

**IXINITY [Coagulation Factor IX (Recombinant)]
BLA STN: 125426/177 CHB/DCEPT/OTAT/CBER**

Memorandum

Date: July 07, 2020

Application: BLA STN: 125426/177

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Clinical Reviewer

Through: Bindu George, MD
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Subject: Clinical Review Memo of Efficacy Supplement

Applicant Aptevo

Product: IXINITY®, Coagulation Factor IX (Recombinant)

Submission Date: February 05, 2020

Action Due Date: December 04, 2020

Recommendation

IXINITY is a recombinant factor IX product currently approved for control and prevention of bleeding and perioperative management of bleeding in adults and children ≥ 12 years. This supplemental BLA is submitted to include a new indication for routine prophylaxis in adults and pediatric subjects 12 years and older. The prophylaxis indication could not be granted in 2015 as approval was blocked by orphan exclusivity held by another factor IX (recombinant) product (Rixubis; expiration of exclusivity on June 26, 2020). This memorandum is to support our decision to grant approval for IXINITY for routine prophylaxis to reduce frequency of bleeding episodes in adults and children ≥ 12 years of age with Hemophilia B.

Review Strategy

For this submission, the clinical reviewer did not review the data submitted during the original BLA application (2012) and Applicant response to the complete response letter from the FDA (dated 02/01/2013) since the data had been analyzed by the previous clinical reviewer for all indications requested by the Applicant. All prior clinical memos were

reviewed. Current clinical protocol, amendments related to deferred pediatric study and annual reports were reviewed. Memos from other disciplines (statistics, clinical pharmacology, APLB) were reviewed as needed. Draft labeling was reviewed and data to support changes to labeling were scrutinized. Key data from clinical review memo as it pertains to labeling changes is excerpted and presented in this memo. Information request pertaining to post marketing adverse events was sent and response has been reviewed.

Clinical Review:

Clinical data is excerpted from the original review memo (by Dr. Irwin Feuerstein in 2014 and 2015) that is relevant to changes in the label in this submission. Where relevant, some information from the original review memo has been added to present the context of the changes in the label.

Data to support the prophylaxis indication was collected in the IB1001-01 Phase 1/2/3 pivotal trial. This multicenter trial had four arms and subjects were assigned to routine prophylaxis or on-demand treatment in the non-randomized, open-label, treatment phase/arm of the trial. General inclusion criteria were severe to moderately severe Hemophilia B with a FIX level ≤ 2 IU/dl, age ≥ 12 years (age up to 5 years allowed in USA), previous FIX treatment for ≥ 150 exposure days (EDs), negative FIX inhibitor status (< 0.6 Bethesda units) and no allergy to hamster proteins. All subjects in the treatment arm of the trial had to have participated in the pharmacokinetic (PK) or factor recovery studies. Treatment phase lasted 6 months and was planned for ~ 50 EDs per subject in ≥ 50 subjects. Subjects could start with either routine prophylaxis or on-demand therapy and could switch per subject and investigator preference. For subjects who switched between prophylaxis and on-demand treatment, outcomes were analyzed for each regimen. Distinction was made between bleeding episode and bleeding event. A bleeding episode could include more than 1 bleeding event. A bleeding episode could include bleeding events involving different joints if they occurred within a 24-hour time period. Frequency of breakthrough bleeding during routine prophylaxis, adverse events (AEs), tolerance and compliance were monitored with clinic visits and subject-reported diaries. Neutralizing (inhibitory) and non-neutralizing (non-inhibitory) antibodies were measured after 5 EDs and then every 3 months.

Overall, 68 subjects enrolled into the treatment phase. 58 of 68 subjects were preassigned to receive routine treatment and 9 subjects were preassigned to receive on-demand. Because subjects could switch regimens, over the length of investigation 61 subjects received routine prophylaxis.

The dose of IXINITY for prophylaxis per protocol was 50-75 IU/kg twice weekly; however, investigator discretion to adjust the dose was allowed and not considered a protocol deviation. Twice weekly doses could be spaced as far apart as 4 days. For prophylaxis, the actual mean dose per infusion was 4225 IU or 55 IU/kg (median 53 IU/kg; range 26-80 IU/kg).

The median annualized bleeding rate (ABR) during prophylaxis is shown in the table below:

	Routine (n = 61)
Treatment Duration (months)	
Mean (± SD)	17.9 (± 9.6)
Median (range)	16.2 (2.4-39.6)
Dose per Infusion (IU/kg)	
Mean (± SD)	55.0 (± 12.8)
Median (range)	53.0 (26.1-80.2)
Total ABR	
Mean (± SD)	3.55 (± 7.19)
Median (range)	1.5 (0.0-47.5)

Breakthrough bleeding occurred in 69% of subjects on routine treatment (n = 42 subjects), totaling 286 bleeding episodes. Therefore, 19 subjects on routine prophylaxis had no bleeds.

The above data support the requested prophylaxis dose in the label of 40-70 IU/kg and the changes made in Section 14 (Clinical Studies) of the label. Furthermore, the package insert permits adjustments of dose based on individual patient profile which would permit the dose ranges for the mean and median dose provided in the table above.

This study was presented to the Pediatric Review Committee (PeRC) on 05/12/2020 since the supplement triggered PREA (Pediatrics Research Equity Act) given that Applicant is coming in for a new indication. PeRC agreed with the assessment in subjects 12-17 years of age. The deferred pediatric which is to include subjects from birth to 12 years of age is due for final submission in December 2021.

Post Marketing:

Safety:

We requested a post-marketing safety update for review of this efficacy supplement. From launch (03/29/2015) to 02/29/2020, 201 subjects have received an estimated 22,691 doses of IXINITY. A total of 19 AEs have been reported with most being non-serious. Of the 5 serious AEs reported, 2 (one each of anaphylaxis and deep venous thrombosis described below) were deemed to be product related and had not been reported in the pivotal clinical trial. No new or unexpected safety risks have been raised.

A 61-year old male developed urticaria, throat irritation and dysphagia following IXINITY use. Symptoms were deemed to be an anaphylactic reaction and resolved with

epinephrine, diphenhydramine and cetirizine. Subject was not re-challenged with IXINITY; he had history of anaphylaxis with other FIX products. A 48-year old female was noted to have right upper extremity deep vein thrombosis (DVT) following an accidental bolus infusion of IXINITY in the same arm. She was anticoagulated for 3 weeks for the DVT.

Given that these adverse reactions have occurred in the post-marketing setting and are actionable e.g. physicians need to be prepared for possible anaphylaxis due to IXINITY, Section 5 of the label (Warnings and Precautions) has been updated in addition to the Post-Marketing section. Symptoms of anaphylaxis described in the subject above have been added to the list of symptoms under Hypersensitivity Reactions in Section 5.1.

PREA Post Marketing Requirement:

As of the Annual report on 05/29/2020, the deferred pediatric study: APVO101-903 in children < 12 years of age with Hemophilia B has 9 subjects enrolled in the 6-12-year age group. Enrollment has been delayed due to the COVID pandemic. Final submission is due December 2021.

Labeling:

The revised USPI was reviewed, commented, and revised by the appropriate discipline reviewers. APLB conducted its review from a promotional and comprehension perspective. Our recommendations for changes to the label were communicated to the sponsor. Labeling issues have been successfully resolved with the Applicant.

Additional changes to the label besides inclusion of the routine prophylaxis, indication, dosage recommendations to support the routine prophylaxis indication and update to Section 5 include revision to the verbiage in the indication statement for the approved indication from “Control and prevention of bleeding episodes” to “on-demand and control of bleeding episodes” to be consistent across such post approval changes to the label for all classes of coagulation products with an “On-demand” indication.

Conclusion:

In conclusion, the data reviewed previously during the original BLA submission support the routine prophylaxis indication and the labeling changes requested in this efficacy supplement. The clinical reviewer recommends approval of the sBLA for the new indication of: Routine prophylaxis to reduce the frequency of bleeding episodes in adults and children ≥ 12 years of age with Hemophilia B.