10593143, 10599757, 10647459, 10664828, 12291779, 12291781, 12295834, 12295838, 12727776, 9907454, 12404174, 11824182, 10487956.

FAERS cases for data mining finding of claustrophobia: 9687869, 9696532, 12582808.