Office of Biostatistics and Epidemiology/Division of Epidemiology
Pharmacovigilance Review Memo

BLA/Supplement Number:	125384/0
Product Name:	Kedbumin – Albumin (Human) 25% solution
Sponsor:	Kedrion, S.p.A.
Indication(s):	• Hypovolemia • Hypoalbuminemia • Prevention of central volume depletion after paracentesis due to cirrhotic ascites. • Ovarian hyperstimulation syndrome (OHSS) • Adult Respiratory Distress Syndrome (ARDS) • Burns • Hemodialysis • Cardiopulmonary Bypass Procedures as part of the priming fluids
Applicant:	Kedrion, S.p.A.
Date(s):	CBER receipt date: 8/3/2010; PDUFA date: 6/3/2011
Review Priority:	Standard (10-month)
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1. Introduction

OBE/DE/TBSB has completed a review of BLA STN 125197 for Kedbumin – Albumin (Human) 25% solution. The purpose of this review is to identify potential safety issues and assess the adequacy of the proposed pharmacovigilance plan (PVP) and post-market safety studies for safety monitoring should this product be licensed. Information on the clinical studies and safety data in this review is derived from FDA Meeting Response Memorandum to the pre-IND meeting 3/24/2009 (CRMTS # 6974), the clinical summaries presented in the BLA, Module 2.2, 2.5, and 2.7, and the sponsor's Risk Management Plan(RMP) , Module 1.16. Tables and diagrams and text in italics in this document are copied from the applicant's submission.

2. Product Background

2.1 Product

Kedbumin is a 25% human albumin solution which is manufactured by Kedrion, S. p. A., from an albumin paste intermediate ----------(b)(4)----------. At this facility, plasma derived therapeutic products are manufactured in accordance with CFR and EU regulations (BLA 2.2, p. 2). Thus, the raw material in Kedbumin is obtained from Source Plasma that is collected in licensed U.S. plasmapheresis centers. The sponsor proposes the following indications for the use of Kedbumin (BLA 2.2, p.2-3):

• *Hypovolemia: Restoration and maintenance of circulating blood volume where volume deficiency is demonstrated and colloid use is appropriate.*
• *Hypoalbuminemia: When the albumin deficit is the result of excessive protein loss, the effect of albumin administration will be temporary unless the underlying disorder is reversed.*
• *Prevention of central volume depletion after paracentesis due to cirrhotic ascites.*
• *Ovarian hyperstimulation syndrome (OHSS).*
• *Adult Respiratory Distress Syndrome (ARDS).*
Burns
• *Hemodialysis: For patients undergoing long term dialysis or for those patients who are fluid-overloaded and cannot tolerate substantial volumes of salt solution for therapy of shock or hypotension.*
• *Cardiopulmonary Bypass Procedures: As part of the priming fluids.*

The route of administration is intravenous (IV) (BLA 1.16, p. 7). The sponsor has marketed human albumin as UMAN ALBUMIN in Italy and other countries for over 40 years (BLA 1.16, p.11).

Albumin plays a role in stabilizing extracellular fluid volume and it is a carrier protein for steroids, fatty acids hormones, enzymes, drugs and toxins (BLA 2.2., p. 2). *Human albumin is a natural constituent of human plasma. When secreted into the bloodstream, it represents 40-60% of total plasma protein* (BLA 1.16, p. 7). *When infused, albumin's effects on plasma volume are dependent upon the volume deficits, initial oncotic pressure, vascular permeability, and the adequacy of the volume resuscitation. Plasma volume expansion is dependent upon the total amount of the protein administered and not on the concentration of the albumin solution. Human albumin may cause adverse reactions similar to those seen after blood transfusions, including chills, urticaria,*

fever, vasodilation, and allergic reactions. There have also been reports of calcium depletion, decreased renal function, and lowered urine output (BLA 2.5, p. 9).

2.2 Regulatory Overview

A Pre-IND meeting was held on 3/26/2009 during which the sponsor (Pre-IND materials question #3) indicated that they did not plan to conduct new clinical trials prior to filing the BLA (FDA Meeting Response Memorandum to the pre-IND meeting 3/24/2009 (CRMTS # 6974)). Licensing of the product is to be based on (1) the documented safety history of use of albumin (from 1 January 2002 to 30 June 2008, ----(b)(4)--- were distributed in Europe; assuming an average dose of 40 g, approximately ---(b)(4)--- doses were administered during the reference period) and (2) medical literature that supports the clinical safety of albumin for the proposed indications. The FDA concurred at the pre-IND meeting that no new clinical trials are needed with the caveat that the sponsor submits its post-marketing safety database at the time of filing (FDA Meeting Response Memorandum to the pre-IND meeting 3/24/2009 (CRMTS # 6974)). As a result, the sponsor's BLA submission (STN125384/0) includes information regarding facility issues and validation results for CMC and OCBQ and summaries of safety and efficacy results from literature regarding albumin and post-marketing safety data sets.

3. Clinical Studies

No clinical trials were conducted with Kedbumin.

4. Safety Database

4.1 Literature Review

Safety information presented in the BLA comes from review of available literature conducted by the sponsor on the use of human albumin. The sponsor conducted a PubMed search in November 2009 to identify all randomized, controlled clinical trials (RCTs) and meta-analyses in which human albumin was compared either with placebo/no treatment or a non-protein volume expander in disorders covered by the proposed indications .

Epidemiologic information from the medical literature on the safety and efficacy for human albumin use for each of the proposed indications is presented in the Risk Management Plan (BLA 1.16, p. 23-33). No previously unidentified or unexpected safety issues with albumin were identified from review of this summary. According to the sponsor, adverse reactions to human albumin administration described in literature are rare and include the following: nausea, vomiting, increased salivation, flushing, urticaria, hypotension, tachycardia, fever, and allergic reactions (including anaphylactic shock). High administration rates are associated with hypervolemia, vascular overload, hemodilution, hypertension, and pulmonary edema (BLA 2.7, p. 52).

4.2 Post-marketing Experience

The sponsor has manufactured and distributed human albumin as UMAN ALBUMIN since 1968 (IBD for the 25% formulation: May 5th, 1984) in 5%, 20%, and 25% concentrations (BLA 1.16, p. 15).

From 1 January 1st, 2002 to March 31st, 2010, approximately --------(b)(4)-------- of UMAN ALBUMIN were sold in Italy and -------(b)(4)------- in other countries (BLA 1.16, p.12). Because the dosage of administration is dependent on the clinical setting of use, the sponsor did not calculate an actual number of exposure days. However, assuming an average dosage of 40 g of albumin used to treat a single patient, the sponsor calculated that ---(b)(4)--- doses were administered during the reference period. During this period, the sponsor received 13 spontaneous case reports, representing 26 adverse events (AEs) (reporting rate of 0.00003%). (BLA 1.16, p. 15-22). Six of the 13 cases were classified as serious events:

-fever
-dyspnea/hypoxia/multi-organ failure/leukocytosis/renal failure
-fever/cyanosis/stridor/tremor
-anaphylactic reaction
-tremor/malaise
-erythema

Three of the 6 serious cases were classified as serious and unexpected, of which 2 were assessed by the sponsor as possibly related to UMAN ALBUMIN:

1. Case IT-Kedrion-2007033: 82 y/o female with a PMH of cirrhosis, breast cancer, diabetes was 1 month into albumin therapy when she experienced cyanosis, pyrexia, stridor, and tremor approximately 2 h after receiving an albumin infusion. Four days later she was pretreated with sodium dexamethasone and hydroxyzine prior to receiving UMAN ALBUMIN. Once again, after approximately 2 h after receiving therapy she experienced the same symptoms, though milder. Due to both the positive challenge and the temporal correlation, the sponsor believes the adverse event was probably related to UMAN ALBUMIN administration.

2. Case IT-Kedrion-2009044: 84 y/o male with a PMH of malignant hepatic neoplasm and pancreatic carcinoma who experienced tremor and malaise following UMAN ALBUMIN administration. The patient's condition improved after drug withdrawal. Outcome of the case is unknown. Kedrion considers the case as "probably related" to UMAN ALBUMIN administration.

No regulatory actions, such as marketing authorization withdrawal, revocation, or suspension, restrictions on distribution, changes in target population or indications, or urgent safety restrictions were taken with UMAN ALBUMIN for safety reasons during this period (BLA 1.16, p. 12).

5. Pharmacovigilance Planning

5.1 Populations not studied

Pediatric use of Kedbumin has not been clinically evaluated. According to the sponsor, Human albumin is authorized for pediatric use and has demonstrated a favorable safety profile.

During the nearly 40 years of postmarketing experience with UMAN ALBUMIN, no case of ADRs in children or newborns has been reported to the sponsor's Pharmacovigilance department *(BLA 1.16, p13).* A literature search conducted by the sponsor in November 2009 revealed no new safety concerns related to pediatric use of human albumin (BLA 1.16, p. 13).

Other populations with limited safety data include pregnant and lactating women, patients with hepatic, renal and other relevant co-morbidities, populations with genetic polymorphisms, and patients of varying racial or ethnic origins. The sponsor's literature review of human albumin use did not reveal safety concerns for albumin use in these populations.

According to the package insert, *KEDBUMIN is classified as Pregnancy Category C. It is not known whether KEDBUMIN can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. KEDBUMIN should be administered to a pregnant woman only if necessary.*

No cases of suspect ADRs during pregnancy or lactation, nor effects on newborns or infants from mothers treated with UMAN ALBUMIN have ever been reported to the sponsor's Pharmacovigilance department (BLA 1.16, p. 14)..

5.2 Potential risks

The sponsor states that a safety risk related to KEDBUMIN is the possibility of pathogen contamination and transmission (BLA 1.16, p22).

Presently, no cases of viral transmission due to UMAN ALBUMIN administration have been received by the sponsor during postmarketing experience (BLA 1.16, p22).

5.3 Proposed Pharmacovigilance Plan (PVP)

5.3.1 Routine Plans

Kedrion proposes routine monitoring and reporting of spontaneously reported adverse events according to applicable FDA regulations (BLA 1.16, p. 34-35)

5.3.2 Actions Plans for Safety Issues

As no safety data specific to Kedbumin was presented in this BLA, any safety issues identified were consistent with risks of any already licensed human albumin product, specifically, the potential risk of viral contamination and transmission.

The measures taken by the sponsor to reduce this risk include (BLA 1.16, p 36):

-Selection of donors by medical examination and viral marker testing
-Testing of plasma pools for relevant viruses
-Virus inactivation steps of the manufacturing process carried out by --(b)(4)-- and Kedrion (detailed in the BLA (1.16, p. 36-38) and evaluated by the Clinical, CMC, and OCBQ reviewers).
Kedrion considers these steps adequate to successfully minimize the potential risk of viral transmission.

6. Assessment and Recommendations

1. The sponsor's proposed PVP adequately defines and describes the identified risks, potential risks, and important missing information. **Possible Safety Concerns as noted by the sponsor include pathogen contamination and transmission.**

2. No serious safety concerns with the use of Kedbumin were identified during this review. Review of the sponsor's post-marketing safety data for its' UMAN ALBUMIN product reveals a relatively low rate of reporting.

2. The sponsor's proposed PV plan which includes routine PV surveillance and adverse event reporting as required by FDA regulation is acceptable.

Letter comments for communication to the sponsor:

None at this time.