M E M O R A N D U M

Department of Health and Human Services

Food and Drug Administration

Center for Biologics Evaluation and Research

Pharmacology / Toxicology Review Memorandum

Date: January 10, 2011 Final Review Memo

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To: Crystal Allard (RPM) and Yiping Jia Ph.D. (Review committee chair)

Subject: BLA 125384

Sponsor: Kedrion S.p.A.

Receipt Date: December 1, 2011

Mid-Cycle Review: January 11, 2011

Recommendation: The standard pharmacodynamic and toxicity studies generally carried out for new substances are not applicable to this product [1,2].

The excipients in the preparation are sodium N-acetyl-DL-tryptophan, caprylic acid and water. Caprylic acid is an 8-carbon straight chain fatty acid known by the name octanoic acid. Caprylic acid and N-acetyl-DL-Tryptophan are commonly used as stabilizers in the human blood-derived therapeutic products. The concentrations of both excipients are the same, 0.0064 – 0.096 mmol/1g protein and are within limits used in other products.

The albumin solutions contain no identified toxicologically critical substances/ impurities. In conclusion, from a pharmacology and toxicological point of view, the product is approvable.

Proposed Indication:

KEDBUMIN 25% - is intended for the restoration and maintenance of circulating blood volume. Indications include:

- 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
- In 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
- In cardiopulmonary bypass procedures as part of the priming fluids

Background:

Kedbumin 25% contains 12.5 grams of protein per 50 ml of solution, of which >96% is human albumin. The product is stabilized by the addition of 0.08 millimole sodium caprylate and 0.08 millimole sodium acetyltryptophan per gram of albumin. The stabilizers are added during the manufacturing process to prevent the albumin molecules from denaturing.

Because of pre-clinical and clinical experience over many years of use with plasma derived human serum albumin no preclinical studies were performed by the applicant. Wherever possible, literature data were provided in the submission.

Overview of Pharmacology:

Albumin is a protein of 584 amino acids. It is highly soluble and has a strong negative charge. Albumin makes up half the normal intravascular protein mass and is responsible for 75%-80% of the plasma colloids osmotic pressure. 9-12 grams of albumin are synthesized in the liver per day in humans. The rate of syntheses is governed by changes in the colloid osmotic pressure and the osmolarility of the extra-vascular space. In humans Albumin has a circulation half-life of approximately 16 hours in humans.

Major physiologic functions:

1) Colloid osmotic pressure effect

2) Binding and transport of molecules
3) Free radical scavenging (heme binding)
4) Inhibition of platelet function and anti-thrombotic effects
5) Capillary membrane permeability

Colloids including albumin are widely used as plasma substitutes for short term replacement of fluid volume.

Overview of Safety:

Adverse effects characteristic of Albumin includes fluid overload, coagulation defects, hemolysis and myocardial depression, related to prekallikrein activator and binding of calcium. Allergic reactions are rare but may occur, usually to contaminants or to polymeric aggregates that form during processing.

Hypervolemia may occur if the dosage and rate of infusion are too high. At the first clinical signs of cardiovascular overload (headache, difficulty breathing, jugular vein congestion) or increased blood pressure, raised central venous pressure and pulmonary edema, the infusion should be stopped immediately and the patients' hemodynamic parameters should be carefully monitored.

Overview of the Non-clinical Testing Strategy:

There are no studies performed by the applicant, and wherever possible, literature data were provided.

Pharmacology:

Albumin is a major storage reservoir of proteins and transporter of amino acids. It is the most osmotically active plasma protein due its abundance and small size and accounts for about 75% of the osmotic activity of plasma. Another major function of albumin is as a general binding and transport protein. Human albumin accounts quantitatively for more than half of the total protein in the plasma and represents about 10% of the protein synthesis activity of the liver[3].

Pharmacokinetics:

There are no pharmacokinetic studies for human albumin in animals provided in the current application. The pharmacokinetic properties in humans are well summarized by EMEA 2005 – the average half-life is about 19 days[3].

Toxicology:
Human albumin is a normal constituent of human plasma and acts like physiological albumin[3]. Human albumin is well tolerated by animal species and, therefore, additional animal studies redundant are not expected to be useful.

Single Dose Toxicity:
In animals, single dose toxicity testing does not permit the evaluation of toxic or lethal doses or a dose-effect relationship due to considerations of volume and protein load in otherwise normal volume animals. No single or acute toxicity have been tested in animal models [3]. Symptoms shown to occur with high volumes of concentrated albumin solutions are volume and protein overload related [4].

Repeat-Dose Toxicity:
Pathological findings with daily administration over 3 months were not related to the test substance (Albumin), but characterized by signs of protein overload, and by protein or antigen/antibody deposits in different organs[3].

Genotoxicity:
To date human albumin has not been reported to be associated with mutagenic potential[3]. ICH guidance on the preclinical safety evaluation of biotechnology-derived pharmaceuticals, currently does not require genotoxicity studies.

Carcinogenicity:
Carcinogenicity studies are not needed for albumin.

Reproductive Studies:
Studies not required[3].

Labeling: Nonclinical assessments of KEDBUMIN have not been performed. 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.

The labeling is acceptable from a toxicology perspective.

References:

1. FDA. Summary Basis for Approval for Octapharm Albumin (Human) 5% and 25%; STN: 12515 (2006).
2. EMEA. Guideline on the Core SPC for Human Albumin Solution (CPMP.PhVWP/BPWG/2231/99 rev.2)2005.
3. (The European Medicines Agency's Committee for Medicinal Products (EMEA), 2005)
4. Simpson LO and Shand BI. Morphological changes in kidneys of mice with proteinuria induced by albumin overload. Br J Exp Pathol. 64 (4), 1983, 396-402