Application Type	BLA
STN	125426/177
CBER Received Date	February 5, 2020
PDUFA Goal Date	December 4, 2020
Division / Office	DCEPT/OTAT
Committee Chair	Kavita Natrajan, M.D.
Clinical Reviewer(s)	Kavita Natrajan, M.D.
Project Manager	Edward Thompson
Priority Review	No
Reviewer Name(s)	Jiang Hu, Ph.D.
Review Completion Date / Stamped Date	
Supervisory Concurrence	Renée C. Rees, Ph.D., Team Leader, Therapeutics Evaluation Branch
	Boguang Zhen, Ph.D., Branch Chief, Therapeutics Evaluation Branch
Applicant	Aptevo BioTherapeutics LLC
Established Name	Coagulation Factor IX (Recombinant)
(Proposed) Trade Name	IXINITY
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	Lyophilized white or almost white powder, in single-use glass vials containing nominally 250, 500, 1000, 1500, 2000, or 3000 international units (IU) per vial
Dosing Regimen	
Indication(s) and Intended Population(s)	To include routine prophylaxis indication and update the prescribing information label

Introduction and Background

This supplemental BLA (sBLA) proposes a labeling change for IXINITY, coagulation factor IX (recombinant). The applicant requests adding to the label the indication of "routine prophylaxis to reduce the frequency of bleeding episodes".

The applicant submitted the original BLA package for IXINITY on 4/6/2012 for the following three indications:

- Control and prevention of bleeding episodes
- Perioperative management
- Routine prophylaxis to reduce the frequency of bleeding episodes

The statistical analyses and datasets for these three indications were reviewed during the original BLA review procedure, which included two complete response submissions (1/27/2014 and 10/28/2014). Three final statistical review memos were written by the statistical reviewer, Chunrong Cheng, Ph.D., for the original BLA.

FDA approved IXINITY on 3/14/2015 for two of the indications: control and prevention of bleeding episodes, and perioperative management, in adults and children >12 years of age with hemophilia B. FDA did not approve the routine prophylaxis indication in 2015 due to the following Orphan Drug Designation FDA had previously granted to RIXUBIS (BLA 125446) on 10/31/2012:

> Prophylactic use to prevent or reduce the frequency of bleeding episodes in patients with hemophilia B (routine prophylaxis in patients where there is no evidence or suspicion of bleeding)

The marketing approval date of RIXUBIS was 6/26/2013 and the exclusivity end date of this Orphan Drug Designation is 6/26/2020.

To further support the proposed labelling change, the applicant submitted in this sBLA Appendix 1 to the final clinical study report for pivotal study IB1001-01; the appendix consists of a subject-level table of annualized bleeding rates (ABR) by cause. Aside from this addition, neither the final clinical study report nor the datasets are updated in this sBLA.

Statistical Review

Of the three final statistical review memos written by Dr. Chunrong Cheng, the one entitled "SECOND CYCLE FINAL MEMO" contains the analysis for routine prophylaxis (dated 7/14/2014 and located at (b) (4) As shown in the memo, the primary endpoint for routine prophylaxis met its pre-specified

success criterion. The proposed labeling change for routine prophylaxis is consistent with the results presented by Dr. Cheng except an issue regarding the scale. In this memo, Dr. Cheng requested the applicant to report the ABR based on the original scale, instead of the square-root transformed scale. The applicant agreed to submit efficacy data on the original scale as indicated in her memo dated 2/25/2015. In the proposed labeling change in this sBLA, the applicant reported the ABR based on the original scale.

As her memo reports only the median ABR for routine prophylaxis, and the label presents both mean and median ABRs, I verified the mean and standard deviation of ABRs (Table 1).

Table 1: Efficacy of Prophylaxis with IXINITY (n=61)

Total ABR	
Mean ± standard deviation	3.55 ± 7.19
Spontaneous ABR	
Mean ± standard deviation	1.07 ± 3.06
Subjects with zero bleeding episodes % (n)	31.1% (19)

Conclusion and Recommendation

The statistical review supports the addition of “routine prophylaxis to reduce the frequency of bleeding episodes” to the IXINITY label.