



Memorandum

DATE: 04/25/2018

TO: Charles Maplethorpe, Medical Officer, CBER/OBRR/DBCD/CRS
Lorraine Wood, RPM, CBER/OBRR/RPMS

FROM: Alpita Popat, PharmD, MBA
CBER/OCBQ/DCM/APLB

THROUGH: Lisa L. Stockbridge, Ph.D.
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SUBJECT: Labeling Review
ALBUMINEX (Human Albumin Solution 5% and 25%)
BLA 1256644/0
Sponsor: Bio Products Laboratory

Background: The sponsor submitted:

New Approval
 Changes Being Effected (CBE) supplement
 Prior Approval Supplement (PAS) Amendment
 Major Amendment

Submission contains:

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

Submission Date: December 8, 2016

PDUFA Action Date: June 19, 2018

APLB Comments/Recommendations

On December 08, 2016, Bio Products Laboratory (Bio Products), submitted an original Biologics Licensing Application (BLA) for ALBUMINEX (Human Albumin Solution 5% and 25%). ALBUMINEX is indicated the treatment of hypovolemia, ascites, burns, nephrotic syndrome, acute respiratory distress syndrome and cardiopulmonary bypass.

A BLA Complete Response (CR) letter was sent on August 25, 2017 to the sponsor. The letter stated that after reviewing the application final approval could not be granted because of CMC and Facility deficiencies. On December 18, 2017, Bio Products resubmitted the application with responses to the CR letter.

On June 19, 2017, APLB recommended that the proposed proprietary name, ALBUMINEX, be found acceptable. A second proprietary name review was completed on April 13, 2018 and no new concerns were found. APLB reviewed the proposed labeling and carton/container labels submitted on April 11, 2018. The following comments are from a promotional and comprehension perspective.

GENERAL

- Apply all comments to the **PRESCRIBING INFORMATION** for ALBUMINEX 5% and ALBUMINEX 25%.
- To improve readability, use bulleted lists and tables wherever possible.
- Use active voice to enhance readability and comprehension.

HIGHLIGHTS (HL)

- The established name is not required in the **Highlights Limitation Statement**. For example:

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ALBUMINEX safely and effectively. See full prescribing information for ALBUMINEX.

- The **Product Title** should present the proprietary name in UPPERCASE lettering, the proper name in lower case lettering within parentheses followed by the dosage form. For example:

ALBUMINEX (human albumin) 5% solution for injection

- In the **DOSAGE AND ADMINISTRATION** section, provide the dosage for each indication rather than the directive to use different dosages for each indication. Consider a table for readability and ease of access to information.

The statement, “ALBUMINEX 5% contains 25 g per dL of human albumin.” belongs in the **DOSAGE FORMS AND STRENGTHS** section rather than this section.

- In the **CONTRAINDICATIONS** section, include the excipients that could cause hypersensitivity reactions. Consider revising the second bullet to follow other products in the same class. For example:

Severe anemia or cardiac failure with normal or increased intravascular volume.

- List **WARNINGS AND PRECAUTIONS** with a concise summary of the adverse reaction/risk and recommendations for the prescriber to prevent, monitor for, or mitigate the risk. For example:
 - Hypersensitivity or allergic reactions have been observed, and may in some cases progress to severe anaphylaxis. Epinephrine should be available immediately to treat any acute hypersensitivity reaction. (5.1)
 - Hypervolemia: Monitor patients who are at risk of hypervolemia or hemodilution. Stop infusion if signs of cardiovascular overload occur. (5.2)
 - Do not dilute solution with sterile water for injection. (5.3)
 - Ensure adequate substitution of other blood constituents. Monitor coagulation status and hematocrit. (5.4)
 - This product is made from human plasma and may contain infectious agents, e.g., viruses and, theoretically, the Creutzfeldt-Jakob disease agent. (5.6)
- Provide a cutoff frequency (a qualifier for “most common”) for the list of adverse reactions in the **ADVERSE REACTIONS** section.

The second sentence is weak and lost, following the paragraph of “most common adverse reactions.” This serious risk belongs with **WARNINGS AND PRECAUTIONS** subsection 5.1. If it also is included in **ADVERSE REACTIONS**, it should be separated from the first paragraph and cross-referenced to 5.1.

- Delete **USE IN SPECIFIC POPULATIONS** from **HIGHLIGHTS**. Pregnancy information must follow the Pregnancy and Lactation Labeling Rule and absence of information is not reported in the **HIGHLIGHTS** for specific populations.
- The **FULL PRESCRIBING INFORMATION** does not include FDA-approved patient labeling. Delete this from the statement from below the **USE IN SPECIFIC POPULATIONS**. For example:

See 17 for PATIENT COUNSELING INFORMATION.

- An initial PI does not include the Revised Date at the end of the **HIGHLIGHTS**.

FULL PRESCRIBING INFORMATION (FPI)

2 DOSAGE AND ADMINISTRATION

- For consistency and ease in style sheet interoperability, this section should be sub-sectioned into two parts with the following headings:

2.1 Dose

2.2 Administration

- Active voice is very important to the readability in this section. To enhance the readability further, consider a table with the dosing for each indication in the **2.1 Dose** subsection and use bullets in the **2.2 Administration** subsection.

4 CONTRAINDICATIONS

- List out the excipients that would cause hypersensitivity reactions. A link to **11 DESCRIPTION** is not adequate.
- Consider more detail for the second bullet (see above comment).

5 WARNINGS AND PRECAUTIONS

- The first sentence in **5.1 Hypersensitivity** should connect this important risk information with ALBUMINEX. The second sentence is wordy and redundant. We recommend revising this section to the following:

Hypersensitivity reactions, including anaphylaxis, can occur with ALBUMINEX. If this occurs, discontinue infusion and institute appropriate treatment. Have medications such as epinephrine available for immediate treatment of acute hypersensitivity reaction.

- Refrain from using vague terminology, such as “with caution.” Instead, describe the necessary action(s). For subsection **5.2 Hypervolemia**, revise the first sentence to active voice and describe the actions necessary. For example,

Hypervolemia or hemodilution can occur with ALBUMINEX infusion, with consequences including, but not limited to, heart failure, pulmonary edema, anuria, hemorrhagic diathesis, esophageal varices, arterial hypertension, and anemia. During infusion, it is important to monitor patients for signs and symptoms of these serious clinical risks.

- Passive voice in **5.3 Hemolysis** is reducing the readability of the important information.
- Subsection **5.6 Infectious Disease** is a section with a regulatory title, **5.6 Transmissible Infectious Agents**, and regulatory wording. (See *Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease by Blood and Blood Products*). Please revise to:

Albumin is a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of

transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD or vCJD have ever been identified for licensed albumin.

All infections suspected by a physician possibly to have been transmitted by ALBUMINEX should be reported by the physician or other healthcare provider to BPL at MedInfo@BPL-US.com or 1-844-427-5872.

6 ADVERSE REACTIONS

- The statement of most common adverse reactions (usually a copy of the **HIGHLIGHTS** adverse reactions statement) belongs between this section heading and **6.1 Clinical Trials Experience**.
- This section is not organized per the regulations and guidance. The first subsection should be **6.1 Clinical Trials Experience**. The second subsection, if one exists, would be **6.2 Postmarketing Experience**. There is no subsection entitled “General,” as this is a vague and uninformative title.
- The first sentence, “In general, human albumin solutions are well-tolerated and no specific, clinically relevant alterations in organ function or coagulopathy have been substantiated” is promotional in tone. Please delete this statement from the **6 ADVERSE REACTIONS** section.

The list of most frequently occurring adverse reactions belong beneath the section heading (as stated above).

- For subsection **6.1 Clinical Trials Experience**, please state the following:

No clinical trials were done using ALBUMINEX.

7 DRUG INTERACTIONS

Revise this section to active voice for readability.

8 USE IN SPECIFIC POPULATIONS

- In the **8.1 Pregnancy** subsection, the statement, “ALBUMINEX x% should be given to a pregnant woman only if clearly needed” is not recommended because it is not considered informative. Please delete this statement.
- The statement “can affect reproduction capacity” does not belong in the **8.1 Pregnancy** subsection. Pregnancy Testing, Contraception, and Infertility information belongs in the **8.3 Females and Males of Reproductive Potential** subsection. If none of the subheadings are applicable, subsection 8.3 can be omitted.
- In the **8.4 Pediatric Use** subsection, the statement “Extensive experience in patients with the use of albumin (human) suggest that children respond in the same manner as adults” is considered promotional in tone. We recommend deleting this statement.
- In the **8.5 Geriatric Use** subsection use the following regulatory statement (21 CFR §201.57(c)(9)(v):

Clinical studies of ALBUMINEX 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.

11 DESCRIPTION

Move the statement, “The vials are closed with a synthetic rubber stopper. The stopper is not made with natural rubber latex,” to **16 HOW SUPPLIED/STORAGE AND HANDLING** section.

16 HOW SUPPLIED/STORAGE AND HANDLING

- Please delete the statement, “ALBUMINEX 5% should be inspected visually for particulate matter and discoloration prior to administration.” This statement is in the **2.2 Administration** subsection, where it belongs.
- Since the vials are closed with synthetic rubber stoppers, please add the statement “The stopper is not made with natural rubber latex”.

17 PATIENT COUNSELING INFORMATION

Use command language and bullets wherever possible to increase readability. For example:

- Inform patients to immediately report the following symptoms to their physician:
 - Anaphylaxis type reactions [*see Hypersensitivity (5.1)*]
 - Potential circulatory overload [*see Hypervolemia (5.2) and Overdosage (10)*].
- Inform patients that because ALBUMINEX 5% is derived from human blood plasma it may contain infectious agents that cause disease (e.g. viruses and, theoretically CJD agent) although the risk of infection from ALBUMINEX 5% has been reduced by the procedures used in donor selection and during manufacture [*see Infectious Diseases (5.6) and Description (11)*].

CONTAINER LABEL

The label affixed to each container of a product was not included in the submission. Please submit container labels for ALBUMINEX 5% and 25%.

PACKAGE LABEL

APLB has no comments.