

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

Date: February 25, 2016

From: Kristine 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 Stockbridge, Ph.D.
Branch Chief
APLB/DCM/OCBQ

To: Thomas Maruna, RPM, CBER/OBRR/DBCD
Victor Baum, M.D., Clinical Reviewer, CBER/OBRR/DHCR/CRB

Subject: **AFSTYLA (Antihemophilic Factor (Recombinant), Single Chain)**
(STN 125591/0)
Sponsor: CSL Behring LLC.

Background

The sponsor submitted:

- Original Biologics License Application
- Changes Being Effected (CBE) supplement
- Prior Approval Supplement (PAS)
- Major Amendment

Submission Date: May 29, 2015

PDUFA Action Date: May 28, 2016

Submission contains:

- Prescribing Information (PI)
- Patient Prescribing Information (PPI)
- Container and/or package labels
- Instructions For Use (IFU)

This labeling review is for a Biologics License Application submitted by CSL Behring on May 29, 2015 for AFSTYLA (Antihemophilic Factor (Recombinant)) Single Chain, indicated for use in adults and children with hemophilia A for control and prevention of bleeding episodes, routine prophylaxis to prevent or reduce the frequency of bleeding episodes, and perioperative management. APLB reviewed the PI, PPI, IFU, and carton/container labels from the label submission received on May 29, 2015.

GENERAL

- Spell out “IU” the first time it is used in the PI.
- Use bullets to increase readability, but do not overuse bullets (e.g., do not bullet a sentence or phrase if it is the only item underneath a heading).
- Avoid bolding text unless required by regulations. Do not bold subheadings within a section. Instead emphasize the subheading by using either using italics or underline.
- Use active voice throughout the entire PI.
- Refrain from the use of research terminology such as: study numbers, Phase I, Phase II, primary endpoint, secondary endpoint, etc. Simply discuss the characteristics of a study and the supported outcomes.

HIGHLIGHTS (HL)

PRODUCT TITLE

Please revise the product title. Because the route of administration is “Intravenous” and the dosage form is “Injection, Powder, Lyophilized, for Solution,” we suggest revising the product title to “Lyophilized Powder for Solution for Intravenous Injection.”

INDICATIONS AND USAGE

Add the subheading, *Limitation of Use*, underneath the indication and before the limitation statement.

DOSAGE AND ADMINISTRATION

- Delete the numerical identifier corresponding to the administration directive. This statement can stand alone without a cross reference.
- Revise the directions to active voice and eliminate redundancy with other sections in the HL.
- Cross reference the monitoring of Factor VIII levels with the precaution regarding false readings with certain testing systems (this precaution should be in the WARNINGS AND PRECAUTIONS section of the HL as well as the FPI).
- Revise the factor VIII empirical level statement for dose calculation. For example,

One international unit (IU) of AFSTYLA per kilogram (kg) body weight is expected to increase the circulating level of Factor VIII by 2 IU per deciliter (IU/dL).

WARNINGS AND PRECAUTIONS

- Include a summary for each warning and precaution in this section of the HL.
- To mitigate risk, consider a boxed warning regarding the importance of the assay type for correct monitoring of Factor VIII when taking AFSTYLA.

ADVERSE REACTIONS

The sentence highlighting the “single” hypersensitivity adverse reaction minimizes the importance and severity of this warning. This is the first warning and does not require repetition within the statement of the common adverse reactions seen in the clinical trials.

USE IN SPECIFIC POPULATIONS

Delete the pregnancy statement. It belongs with the former pregnancy category C, which no longer exists. It is not required in the HL conforming to the Pregnancy and Lactation Labeling Rule.

FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

Please see above comment regarding adding “Limitation of Use” subsection header.

DOSAGE AND ADMINISTRATION

- Revise this section to active voice for readability.
- Under subheader **2.2 Preparation and Reconstitution**, delete the second and fourth bullets as this information is already mentioned and belongs in section 16 HOW SUPPLIED/STORAGE AND HANDLING.
- In Table 3, we suggest the following revisions to enhance comprehension:
 - ◆ Step 11, delete the last statement pertaining to attaching the syringe to a suitable IV administration set. This information belongs under the **2.3 Administration** subheader.
 - ◆ Revise the first sentence in step 12 to read as “After reconstitution, use immediately or within 4 hours.”
 - ◆ Step 14, revise the statement to read “If the dose requires more than one vial, reconstitute each vial using a separate, unused MIX2Vial transfer set. Repeat step 10 to pool the contents of the vial into one syringe.”
- Under subheader **2.3 Administration**, we recommend the following:

- ◆ Move third bullet regarding using aseptic technique as the first bullet in this subsection.
- ◆ Revise the fourth bullet to state “Administer AFSTYLA at room temperature immediately or within 4 hours after reconstitution.”
- ◆ Delete the fifth bullet as this is a practice of medicine statement.
- ◆ Consider adding in a recommended infusion rate or limit.

DOSAGE FORMS AND STRENGTHS

Add a statement referring that the actual potency is printed on the vial and container labels.

CONTRAINDICATIONS

Identify the non-endogenous excipients in the product (e.g., polysorbate 80), and add a cross reference to section 11 DESCRIPTION.

WARNINGS AND PRECAUTIONS

- Consider whether the issue concerning assay type in monitoring Factor VIII levels requires elevation to a BOXED WARNING.
- Use active voice and avoid redundancy within the subsections.

ADVERSE REACTIONS

- The sentence highlighting the “single” hypersensitivity adverse reaction minimizes the importance and severity of this warning. This is the first warning and does not require repetition within the statement of the common adverse reactions seen in the clinical trials.
- Please provide more details of the overall clinical trial database including the demographics of the exposed population, and any critical exclusions from the safety database.
- Delete the following sentences from **6.1 Clinical Trials Experience**. They are promotional in tone and minimize the risk of AFSTYLA in the absence of a robust prospectively designed safety study. Furthermore, they contradict the WARNINGS AND PRECAUTIONS for this product:

No subject withdrew from either study due to an adverse event. No neutralizing antibodies (inhibitors) to Factor VIII or antibodies to host cell proteins were detected with the use of AFSTYLA. No events of anaphylaxis or thrombosis were reported.

- Be consistent in using the terms “trials” and “studies” in this section.
- In Table 4, please revise the table header “MedRDA Preferred Term” to “Adverse Reactions.”
- Delete the footnote in Table 4, as it is not necessary. An adverse reaction, by definition, is an

adverse event for which there is some basis to believe that the event is related to the drug/product. Only adverse reactions are included in **6.1 Clinical Trials Experience**.

- The Immunogenicity subsection is promotional in tone. The leading statement, “No subject developed neutralizing antibodies,” is inconsistent with the second warning, and it is based on a very small sample. This section should begin with language alerting the reader that the comparison of antibody formation with other products could be misleading because of various factors, including the sensitivity and specificity of the assay performed. If low (or no) incidences are highlighted, it is important to balance this by clearly conveying the small sample size and the fact that the numbers seen in the study may not reflect the incidence in the general population. Revise the term “adverse event” to “adverse reaction.” For readability, refrain from the use of double negatives.

USE IN SPECIFIC POPULATIONS

Please refer to the guidance [*Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products-Content and Format*](#) for information on appropriate edits to this section.

DESCRIPTION

Add information stating that the actual potency is provided on each vial container and carton.

CLINICAL PHARMACOLOGY

Revise the subsection **12.1 Mechanism of Action** to include only established or reasonably well characterized mechanism(s) of action. Avoid unsupported suggestions of therapeutic advantage based on the mechanism of action (for example, truncated chain versus full length chain). This type of claim appears promotional.

NONCLINICAL TOXICOLOGY

When there is no data, this section may be deleted.

CLINICAL STUDIES

In tables 7 and 9, we suggest deleting the footnotes describing the hemostatic efficacy and including this information in the body of the text. Currently, the terms excellent, good and moderate appear in running text with no qualification. This makes the text promotional in tone. In the footnote, the text is very dense and hard to read. It likely will not be read, thus leaving the superlatives unqualified.

HOW SUPPLIED/STORAGE AND HANDLING

This section is too short to be sub-sectioned. Simplify language with active voice and reduce redundancy.

PATIENT PACKAGE INSERT

- Use consumer friendly terms throughout this document (for example, give (administer); mix (reconstitute)).
- Reiteration of the proprietary name, AFSTYLA, in each sentence in this document minimizes the information in the sentence and decreases readability.

INSTRUCTIONS FOR USE

- Present the product name at the beginning of this document just in case it is detached from the PI or the PPI.
- Revise the administration directive as “For intravenous use after reconstitution only.”
- The fifth bullet may be revised using consumer friendly language to the following or similar phrasing “Look at the mixed (reconstituted) solution. Do not use AFSTYLA if the reconstituted solution is cloudy, contains any particles, or is discolored.”
- For step 11, delete the last sentence “Attach the syringe to a suitable IV administration set.” This instruction belongs in the Administration section.
- Revise the first sentence in step 12 to “After reconstitution, use immediately or within 4 hours.”
- For step 14, revise these instructions to the following “If the dose requires more than one vial, use a separate unused Mix2vial transfer set for each product vial. Repeat step 10 to pool the contents into one syringe.”
- Add the administration instructions. Consider adding in an infusion rate or infusion rate limit.
- Delete the statement “This Patient Package Insert has been approved by the US Food and Drug Administration.” This statement is only for medication guides.

CARTON AND CONTAINER LABELS

- Revise the presentation of the potencies on the labels (vial and carton) to reflect the nominal potencies. For example, “1000 IU Range.”
- Add the actual potency on each vial container label.
- Add latex information on the carton labels.

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

Firm name: CSL Behring

Letter type: Labeling Review

Bcc:

HFM-602 APLB chron file

HFM-602 APLB product files

History

Prepared: Kristine Khuc 1/29/16

Concur w/ comments: Lisa Stockbridge 2/19/16

Final: Kristine Khuc 2/25/16

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Concurrence box:

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