Memorandum

DATE: April 19, 2018

TO: Candace Jarvis, RPM, CBER/OTAT/DRPM/RPMBI
Olukayode Owosela, RPM, CBER/OTAT/DRPM/RPMBI
Megha Kaushal M.D., Clinical Reviewer, CBER/ OTAT/DCEPT/CHB

FROM: Kristine T. Khuc, Pharm.D.
Consumer Safety Officer
Advertising and Promotional Labeling Branch (APLB)
Division of Case Management (DCM)
Office of Compliance and Biologics Quality (OCBQ)

THROUGH: Lisa L. Stockbridge, Ph.D.
Branch Chief
APLB/DCM/OCBQ

SUBJECT: JIVI (antihemophilic factor (recombinant), PEGylated)
BLA: 125661/0
Sponsor: Bayer Healthcare

Background

The sponsor submitted:
_x_ New Approval
___ Changes Being Effected (CBE) supplement
___ Prior Approval Supplement (PAS)
___ Major Amendment

Submission contains:
_x_ Prescribing Information (PI)
_x_ Patient Package Insert (PPI)
_x_ Package and/or container labels
___ Other

Submission Date: August 30, 2017

PDUFA Action Date: **August 30, 2018**

APLB Comments/Recommendations

This review is for an original BLA submission by Bayer Healthcare for JIVI (antihemophilic factor (recombinant), PEGylated). APLB reviewed the draft labeling dated March 6, 2018. The following comments are form a promotional and comprehension perspective.

GENERAL

Use active voice and command language whenever possible throughout the PI.

HIGHLIGHTS

PRODUCT TITLE

Present the proper name in small case lettering. In the second row, present the dosage form then the route of administration of the product. For example,

> **JIVII® (antihemophilic factor (recombinant), PEGylated-aucl)**
> **lyophilized powder for solution, for intravenous injection**

INDICATIONS AND USAGE

The description of the pharmacologic class of the product is too lengthy and hard to read. Simplify the indication to the following:

> JIVI, antihemophilic factor (recombinant), PEGylated, is a recombinant DNA-derived coagulation Factor VIII concentrate indicated for use in previously treated adults and adolescents (12 years of age and older) with hemophilia A …

CONTRAINDICATIONS

Please list out all the constituents suspected of causing hypersensitivity reactions. This information is buried in section 11 and requires the reader to determine which constituents are likely to cause hypersensitivity.

USE IN SPECIFIC POPULATIONS

Move the sentence regarding JIVI is not indicated for children <12 years and PUPS to the limitations of use in the INDICATIONS AND USAGE section. Underneath, this section, briefly describe why JIVI is not for use in children <12 years of age or in PUPs.

FULL PRESCRIBING INFORMATION: CONTENTS

Ensure any changes in the table of contents is consistent with the FULL PRESCRIBING INFORMATION.

FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Please refer to the comments above.

DOSAGE AND ADMINISTRATION

- By including Bayer's phone number, this is soliciting open discussion with the applicant. Therefore, under subsection 2.2, delete the bullet containing the applicant's phone number. The carton label already lists this information.

- Delete the sentence "The procedures below are provided as general guidelines for the reconstitution of JIVI using the sterile vial adapter with a 15 micrometer filter and a prefilled diluent syringe, which together serves as a needleless reconstitution system." This sentence states that the following instructions are "general guidelines," and introduces doubt concerning the directions for using the product.

- Under subsection 2.3, revise the parenteral product regulatory language to the following:

  "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit." Also, delete the sponsor's contact information here. Typically, the sponsor's contact information is found on the carton package label.

DOSAGE FORMS AND STRENGTHS

Include the appearance of the lyophilized powder.

WARNINGS AND PRECAUTIONS

In subsection 5.3 Immune Response to PEG, delete the sentence describing the immune response as transient and to resume their previous factor VIII therapy without delay. This sentence minimizes this risk of immune responses to PEG.

ADVERSE REACTIONS

- Avoid using research terms, such as "Phase I" or "Phase 3" studies in the PI.

- For the table describing adverse reactions, report the incidence rate in whole numbers.

- In the Immunogenicity subsection, delete the sentence "No *de novo* or confirmed case of inhibitor against Factor VIII occurred." This sentence contradicts and minimizes the second safety warning under WARNINGS AND PRECAUTIONS.

USE IN SPECIFIC POPULATIONS

- In subsection 8.1 Pregnancy, delete the sentence, “JIVI should be given to a pregnant woman only if clearly needed.” This sentence is uninformative to the prescriber.

- In subsection 8.4 Pediatric Use, there is required wording. Please use the following regulatory wording at the beginning of this subsection:

  > The safety and effectiveness in pediatric patients below the age of 12 have not been established.

- Under the subsection 8.5 Geriatrics, please revise this subsection using the following regulatory wording:

  > Clinical studies of JIVI did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the (dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

DESCRIPTION

- Typically, this section is organized into 3 parts. Consider revising this section as follows for better clarity and comprehension:

  > Paragraph 1: General description of the final drug product, including attributes of the final product.
  >
  > Paragraph 2: General description of the active ingredient, including quality attributes related to the product’s molecular structure.
  >
  > Paragraph 3: General description of the manufacturing process including specific information relating to the quality and safety of the product.

- Add the appearance of the reconstituted product solution.

CLINICAL PHARMACOLOGY

- Under subsection 12.1, please revise the mechanism of action of JIVI to include only established or reasonably well-characterized mechanism(s) of action. Avoid speculation or unsupported suggestions of therapeutic advantages based on mechanism of action.

- Under the Pharmacokinetic subsection, consider deleting the PK information on Kogenate FS. This subsection should contain only the PK data for the product.

CLINICAL STUDIES

- Do not use subsection numbers (i.e., 14.1, 14.2) for each of the subheaders under this section. Instead, use italics or underline to format these subheaders because stylesheets may not support subsection numbers in this section.

- For table 7, delete this statement in the footnotes "For guidance to the patient or their caregivers, the following definitions for response to treatment were provided." Consider footnoting this information.

HOW SUPPLIED/STORAGE AND HANDLING

Subsectioning this section when information is minimal will reduce readability.

PATIENT COUNSELING INFORMATION

- Delete the fifth bullet directing the patient to discard all equipment in an appropriate container as this information is for the patient and is found in the patient labeling.

- Revise the bullet points for readability. For example,

  Advise the patient:
  - To read the FDA-approved patient labeling…
  - The early signs of hypersensitivity reactions…
  - To contact their physician or healthcare provider if inhibitor formation…
  - To consult their physician or healthcare provider for allergic reactions to PEG…
  - To consult their physician or healthcare provider prior to travel...

PATIENT PACKAGE INSERT

- Underneath the header "What is JIVI?" add information stating that JIVI is not for use in children <12 years of age or in previously untreated patients.

- Underneath the header "What should I tell my healthcare provider before I use JIVI?" include a bullet point regarding pregnancy or planning to become pregnant.

- To enhance readability, bullet the information contained under the header "What are the possible side effects of JIVI?" Also, group related information together. Create a bullet for allergic reactions and another bullet for inhibitor formation. For example,

  - Allergic reactions can occur with JIVI. Call your healthcare provider right away if you get tightness of the chest or throat, dizziness, decrease in blood pressure, or nausea.

  - Your body can make antibodies (called "inhibitors") against JIVI, which will stop it from working properly. If your usual dose of JIVI does not control your bleeding, tell to your healthcare provider right away because you may have inhibitors. Your

healthcare provider will test your blood to confirm this. Your may have to consider other treatment options.

- Under the header "How do I store JIVI?" delete the last two bullets regarding unused product and do not use if product is not clear because that information does not belong here.

- Include the applicant's contact information (phone number or website address) in the last sentence underneath the header "What else should I know about JIVI and hemophilia A?"

INSTRUCTIONS FOR USE

- Above the "Reconstitution" header, we suggest the following revision:

  Use only the components for reconstitution and administration that are provided with each package of JIVI. If a package is opened or damaged, do not use this component. If these components cannot be used, please contact your healthcare provider.

  Prepare a clean flat surface and gather all the materials needed for the infusion. Wash your hands before performing the following procedures.

  Reconstitution

  Table & figure

- Underneath the "Pooling" header, provide a definition for pooling. For example,

  Pooling is a process of combining the contents of multiple vials into a syringe.

CARTON AND CONTAINER LABELS

Include the suffix -aucl in the proper name of the product.

If you have any questions regarding this review, please contact Kristine T. Khuc, Consumer Safety Officer at 240-402-8982.