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 Associate Director for Medical Policy, OBE, CBER
From:	Bethany Baer, MD Medical Officer, PVB, DE, OBE, CBER
Subject:	IXINITY Safety and Utilization Review for the Pediatric Advisory Committee
Sponsor:	Aptevo BioTherapeutics LLC
Product:	IXINITY [Coagulation Factor IX (Recombinant)]
STN:	125426/156
Indication:	Indicated in adults and children ≥12 years of age with hemophilia B for control and prevention of bleeding episodes, and for perioperative management
Meeting Date:	Pediatric Advisory Committee Meeting, April 2019

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 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 initial approval of IXINITY on April 29, 2015.

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

IXINITY is a recombinant coagulation factor IX produced in a Chinese hamster ovary (CHO) cell line. It is a single chain glycoprotein with an amino acid sequence identical to the Thr148 allelic form of plasma-derived factor IX. During the Biologics License Application (BLA) process, a hydrophobic interaction chromatography (HIC) step was added to the manufacturing process to remove host cell proteins. The subsequent product was referred to as "polished" or "modified" and is the form that was licensed as IXINITY.

1.3 Regulatory History

IXINITY was approved in the U.S. on April 29, 2015, for control and prevention of bleeding episodes, and for peri-operative management, in adults and children ≥12 years of age with hemophilia B. The current manufacturer, Aptevo BioTherapeutics LLC, acquired the product in 2016. Previous manufacturers have been Inspiration Biopharmaceuticals, Cangene, and Emergent BioSolutions. IXINITY is approved only in the U.S.

2 MATERIALS REVIEWED

- FDA Adverse Events Reporting System (FAERS)
  - FAERS reports for IXINITY for dates April 29, 2015 – August 31, 2018
- Manufacturer's Submissions
  - IXINITY U.S. package insert, dated April 2018
  - Letter regarding dose distribution data, received October 26, 2018
  - Pharmacovigilance Plan, Version 2, dated Jan. 24, 2014
- FDA Documents
  - IXINITY Approval Letter, dated April 29, 2015 and revision dated May 14, 2015
  - Division of Epidemiology Pharmacovigilance Review Memorandum, dated Dec. 12, 2012

- Division of Epidemiology Pharmacovigilance Review Memorandum (IXINITY Pharmacovigilance Plan Version 2), dated May 27, 2014
- Division of Epidemiology Memorandum Addendum, dated Feb. 18, 2015

- Publications (see Literature Search in section 7)

3 LABEL CHANGES IN REVIEW PERIOD

There have been no label changes related to safety concerns for IXINITY since licensure.

4 PRODUCT UTILIZATION DATA

Aptevo BioTherapeutics LLC provided distribution data for the U.S. for the years 2015 through June, 2018:

Table 1: IXINITY Sales to Distributors (in IUs)

2015	2016	2017	2018 (through June)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

Of note, since IXINITY is only commercially available in the U.S., there is no distribution outside the U.S.

These estimates were provided by the manufacturer for FDA review. Distribution data is protected as confidential commercial information and may require redaction from this review.

5 PHARMACOVIGILANCE PLAN AND POSTMARKETING STUDIES

5.1 Pharmacovigilance Plan

The manufacturer's current Pharmacovigilance Plan for IXINITY is Version 2, dated Jan. 24, 2014. There are no identified risks for IXINITY. Important potential risks for IXINITY are: immunogenicity (including inhibitor development and lack of efficacy), thrombogenicity, hypersensitivity (including anaphylaxis), and nephrotic syndrome (see Table 2). These events are general risks for all factor IX replacement products.

Table 2: IXINITY Safety Concerns and Planned Pharmacovigilance Actions[1]

Identified Risks	
None	
Potential Risks	**Planned Pharmacovigilance Actions**
Immunogenicity	Routine pharmacovigilance
Thrombogenicity	Routine pharmacovigilance
Hypersensitivity (including anaphylaxis)	Routine pharmacovigilance
Nephrotic syndrome	Routine pharmacovigilance
Missing Information	**Planned Pharmacovigilance Actions**
Elderly patients (>65 years old)	Routine pharmacovigilance
Patients with hepatic insufficiency	Routine pharmacovigilance
Patients with renal insufficiency	Routine pharmacovigilance
Children (<12 years old) previously treated patients	Routine pharmacovigilance Postmarketing Study IB1001-02
Children previously untreated patients	Routine pharmacovigilance
Use in immune tolerance therapy	Routine pharmacovigilance

Regarding the potential risk of immunogenicity, IXINITY did not have any subjects develop inhibitors in the clinical trials. 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. The IXINITY package insert includes instructions for monitoring for inhibitor development. While there were no inhibitors seen in the clinical trials, some subjects developed non-inhibitory antibodies to factor IX and/or anti-CHO antibodies to the host cell proteins. There were no clinical adverse events correlated with the development of these antibodies. As discussed earlier in this memorandum, a manufacturing change was made prior to approval to add a step to remove host cell proteins from the product. Patients on the new "polished" or "modified" product showed no new development of anti-CHO antibodies. Non-inhibitory binding antibodies and host cell protein antibodies are not routinely tested in the postmarket setting.

Hypersensitivity reactions can be due to inhibitor development or other antibody formation. There were no severe allergic reactions to factor IX seen during the IXINITY clinical studies. The IXINITY package insert lists contraindications which include a known hypersensitivity to IXINITY, the excipients, or to hamster protein.

Thromboembolic events are potential risks for any factor that involves the clotting cascade, like factor IX. There were no thrombotic events during the IXINITY clinical trials.

Nephrotic syndrome has been reported in the literature following high doses of a plasma-derived factor IX for immune tolerance induction. IXINITY is not approved for use for immune tolerance induction.

[1] IXINITY Pharmacovigilance Plan, Version 2.

IXINITY does not have a requirement for a postmarketing safety study or Risk Evaluation and Mitigation Strategy (REMS).

5.2 Postmarketing Requirement Study IB1001-02

The initial approval of IXINITY included a Postmarketing Requirement (PMR) study, IB1001-02, under the Pediatric Research Equity Act (PREA) to evaluate the use of IXINITY in previously treated children ages 0 to 12 years old.
Study status: The study has been delayed due to issues with the study drug and delays involving study participants, sites, and management. FDA granted a deferral extension for this PREA PMR and the revised Final Report Submission date is December 14, 2021.

6 ADVERSE EVENT REVIEW

6.1 Methods

The FDA Adverse Event Reporting System (FAERS) was queried for adverse event reports following the use of IXINITY between April 29, 2015 (initial approval) and August 31, 2018. 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 IXINITY during the review period are listed in Table 3 below. There were 5 reports, all in adult patients.

Table 3: FAERS Reports for IXINITY (Apr. 29, 2015 through Aug. 31, 2018)

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	0	0	0	0	0	0	0	0
≥18 years	3	0	0	0	2	0	5	0
Unknown	0	0	0	0	0	0	0	0
Total	3	0	0	0	2	0	5	0

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

6.2.1 Deaths

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

6.2.2 Serious Non-fatal Reports

During the reporting period, there were 3 serious, non-fatal reports in adults. The adverse events are described below:

- A 38-year-old man with hemophilia B and rheumatoid arthritis had received IXINITY for about a month on an as needed basis. He developed rhabdomyolysis and acute kidney injury after vigorous exercise lifting weights. He recovered after two weeks.
- A 61-year-old man with hemophilia B received IXINITY in preparation for a tooth extraction. Shortly after the infusion, he had a scratchy throat, difficulty swallowing, and hives. He was observed in the hospital overnight for symptoms consistent with a hypersensitivity reaction.
- A 49-year-old man had been receiving IXINITY but switched to Rixubis due to a supply issue. He developed symptoms of "feeling run down" and was found to have decreased red blood cell count, and potentially a decreased white blood cell count (report had conflicting information regarding the white blood cell count). He was treated with a blood transfusion. He had not had any known recent bleeding episodes. The report stated that the cause for the decreased blood counts was not known, but the patient was improving.

6.2.3 Non-serious Reports

During the reporting period, there were 2 non-serious reports, both in adult males. One case involved headache, dizziness, and rise in blood pressure in a patient with a history of hypertension. The other case involved headache, body aches, and fever.

6.3 Data mining

Data mining was performed to evaluate whether any events following the use of IXINITY 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 for the data mining analysis of Sep. 13, 2018. 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 did not identify any preferred terms (PTs) with a disproportional reporting alert for IXINITY. (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).

6.4 Periodic Adverse Event Reports (PAERs)

The manufacturer's postmarketing periodic safety reports for IXINITY covering the surveillance period were reviewed. There were between 0 and 2 initial reports received by the sponsor in each report. 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 U.S. National Library of Medicine's PubMed.gov database on Oct. 16, 2018, for peer-reviewed literature, with the search term "IXINITY" or "IB1001" retrieved 5 articles.[2] The articles were reviewed, and the safety conclusions are listed in the table below. No new safety concerns for IXINITY were identified in these articles. Of note, four of the five articles (all except for Brennan, et al.) include authors associated with IXINITY's sponsor.

Article	Safety Conclusion
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.	This randomized, double-blind, cross-over pharmacokinetics study of 32 subjects compared the recombinant factor IB1001 in the investigational phase to Benefix. IB1001 was found to be non-inferior to Benefix. There were no safety concerns identified by the authors in this study.
Monroe DM, Jenny RJ, Van Cott KE, Buhay S, Saward LL. Characterization of IXINITY® (Trenonacog Alfa), a Recombinant Factor IX with Primary Sequence Corresponding to the Threonine-148 Polymorph. Adv Hematol. 2016;2016:7678901.	This article characterized IXINITY by performing several different laboratory analyses of the product. Gel electrophoresis, chromatography, mass spectrometry, and activity assays were included in the tests performed. The authors concluded that the product was pure and had posttranslational modifications consistent with the plasma-derived FIX with the Thr148 polymorphism.

[2] IB1001 was the name of the product during development.

Article	Safety Conclusion
Cheung P, Emanuel A, Heward J, et al. Reduced immunogenic response to residual CHO cell protein in recombinant factor IX (IB1001) drug product in normal healthy rabbits. Haemophilia. 2016 Feb 25.	This Letter to the Editor described a study comparing the immunogenicity of the "polished" IB1001 product after addition of the hydrophobic interaction chromatography (HIC) step with the immunogenicity of the original IB1001 product that was not treated with the HIC step. The authors concluded that the addition of the HIC step removed residual CHO proteins and decreased the product's immunogenicity in rabbits. Reviewer's note: The HIC purification step was added to the product manufacturing prior to FDA initial approval of IXINITY.
Brennan Y, Curnow J, Favaloro EJ. Trenonacog alfa for prophylaxis, on-demand and perioperative management of hemophilia B. Expert Opin Biol Ther. 2018 Jan;18(1):95-100.	This review article on IXINITY primarily describes the clinical trials. The authors concluded that IXINITY "appears to be an effective and safe treatment option for patients with hemophilia B...."
Collins PW, Quon DVK, Makris M, et al. Pharmacokinetics, safety and efficacy of a recombinant factor IX product, trenonacog alfa in previously treated haemophilia B patients. Haemophilia. 2018 Jan;24(1):104-112.	This publication describes the clinical trial studies for IXINITY.

8 CONCLUSION

This postmarketing pediatric safety review of passive surveillance adverse event reports, the sponsor's periodic safety reports, and the published literature for IXINITY does not indicate any new safety concerns. The PAC review was initiated due to initial approval in patients ≥12 years of age. There were no adverse events reported in the pediatric age group (<18 years) during the review period and very few adverse events reported in adults. There were no reports of death. No unusual frequency, clusters, or other trends for adverse events were identified that would suggest a new safety concern.

9 RECOMMENDATIONS

FDA recommends continued routine safety monitoring of IXINITY. The results of the pediatric study will be reviewed when available.