



U.S. FOOD & DRUG
ADMINISTRATION

Memorandum

DATE: April 18, 2023

TO: Eden Chane, RPM, OTP/ORMRR/DRMRR1/RMSB1
Ze Peng, Ph.D., Committee Chair, OTP/OPPT/DH/HB1
Karl Kasamon, M.D., Clinical Reviewer, OTP/OCE/DCEH/BHB

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

SUBJECT: **BALFAXAR [prothrombin complex concentrate, human-lans]**
BLA: 125776/0
Sponsor: Octapharma

Background

The sponsor submitted:

☒ New Approval
☐ Changes Being Effectuated (CBE) supplement
☐ Prior Approval Supplement (PAS)
☐ Major Amendment

Submission contains:

☒ Prescribing Information (PI)
☐ Patient Package Insert (PPI)
☒ Package and/or container labels
☐ Other

Submission Date: July 28, 2022

PDUFA Action Date: **July 28, 2023**

APLB Comments/Recommendations

This labeling review is for an original Biologics License Application submitted by Octapharma for BALFAXAR [prothrombin complex concentrate, human]. Octapharma originally submitted a proposed (b) (4) indication for their product. However, on February 14, 2023, in response to an information request from FDA, the (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) The current revised proposed indication is “BALFAXAR, prothrombin complex concentrate, human-lans, is a blood coagulation factor replacement product, indicated for the urgent reversal of acquired coagulation factor deficiency induced by Vitamin K antagonist (VKA, e.g., warfarin) therapy in adult patients with need for an urgent surgery/invasive procedure.”

APLB reviewed the draft labeling, containing revisions to the PI from the review committee on March 24, 2023. APLB reviewed the package and container labels submitted by Octapharma on July 28, 2022. Our comments are from a comprehension and promotional perspective.

GENERAL

- Please add the suffix, -lans, to the proper name. For example,
prothrombin complex concentrate, human-lans
- Use active voice and command language throughout the PI whenever possible.
- Throughout this PI, delete information pertaining to the use of BALFAXAR as a factor (b) (4) This is not within the scope of the indication.
- In some parts of the PI, there is a statement regarding the actual potency of the coagulation factors and Proteins C and S are stated on the carton; however, this is not the case. The nominal potency is listed instead. The only actual potency listed on the carton package is for factor IX. Please revise.

HIGHLIGHTS (HL)

PRODUCT TITLE

Within the PRODUCT TITLE, avoid leaving white space between the name, route of administration, dosage form, and the initial approval date. The dosage form is presented before the route of administration. We recommend the following presentation:

**BALFAXAR [prothrombin complex concentrate, human-lans]
Lyophilized powder for solution, for intravenous use
Initial U.S. Approval: 2023**

BOXED WARNING

- In the BOXED WARNING, the required statement underneath the header is missing.

Place the required verbatim statement centered, italicized, and bolded.

See full prescribing information for complete boxed warning.

- In the second bullet, place the numerical cross-reference at the end of the sentence.

DOSAGE AND AMINISTRATION

In this section, avoid using an asterisk symbol because the asterisk is already used in the table of contents. Please use another symbol.

CONTRAINDICATION

For this section, cross reference to the same section, which appears in the FULL PRESCRIBING INFORMATION. For example, cross reference to section 4 rather than section 11.

ADVERSE REACTIONS

In the ADVERSE REACTIONS section, round the adverse reaction rate to the nearest whole integer.

REVISION DATE

Delete the Revision Date because this will be the original approval.

FULL PRESCRIBING INFORMATION (FPI)**PRODUCT TITLE**

It is unnecessary to have the Product Title here, however; if retaining, the dosage form of the product should precede the route of administration. See comment above.

BOXED WARNING

In the second bullet, revise the language to be consistent with the language appearing in the BOXED WARNING in the HIGHLIGHTS.

DOSAGE AND ADMINISTRATION

- Revise this section using active voice and command language whenever possible.
 - In subsection 2.2, delete the administration directive since this subsection is describing the preparation and reconstitution instructions rather than the administration
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instructions. Also, avoid using qualifiers such as “quickly.” Instead, state the timepoint or just delete.

- Directly underneath subsection 2.3, state the administration directive.

WARNINGS AND PRECAUTIONS

- Under subsection 5.2, delete information pertaining to (b) (4) dosing because this information is not within the scope of the indication or dosing recommendation for this product. Revise this subsection using command language and active voice to enhance readability.
- Avoid vague phrases such as “close monitoring should be exercised.” Revise this sentence by adding monitoring parameters or signs and symptoms.

ADVERSE REACTIONS

- Underneath subsection 6.1 Clinical Trials Experience, it may be unnecessary to have a subheader entitled “Controlled Clinical Studies.” This can be described in the study design. Maintain consistency with the use of the term “trial” vs. “study.”
- In Table 2, replace the product name “Octaplex” with “BALFAXAR.” In the second row, simplify the header, for example, “Embolic and thrombotic events.” Avoid using abbreviations (e.g., define “IP.”)

USE IN SPECIFIC POPULATIONS

- Underneath subsection 8.1, please delete the uninformative sentence “BALFAXAR should be prescribed for a pregnant woman only if clearly needed.”
- Underneath subsection 8.2, delete the last sentence “Because many drugs are excreted in human milk, use BALFAXAR only if clearly needed when treating a nursing woman.”
- In addition, include the verbatim statement at the end of the Risk Summary sub-subsection header.

“The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for BALFAXAR and any potential adverse effects on the breastfed child from BALFAXAR or from the underlying maternal condition.”

- In subsection 8.5 Geriatric Use, please delete the (b) (4) information.

CLINICAL PHARMACOLOGY

Subsection 12.2 is quite lengthy and seems to contain unnecessary details describing the different coagulation factors of the coagulation pathways and where they made. Consider deleting this information.

CLINICAL STUDIES

- Avoid using research terms, such as “Phase III” which may decrease readability. Instead, just describe each study.
- Delete trailing zeros. For example, 10.0 mg. This may be misread as 100 mg.
- Within subsection 12.2, there is a statement, which cross-references to this section regarding the relationship between the INR value and clinical hemostasis. However, in section 14 it is not apparent that this information is presented here. Consider adding this information to give context to this efficacy endpoint.

HOW SUPPLIED/STORAGE AND HANDLING

Add the color scheme of the two dosage strengths to the table.

PACKAGE AND CONTAINER LABELS

Add the suffix, -lans, to the proper name of the product.

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