DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
1401 Rockville P ke
Rockville, MD 20852-1448

Our STN: BL 125384/0

Kedrion, S.p.A.
Attention: Mr. Urs E. Aeberli
FFF Enterprises, Inc.
January 20, 2011
Sent by email: uaeberli@fffenterprises.com

Dear Me. Aeberli:

We are reviewing your August 2, 2010 submission to your original BLA for Albumin (Human). We have the following questions and comments regarding the package insert submitted with the original BLA:

General

- The proposed labeling has inherently inconsistent heading, formatting, and numbering. It fails to provide required wording when necessary and it has content under incorrect headings and subheadings. Please revise this PI according to the new format and labeling requirements (21 CFR 201.56 and 201.57).

- Reorganize **WARNINGS AND PRECAUTIONS** into subheadings with headings that address each risk (i.e., not **5.1 WARNINGS AND 5.2 PRECAUTIONS**). These should be prioritized based on relative public significance and decreasing order of importance. The various subheadings should be reflected in the HIGHLIGHTS with a brief summary of the content of each subheading.

- Use command language wherever possible.

- Do not use a "slash mark" (/) to separate doses since it is commonly mistaken for the number 1. Instead, use "per." For example, do not use 5 mg/10 mL. Use 5 mg per 10 mL.

- Avoid using vague, misleading, or promotional terms such as "rare" and "very rarely."

- For consistency, we recommend you refer to the dosing of Kedbumin only in terms of "g per mL."

Highlights of Prescribing Information

- The Highlights are limited in length to one-half page (e.g., would fit on one-half page if printed on 8.5" x 11" paper, single spaced, 8 point typefont with ½ inch margins on all sides, in a two-column format). Although there are exceptions (i.e., space for boxed warning), there is no reason why this PI should fail to meet the format requirement for the HIGHLIGHTS and the Table of Contents.

- Immediately, under the **DOSAGE AND ADMINISTRATION** heading, please insert "Intravenous Administration Only."

- In the **INDICATIONS AND USAGE** section, revise "KEDBUMIN™ is indicated for:" to "KEDBUMIN™ is an albumin indicated for:"

- Please delete the sentence, "*The choice of albumin rather than an artificial colloid by the physician will be based on the individual patient's clinical situation.*" This is a practice of medicine statement and should not be included in the PI.

- In the **CONTRAINDICATIONS** section, there should be statement about the contraindication of Kedbumin in severely anemic patients and in patients with cardiac failure. Additionally, please include a cross reference to the **CONTRAINDICATIONS** section of the full prescribing information.

- In the **USE IN SPECIFIC POPULATIONS** section, please revise the following statement, "*Unknown whether 25% human albumin can cause fetal harm or effect reproduction (8.1)*" to state, "*Pregnancy: Based on animal data, may cause fetal harm," or "No human or animal data. Use only if clearly needed." Conclude the entire statement with a cross-reference to Pregnancy subsection (8.1).*

- The date of the approval, in bold type, must be presented at the end of Highlights. The preferred format is "Revised: Month Year" or "Revised: Month/Year" (i.e., Revised: June 2003 or Revised: 6/2003).

- The statement, "*FDA-approved patient labeling" in the statement, "See (17) for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling*" references an "*FDA-approved patient labeling."* Is there an FDA-approved patient labeling? If not, we recommend deleting this part of the sentence.

Full Prescribing Information: CONTENTS

- When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

- Be mindful that many subsections have designated numbering. The numbers presented here are incorrect.

- Use a two-column format for the Table of Contents and limit this section to one-half page (see above comment).

- Place a horizontal line between Highlights and Table of Contents sections to separate Highlights information from the table of contents.

Full Prescribing Information

- In the INDICATIONS AND USAGE section we recommend deleting, "*KEDBUMIN™ [Albumin (Human) U.S.P.] sterile, aqueous solution for single dose intravenous administration is indicated for emergency treatment of hypovolemia with or without shock. Its effectiveness in reversing hypovolemia depends largely upon its ability to draw interstitial fluid into the circulation. Consequently it is most effective in patients who are well hydrated. When blood volume deficit is the result of hemorrhage, compatible red blood cells or whole blood should be administered as soon as possible [1, 2].*
The choice of albumin rather than an artificial colloid by the physician will be based on the individual patient's clinical situation, based on official recommendations." This information primarily describes the mechanism of action and does not belong in the INDICATIONS AND USAGE section of the PI."

- Immediately, under the **DOSAGE AND ADMINISTRATION** heading, please insert "Intravenous Administration Only."

- The inclusion of a section for each indication makes the **DOSAGE AND ADMINISTRATION** section difficult to follow. In certain sections of the **DOSAGE AND ADMINISTRATION**, only the dose is presented (e.g., 50-75 g). The phrasing lacks context, and it is redundant and cumbersome. We recommend that the individual sections be deleted and replaced by a table. For clarity, this section may be divided into two subsections, **2.1 DOSAGE** and **2.2 ADMINISTRATION**. With many of the concepts combined, there is no need for a "General Recommendation" section.

- The **DOSAGE AND ADMINISTRATION** section states:

  > *"Albumin solutions should not be mixed with other medicinal products including blood and blood components but can be administered concomitantly with other parenterals such as whole blood, plasma, saline, glucose or sodium, lactate when medically necessary.*
  > *Albumin solutions should not be mixed with protein hydrolysates or solutions containing alcohol since these combinations may cause protein precipitation*."

  Replace the general term "Albumin solutions" with the trade name, KEDBUMIN™, as this information concerns Kedbumin. Additionally this paragraph should be in the **DRUG INTERACTIONS** section of the PI.

- The following verbatim statement is required for parenteral solutions [21 CFR 201.57(c)(3)]:

  > "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever the solution and container permit."

Delete the warning, *"Do not use parenteral solution if turbid or contains sediment."* This concept is covered in the **DOSAGE AND ADMINISTRATION** section.

- Include a statement regarding the warning that hemolysis may occur if KEDBUMIN is diluted with sterile for injection. Cross reference this to the hemolysis precaution.

- The **WARNINGS AND PRECAUTIONS** section states:

  "KEDBUMIN™ should not be administered if the solution appears turbid or contains sediment. Do not begin administration more than four hours after the container has been entered. Discard any unused material." Delete this statement.

  The concept belongs in the **DOSAGE AND ADMINISTRATION** section (see above comment).

- The following is a suggested revision to the **WARNINGS AND PRECAUTIONS**:

  "5. WARNINGS AND PRECAUTIONS

  5.1 Hypersensitivity Reactions…

  5.2 Hypovolemia

  KEDBUMIN™ should be used with caution in conditions where hypervolemia and its consequences or hemodilution could pose a special risk (10). Examples of such conditions may include but are not limited to:

  - Heart failure
  - Arterial hypertension
  - Esophageal varices
  - Pulmonary edema
  - Hemorrhagic diathesis
  - Severe anemia
  - Renal and post-renal anuria

  5.3 Hemolysis

  Do not dilute KEDBUMIN™ with Sterile Water for Injection, as this may cause hemolysis in recipients. There is a risk of potentially fatal hemolysis and acute renal failure from the use of Sterile Water for Injection as a diluent for 25% albumin [14]. Suitable solutions for dilution include 5% glucose and 0.9% sodium chloride [2.2].

  5.4 Large Volumes

  When replacing comparatively large volumes of albumin, control of coagulation and hematocrit is essential. Ensure adequate substitution of other blood constituents such as coagulation factors, electrolytes, platelets, and erythrocytes.

[NOTE: The statement, "*Additionally, the product should be warmed to room temperature if large volumes are to be administered.*" should be move to the DOSAGE AND ADMINISTRATIVE section.]

5.5 Hydration

The colloid osmotic effect of KEDBUMIN™ 25% is approximately four times that of human blood. Therefore, when concentrated albumin is administered, ensure adequate hydratrion of the patient. Carefully monitor to guard against circulatory overload (See 10 **OVERDOSE).**

Hemodynamic performance should be monitored regularly. This may include arterial blood pressure and pulse rate, central venous pressure, pulmonary artery occlusion pressure, urine output, electrolyte levels, and hematocrit/hemoglobin.

5.6 Infectious Diseases

KEDBUMIN™ contains albumin, 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. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin.

All infections thought by a physician or other healthcare provider to have been transmitted by this product should be reported to "PV Partner", Inc at 1-8XX-XXX-XXXX.

- Should there be a Postmarketing Experience subsection or even a Clinical Trials Experience subsection?

- In the USE IN SPECIFIC POPULATIONS section, the following subsections have required numbering:

  8.1 Pregnancy
  8.4 Pediatric Use

  Renal impairment must be numbered following the last pre-designated number. Thus, it is would be **8.6 Renal Impairment**.

- The DESCRIPTION section states:

  ----------*(b)(4)*----------

  This statement is vague and misleading in the absence of quantitative data that supports it. Please delete.

- The CLINICAL PHARMACOLOGY section states:

"*Albumin solutions were originally developed in the 1940s for the military as plasma replacement therapy. Since then albumin has been administered for multiple indications including hypovolemia, shock, burns, surgery, trauma, cardiopulmonary bypass, acute respiratory distress syndrome (ARDS), hemodialysis, acute liver failure, and ascites.*

There are no known cases of viral transmission resulting from the use of KEDBUMIN. However, as with all products derived from human plasma, KEDBUMIN has a theoretical risk of transmitting blood-borne pathogens such as viruses and prions.

In vitro studies demonstrated that the manufacturing process for KEDBUMIN provides significant reduction of both enveloped and non-enveloped viruses."

The CINICAL PHARMACCOLOGY section only should include information relating to human clinical pharmacology and actions of the drug product in humans. Information based on *in vitro* data using human biomaterials or animal models, or relevant details about *in vivo* study results from human data may be included if essential to understanding dosing or drug interaction information. Therefore, we recommend deleting the above information.

- The NONCLINICAL TOXICOLOGY section states, "*The active ingredient of this product, human albumin, is a normal constituent of plasma. KEDBUMIN is administered at physiological levels. The tolerability, pharmacodynamic, and clinical characteristics of albumin have been documented over decades of clinical use. It is commonly recognized that animal studies have no practical relevance for human albumin [16][17].*"

  The NONCLINICAL TOXICOLOGY section is not required and, if included, must discuss animal data. Thus, we recommend that this section be deleted.

- Please ensure that all the studies in the CLINICAL STUDIES section pertain to the product Kedbumin **25%** and its approved indications. This section should not be written as a literature review or anecdotal information. Rather, it should discuss the studies themselves and only those studies important to the physician's understanding of the safe and effective use of the product. The CLINCAL STUDIES section should include only those studies that provide the primary support for effectiveness, description of population(s) (including number enrolled, completed, discontinuations), different effects in subpopulations, absence of expected effectiveness, study result data, etc. Do not include author impressions or projections. Do not include terms such as "statistically significant" without showing data. Comparative terms (e.g. superior) must be accompanied by adequate and well-controlled comparative clinical studies. Mortality claims must be supported by adequate and well-controlled clinical studies designed to demonstrate mortality. Pediatric studies should be included in the Pediatric section of USE IN SPECIFIC POPULATION. We suggest that this section be heavily edited and revised as appropriate.

- In the REFERENCES section, the references should be edited to delete outdated references. Please ensure that any remaining references are cited in the text if in the PI.

- Revise the PATIENT COUNSELING INFORMATION section to command language. This section should provide information for prescribers to convey to patients to use the drug safely and effectively (e.g., precautions concerning driving, concomitant use of other substances that may have harmful additive effects, adverse reactions reasonably associated with use of the drug, potential risks and benefits of use of the drug in pregnancy).

APLB has no objections to the proposed package label at this time.

The above comments are provided from a comprehension and advertising and promotional labeling perspective to assist you in revising the proposed labeling materials. We note that significant revision is required to the PI in order to make it consistent with the regulations provided in 21CFR 201.56 and 201.57. If you have any questions, please contact Michael Brony at 301-827-6342.

The review of this submission is on-going and issues may be added, expanded upon, or modified as we continue to review this submission.

Please submit your response as an amendment to this file containing an updated package insert by February 2, 2011. If you anticipate you will not be able to respond by this date, please contact the Agency immediately so a new response date can be identified. The action due date for this file is June 3, 2011.

If you have any questions, please contact me at (301) 827-3927.

Sincerely,

Crystal Allard
Regulatory Project Manager
FDA/CBER/OBRR/DBA/RPMB