MEMORANDUM

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

Date: February 24, 2015

From: Loan Nguyen, Regulatory Review Officer
OCBQ/DCM/APLB

Through: Lisa Stockbridge, Branch Chief
OCBQ/DCM/APLB

To: Edward Thompson, RPM, OBRR/DBA/RPMB
Chava Kimchi-Sarfaty, Chairperson, Product Reviewer, OBRR/DHRR/LH
Irwin Feuerstein, Clinical Reviewer, OBRR/DHCR/CRB

Subject: Labeling Review - Comments on product labeling (prescribing information, patient package insert, instructions for use, and carton/vial labels)

Product: **IXINITY (Coagulation Factor IX [Recombinant])**
BLA STN: **125426/0**
Sponsor: Cangene Corporation

Background

The sponsor submitted:

☒ New Approval
☐ Major Amendment
☐ Prior Approval Supplement
☐ Changes Being Effected Supplement

Submission contains:

☒ Prescribing Information
☒ Patient Package Insert
☒ Vial/Carton labels
☒ Other: Instruction for Use

This labeling review is for the original application (BLA STN 125426) submitted on March 8, 2013 by Cangene Corporation (Cangene) for IXINITY (Coagulation Factor IX [Recombinant]). The action due date for this application is April 29, 2015.

APLB has reviewed the following:

(1) prescribing information (PI), patient package insert (PPI), and instructions for use (IFU) provided by the review team (accessed on February 9, 2015), and
(2) carton/vial labels submitted by the sponsor on April 16, 2014.

Annotated PI, PPI, and IFU are attached to the memo to facilitate discussion.

OVERALL

- Please note the following regarding the use of trademark or registered trademark symbol (i.e., "TM" or "®"): The sponsor can add these symbols at will in Word and Adobe versions. However, these symbols may not appear in the renderings of labeling in SPL format due to style sheet restrictions.

- For the presentation of the proprietary and proper names, please consider the following:

    - The proprietary name, i.e., IXINITY, will appear in upper case letters in SPL format. For consistency, present it in upper case letters in the Word and Adobe versions as well.

    - For drugs, generic names (i.e., USAN names) are presented in all lower case letters (e.g., acetaminophen). However, for most biological products regulated by CBER, USAN names are not available. It has been customary to present the proper names in lower case with the first letter of the words capitalized (i.e., Coagulation Factor IX [Recombinant]). For consistency with other approved biological products, please consider using the same format until a unified decision regarding this aspect is reached within the center.

- Ensure that the section and subsection headings in the Highlights (HL) and the Contents (TOC) match the section and subsection headings in the Full Prescribing Information (FPI).

PRESCRIBING INFORMATION (PI)

Except as noted in the annotated PI (attached) and the comments below, APLB concurs with the revisions made by the review team. The following comments and recommendations are in addition to all the changes already made.

Highlights (HL)

- Please incorporate the established pharmacologic class (EPC) into the indication statement. To find the EPC for this product, follow the following directions:

    - Go to http://elist/prpllr/public/query/
    - Using the "Choose query" drop-down menu, choose "Substance and Pharmacologic Class Indexing"
    - Enter "coagulation factor IX recombinant human" as the "Active Moiety Name" then click "Next" in the first row on the page

- The EPC is listed in the column entitled "FDA Text Phrase"

- Since the route of administration is "Intravenous" and the dosage form is "Injection, Powder, Lyophilized, for Solution," APLB suggests "Lyophilized Powder for Solution for Intravenous Injection" for the presentation of route of administration and dosage form. Please move this phrase to a separate line beneath the product' names.

  For references, refer to the following websites for lists of acceptable routes of administration and dosage forms:

  Route of administration:
  http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162034.htm

  Dosage forms:
  http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162038.htm

- Upon approval, ensure that the 4-digit year is entered in the "Initial U.S. Approval."

- Delete the subheading in the DOSAGE AND ADMINISTRATION section if there is only one subheading. If space permits (i.e., within the ½ page limit in length), a dosing table with more detailed information may be considered as an alternative or in addition to the formula.

- Do not include the absence of information about the safety and effectiveness of a drug in specific population under the USE IN SPECIFIC POPULATIONS section. Consider deleting the second and third bullets relating to nursing mothers and pediatrics. It is customary to have the information relating to pregnancy in this section in addition to any clinically important differences in response or use of the drug in other specific populations.
- Revise the last statement to "See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling."

- Do not use a revision date when the label is initially approved. After initial approval, ensure that the revision date is the month/year that the application is approved and the preferred format is "Revised: Month Year" or "Revised: MM/YYYY." For example, "Revised: April 2015" or "Revised: 04/2015."

Contents (TOC)

Ensure that the section and subsection headings in the TOC match the section and subsection headings in the revised FPI.

Full Prescribing Information (FPI)

2 DOSAGE AND ADMINISTRATION

- Reformat the section into 3 subsections as follows:

  2.1 Dose
  2.2 Preparation and Reconstitution
  2.3 Administration

- For the dosing tables, consider adding a Dosing Frequency column for table 1 and place the Dosing Frequency column before the Duration of Therapy column in table 2.

- For the preparation, reconstitution and administration steps, use command language with short and succinct instructions. Do not include practice of medicine. Please see annotated PI for the suggested editorial edits.

4 CONTRAINDICATIONS

Revise the contraindication to make it one complete sentence.

5 WARNINGS AND PRECAUTIONS

- Be consistent with terminology, For example, use the term "factor IX containing products" or use "factor IX products."

- For subsection 5.2 relating to the risk of inhibitor formation, "Neutralizing Antibodies," "Inhibitors," "Inhibitor Formation," etc., have been used as sub-headers. Please use a consistent term across blood factor products for this same risk.

- For subsection 5.3 relating to the risk of nephrotic syndrome, please specify the product(s) associated with the reported cases.

- Present the monitoring laboratory tests in bullet format for better readability.

6 ADVERSE DRUG REACTIONS

- Only include adverse reactions (ARs) as defined in 21 CFR 201.57(c)(7) in this section. Please revise the paragraph above table 3 to include overall clinical trial database from which the AR data have been drawn, including overall exposure (number of patients, dose, duration), demographics of exposed population, designs of trial, and any critical exclusions from safety database. For example,

  > During the clinical studies conducted in previously treated patients (PTPs) with *[severe, moderate, etc.]* hemophilia B, 77 patients (including 11 patients < 18 years of age) *[add demographic data]* were treated with at least one dose of IXINITY with the total number of 9641 infusions. Fifteen adverse reactions were reported among 7 of the 77 patients. Table 3 presented the summary of the adverse reactions reported in > 1% of the patients.

- Third party rendering of the content of labeling into different stylesheets may result in the elimination of subsections 6.3 and 6.4. For this reason, consider including subsections for Immunogenicity and Thrombogenicity within subsection 6.1 (i.e., italicized subheadings within 6.1).

- Please present the required regulatory language as the first paragraph for the current subsection 6.4 Postmarketing Experience (note that the title of the subsection is not hyphenated).

8 USE IN SPECIFIC POPULATIONS

Revise the subsections as follows:

8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

11 DESCRIPTION

Consider the following format for this section as it has been used in the PIs of the most recent approved blood products. APLB finds this format helpful in term of readability and comprehension.

Paragraph 1: General description of the final drug product. The description may include important quality attributes of the final product.

Paragraph 2: General description of the active ingredient, including important quality attributes related to molecular structure and product safety

Paragraph 3: General description of the manufacturing process including information important to understanding the quality and safety of the product.

12 CLINICAL PHARMACOLOGY

- For subsection 12.1, consider simplifying the mechanism of action as follows:

  IXINITY temporarily replaces the missing coagulation Factor IX that is needed for effective hemostasis.

- For subsection 12.3

  - Consider deleting the 2nd paragraph relating to the comparison of IXINITY's $AUC_{0-\infty}$ to that of another recombinant factor IX product. This would allow comparative claims that are not adequately substantiated.

- For readability, consider presenting the last paragraph relating to the effects of the body mass index on the pharmacokinetic parameters of 32 subjects before the data relating to repeat dosing.

- The paragraph above Table 5 implies that there are data to support unapproved indication (i.e., routine prophylaxis). Please delete or revise.

14 CLINICAL STUDIES

Consider revising the section for readability and comprehension. Below are some of the general recommendations in addition to the suggested editorial edits shown in the annotated PI.

- Use consistent terms, either "patients" or "subjects, not both interchangeable.

- Avoid trailing zeros, especially in the text. For example, use "50" instead of "50.0."

- Table 7 can be summarized in text. Reserving the table format for data that needs emphasis.

- Please clarify that the product can be administered as continuous infusion for perioperative management. If so, consider adding this information to section 2 DOSAGE AND ADMINISTRATION.

16 HOW SUPPLIED/STORAGE AND HANDLING

- It is not necessary to subsection this section.

- Delete or revise the first paragraph since the information is already presented in other sections in the PI.

- Provide latex information if available.

17 PATIENT COUNSELING INFORMATION

- The first statement underneath the section heading should be "Advise the patients to read the FDA-approved patient labeling (Patient Information and Instructions for Use)." Consider add this statement as the first bullet and delete the last bullet containing the same information as this statement.

- Add manufacturer information at the end of the FPI if the FDA-approved patient labeling is a separate document or is to be detached and distributed to patients.

PATIENT PRODUCT INFORMATION (PPI)

If the PPI is intended to be detached from the FPI and distributed to the patients, ensure that the following information is presented at the end of the document:

- Manufacturer information (name and location of business [street address, city, state and zip code]). U.S. License number can be added as well.
- Revision date.

INSTRUCTIONS FOR USE (IFU)

- Ensure that the information presented here is consistent with the information in the FPI (i.e., section 2.2 and 2.3).

- If the IFU is intended to be detached from the FPI and distributed to the patients, ensure that manufacturer information and revision date are presented at the end of the document:

VIAL AND CARTON LABELS

The sponsor only submitted draft carton and vial labels with the application. Please request mock-up carton and vial labels.

If you have any questions regarding this review please contact Loan Nguyen, Pharm.D., Regulatory Review Officer at 240-402-9030.

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