DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration

1401 Rockville Pike
Rockville, MD 20852-1448

CLINICAL REVIEW MEMO

Application type	BLA review
Application number	125384
Receipt date	3 August 2010
PDUFA goal date	3 June 2010
Division/Office	Hematology/Blood
Reviewer's name	Laurence Landow MD
Applicant	Kedrion
Established name	25% human serum albumin
Proposed trade name	Kedbumin
Pharmacologic class	Albumin
Formulations	25% human albumin solution
Dosage form(s)	50 mL vial
Route(s) of administration	Intravenous
Dosing regimen	Varies by indication
Indications & intended populations	Restoration and maintenance of circulating blood volume for • Hypovolemia • Hypoalbuminemia • Prevention of central volume depletion after paracentesis due to cirrhotic ascites • Ovarian hyperstimulation syndrome • ARDS • Hemodialysis • ----------(b)(4)---------- • Burns • Cardiopulmonary bypass procedures

1. EXECUTIVE SUMMARY

Kedrion SpA has submitted a BLA for its 25% serum albumin product, which has been marketed in Europe since 1968. The sponsor seeks the same nine indications granted other albumin manufacturers, i.e., restoration and maintenance of circulating blood volume for (1) hypovolemia, (2) hypoalbuminemia, (3) prevention of central volume depletion after paracentesis due to cirrhotic ascites, (4) ovarian hyperstimulation syndrome, (5) ARDS, (6) hemodialysis, (7) ----------(b)(4)----------, (8) burns, and (9) cardiopulmonary bypass procedures. Review of the Kedrion EU postmarketing database raises no significant safety concerns.

The sponsor has requested a Full Pediatric Research Equity Act (PREA) waiver for all age groups because "necessary pediatric studies with the product are highly impractical given the nature of the risk/benefit and safety profile of the product." At a meeting of the PeRC on May 18, 2011, consensus was reached between PeRC members and DH that (a) a waiver should be granted for all indications in the 12-16 y/o subpopulation based on extrapolation from the adult population for efficacy and bridging studies for safety, (b) a waiver should be granted for hemolytic disease of the newborn, prevention of central volume depletion after paracentesis due to cirrhotic ascites, and ovarian hyperstimulation syndrome in the 0-12 y/o subpopulation based on insufficient number of patients/nonexistence of the disease in the pediatric population, and (c) a deferral should be granted for the remaining six indications. Consensus also was reached on a draft protocol proposed by the sponsor to evaluate product safety for the treatment of hypovolemia in the 0-12 y/o subpopulation (*"A prospective, randomized, multicenter, controlled, open label study to evaluate the safety of Kedbumin 25% compared to normal saline solution in the treatment of postsurgical hypovolemia associated with hypoalbuminemia in pediatric patients undergoing major elective surgery"*), with a recommendation that moderate-severely hypoalbuminemic patients be excluded from the trial because it would be unsafe to withhold albumin if such patients were randomized to the normal saline treatment cohort. The final protocol was submitted on 20 May 2011 and is acceptable.

Recommendation: I recommend approval of the product for restoration and maintenance of circulating blood volume.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Regulatory History

21CFR601.25 was issued in 1973, with numerous amendments thereafter. It required FDA to review all biologics licensed prior to 1 July 1972 and determine whether they were safe, effective, and not misbranded.[1]

To make this determination, FDA convened several expert panels to review viral vaccines, bacterial vaccines, and blood and blood derivatives. The blood/blood derivatives panel met for the first time in 1975, and for the last time in 1978. Their recommendations were published in 1985.

For albumin, the panel was asked to conduct two reviews: the first was a review of albumin use in general, and the second was a specific review for each manufacturer's product. For the latter, the panel was asked to assess the product according to 3 predefined categories.

[1] 21CFR601.25: "Review procedures to determine that licensed biological products are safe, effective and not misbranded under prescribed, recommended, or suggested conditions of use"

- Category I: safe, effective, and not misbranded. Can be marketed.
- Category II: does not meet one of the above requirements. Must be withdrawn by the sponsor.
- Category III: insufficient evidence to determine whether the product is safe, effective and not misbranded
- Category IIIa: marketing can continue as long as such evidence is presented within a prespecified time period
- Category IIIb: the product can no longer be marketed until sufficient evidence is presented.

Public Citizen sued FDA for allowing IIIa products to continue to be marketed. Eventually, the court declared that marketing products in Category IIIa was illegal.

At the time of the last application for a human albumin product (Octapharma, 2007), OBRR made the determination that the same indications granted after 1 July 1972 to manufacturers of human albumin products would be granted to future manufacturers as long as the CMC specifications were acceptable and the level of clinical evidence supporting safety and efficacy was equivalent to applications for human albumin products submitted prior to 1 July 1972.

My assessment of existing (and for the most part, inadequate) scientific literature for indications previously granted to all manufacturers of licensed albumin products is as follows:

- Albumin is safe and effective for restoration and maintenance of hypovolemia. The strongest RCT to date supporting use of albumin for fluid resuscitation is the SAFE study (*N Engl J Med* 2004;350:2247-56), which randomized a heterogeneous cohort of hypovolemic ICU patients (N=6997) to albumin (4%) or normal saline. Similar outcomes, including 28-day mortality, were observed between treatment arms, thereby providing direct support for use of albumin in hypovolemic shock.
- Bridging of safety data from the SAFE study and other studies, combined with the product's inherent oncotic and protein-binding characteristics, lend support for use of albumin (a) as therapy for prevention of central volume depletion following the removal of 4 L of ascitic fluid, (b) as a component of the cardiopulmonary pump prime to avoid induction of excess edema, (c) for induction of diuresis in acute nephrosis, (d) in augmenting retention of extracellular fluid within the intravascular space in Adult Respiratory Distress Syndrome (ARDS), (e) for temporary correction of hypoalbuminemia, and (f) in the treatment of neonatal hyperbilirubinemia.
- There is inconsistent support for Ovarian Hyperstimulation Syndrome (one 2003 negative RCT of 988 patients but several smaller (10-60 patients per arm) positive trials and a positive Cochrane review of pre-2003 studies)

2.2 Previous worldwide experience with human albumin products

Several safety studies of human albumin products have been published over the past 20 years.

A pharmacovigilance study covering the period 1990 to 1997 observed an incidence of 1.29 per million doses (point estimate) for all spontaneously reported SAEs worldwide (*Crit Care Med* 2001;29:994-6). No deaths were judged to be probably attributable to albumin, and the incidence of fatal events possibly related to albumin was 5.24. Because they rely on spontaneously reported data, pharmacovigilance studies tend to underestimate the true incidence.

A study funded by PPTA of all SAEs — fatal and non-fatal — reported worldwide to regulatory authorities by albumin manufacturers from the beginning of 1998 to the end of 2000 found a somewhat higher incidence of 5.28 (*Br J Anaesth* 2003;91:625-630). According to the authors, fatal events possibly related to the product were rare, with an incidence of 0.185. The total incidence (4.65) of non-fatal events characterized as probably (0.208) or possibly (1.14) attributable to albumin, was low.

These figures should be put in the context of heightened awareness regarding albumin safety after publication of the 1998 Cochrane meta-analysis of 30 clinical trials using albumin to treat critically ill patients with hypovolemia, burns, and hypoalbuminemia (*BMJ* 1998;317:235-240). The Cochrane meta-analysis estimated that albumin administration was associated with increased mortality risk in each patient category. In contrast, a larger meta-analysis published subsequently and funded by PPTA (*Ann Intern Med* 2001;135:149-164) concluded albumin therapy had no significant effect on overall mortality. The controversy was essentially resolved after the SAFE study failed to find higher mortality rates in patients randomized to 4% albumin vs normal saline.

2.3 Postmarketing experience with the sponsor's 25% human albumin formulation licensed in Europe (UMAN Albumin)

Kedrion has marketed albumin products in Italy and several other countries for over 40 years. The 25% formulation (UMAN ALBUMIN) has been marketed outside the U.S. since 1984.

For the eight year period extending from 1 January 2002 to 31 March 2010, approximately --------(b)(4)-------- of the product were sold in Italy and -------(b)(4)------- in other countries (sponsor). Assuming an average dosage of 40 g of UMAN ALBUMIN to treat a single patient, the sponsor calculates approximately ----(b)(4)--- doses were administered.

Spontaneous reporting related to UMAN ALBUMIN for the period 1 JAN 2002 to 31 MAR 31 2010 totaled 13 cases corresponding to 26 ADRs, most of which were not serious.

Three cases were classified as serious and unexpected and are described below.

1. Case IT-Kedrion-2004013: 77 y/o female with a PMH of ascites, chronic hepatitis and pleuritis who died after having experienced dyspnea, hypoxemia, MOF, and acute kidney failure following treatment with UMAN ALBUMIN (20 g/day) and talc (2 g/day for pleuritis). Six days later the patient developed ARDS which was intractable to treatment and died. The reporter attributed her death to be unlikely related to albumin and possibly related to the talc. No postmortem results were available.

2. Case IT-Kedrion-2007033: 82 y/o female with a PMH of cirrhosis, breast cancer, diabetes and being treated for cirrhosis with hypoalbuminemia, was started on UMAN ALBUMIN at a dose of 2vials/day twice a week. One month into therapy, the patient experienced cyanosis, pyrexia, stridor, and tremor

3. 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.

One case was classified as serious and expected.

1. Case IT-Kedrion-2009012: 71 y/o male patient with hypovolemia who experienced an anaphylactic reaction characterized by a papuloerythematous rash of the trunk and bronchospasm after receiving two doses of UMAN ALBUMIN. The reaction was reported as serious and expected [sic]. The drug was withdrawn and the patient completely recovered but the event prolonged hospitalization.

3. Labeling comments

Several iterations of the draft labeling were reviewed and comments sent to the sponsor. The final labeling is acceptable (see Appendix).

Section 8.4 Pediatric Use
The pediatric use of Kedbumin has not been clinically evaluated. If administered to children the dosage will vary with the clinical state and body weight of the individual. Typically, a dose one-fourth or one-half the adult dose may be administered. The usual rate of administration in children should be one-fourth the adult rate. Physicians should weight the risks and benefits of Kedbumin in the pediatric population.

4. Requested Waiver for pediatric studies
The sponsor requested a waiver for a pediatric assessment for the following reason: "Necessary pediatric studies with KEDBUMIN are highly impractical given the nature of the risk/benefit and safety profile of the product."

Fluid overload and frank pulmonary edema are potential risks associated with use of the product in the pediatric population. Data from an unblinded safety study in which subjects are randomized to receive 25% albumin or crystalloid for treatment of postoperative hypovolemia could be informative to clinicians. Discussions were held with the sponsor and consensus reached on a protocol, including timelines for study completion (September 30, 2013) and submission of a final study report (December 31, 2013).

At a meeting of the PeRC on May 18, 2011, consensus was reached between PeRC members and DH that (a) a waiver should be granted for all indications in the 12-16 y/o subpopulation based on extrapolation of efficacy from the adult population and bridging studies for safety, (b) a waiver should be granted for ----------(b)(4)---------- prevention of central volume depletion after paracentesis due to cirrhotic ascites, and ovarian hyperstimulation syndrome in the 0-12 y/o subpopulation based on insufficient number of patients/nonexistence

of the disease in the pediatric population, and (c) a deferral should be granted for the remaining six indications. In addition, consensus was reached on a draft protocol proposed by the sponsor to evaluate safety using the product for the treatment of hypovolemia in the 0-12 y/o subpopulation (*"A prospective, randomized, multicenter, controlled, open label study to evaluate the safety of Kedbumin 25% compared to normal saline solution in the treatment of postsurgical hypovolemia associated with hypoalbuminemia in pediatric patients undergoing major elective surgery"*), with a recommendation that moderate-severely hypoalbuminemic patients be excluded from the trial because it would be unsafe to withhold albumin if such patients were randomized to the normal saline treatment cohort. The final protocol was submitted on 20 May 2011 and is acceptable.

Appendix (final labeling)

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

KEDBUMIN™ [Albumin (Human) U.S.P.] sterile, aqueous solution for single dose intravenous administration

Initial U.S. Approval: TBD

----------INDICATIONS AND USAGE----------

KEDBUMIN™ is a 25% albumin solution indicated for:

- Hypovolemia (1.1) and Hypoalbuminemia (1.2)
- Prevention of central volume depletion after paracentesis due to cirrhotic ascites (1.3)
- Ovarian hyperstimulation syndrome (OHSS) (1.4)
- Adult Respiratory Distress Syndrome (ARDS) (1.5)
- Burns (1.6)
- Hemodialysis patients undergoing long term dialysis (1.7)
- Patients who cannot tolerate substantial volumes of salt solution (1.7)
- Priming as part of a cardiopulmonary bypass fluids (1.8)

----------DOSAGE AND ADMINISTRATION----------

Intravenous Administration Only. KEDBUMIN™ may be diluted with 5% glucose or 0.9% sodium chloride. Concentration, dosage, and infusion-rate should be adjusted to the patient's individual requirements and indication (2.1). Daily dosage should not exceed 2g per kg body weight.

Indication: Dose	
Hypovolemia:	Adults: Initial dose 25 g is suggested.
Hypoalbuminemia:	50-75 g
Prevention of Central Volume Depletion after Paracentesis due to Cirrhotic Ascites:	Adults: 6-8 g for every 1000 mL of ascitic fluid removed
OHSS:	Adults: 50 to 100 g over 4 hours and repeated at 4-12 hour intervals as necessary. 10-50 g; single infusion
ARDS:	Adults: 25 g over 30 minutes and repeated at 8 hours for 3 days if necessary
Burns:	Determined by direct observation of vital sign or measurement of either plasma oncotic pressure or protein content
Hemodialysis:	100 mL
Cardiopulmonary Bypass:	Estimated from the difference between the desired and actual total serum protein concentration times the estimated plasma volume (approx 40mL per kg) times 2

----------DOSAGE FORMS AND STRENGTHS----------

KEDBUMIN™ is a sterile, single dose solution containing 0.25 g per mL human albumin in the following presentation:

- 12.5 g albumin per 50 mL single dose vial (3)

----------CONTRAINDICATIONS----------

- Severe anemia or heart failure in the presence of normal or increased intravascular volume (4).
- Hypersensitivity to albumin, the excipients, or components of the container.

----------WARNINGS AND PRECAUTIONS----------

- Risk of transmission of infectious agents (5.1).
- Caution where hypervolemia and its consequences or hemodilution could represent a special risk (5.2)
- Do not dilute with water for injections (5.2)

----------ADVERSE REACTIONS----------

The most common adverse reactions include fever, chills, rash, nausea, vomiting, tachycardia, and hypotension (6).

To report SUSPECTED ADVERSE REACTIONS, contact KEDRION at 1-855-427-6378 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: no human or animal data. Use only if clearly needed (8.1).
- Pediatric use: ages 12-16 years use as in adults (8.4)

See (17) for PATIENT COUNSELING INFORMATION.

Revised: Month Year

FULL PRESCRIBING INFORMATION CONTENTS*

***Sections or subsections omitted from the Full Prescribing Information are not listed.**

FULL PRESCRIBING INFORMATON

1. INDICATIONS AND USAGE

1.1 Hypovolemia

For restoration and maintenance of circulating blood volume where volume deficiency is demonstrated and colloid use is appropriate.

1.2 Hypoalbuminemia

KEDBUMIN™ is indicated for severe albumin deficiency caused by illness or active bleeding. When albumin deficiency results from excessive protein loss, the effect of albumin administration will be temporary unless the underlying disorder is reversed.

1.3 Prevention of Central Volume Depletion after Paracentesis due to Cirrhotic Ascites

KEDBUMIN™ is indicated for maintenance of cardiovascular function following ~~the~~ removal of large volumes of ascitic fluid due to cirrhosis [1, 2].

1.4 Ovarian Hyperstimulation Syndrome (OHSS)

KEDBUMIN™ is indicated as a plasma expander in the fluid management ~~in~~ of severe forms of ovarian hyperstimulation syndrome (OHSS) [3, 4].

1.5 Adult Respiratory Distress Syndrome (ARDS)

KEDBUMIN™ is indicated in conjunction with diuretics to correct fluid volume overload associated with ARDS [5].

1.6 Burns

KEDBUMIN™ is indicated after > 24 hours post burn in patients experiencing severe albumin depletion in order to favor edema re-absorption [6].

1.7 Hemodialysis

KEDBUMIN™ is indicated in 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 [7].

1.8 Cardiopulmonary Bypass

KEDBUMIN™ is indicated in cardiopulmonary bypass procedures as part of the priming fluids [8, 9].

2. DOSAGE AND ADMINISTRATION

Intravenous Administration Only.

2.1 Dosage

The concentration of the albumin preparation, dosage, and infusion-rate should be adjusted to the patient's individual requirements and indication.

Indication	Dose
Hypovolemia	Adults: Initial dose of 25 g is suggested. Pediatric dosage should be adjusted based upon on age, weight and clinical conditions
Hypoalbuminemia	50-75 g
Prevention of Central Volume Depletion after Paracentesis due to Cirrhotic Ascites	Adults: 6-8 g for every 1000 mL of ascitic fluid removed
OHSS	Adults:-50-100 g over 4 hours and repeated at 4-12 hour intervals as necessary. 10-50 g; :single infusion
ARDS	Adults: 25 g over 30 minutes and repeated at 8 hours for 3 days if necessary

Burns	The amount of albumin required to achieve adequate plasma volume and protein content should be determined by direct observation of vital signs or measurement of either plasma oncotic pressure or protein content
Hemodialysis	100 mL
Cardiopulmonary Bypass	Required dose can be estimated from the difference between the desired and actual total serum protein concentration multiplied by the estimated plasma volume (approximately 40mL per kg) times 2 (to account for extravascular deficit, which absorbs about half of the administered dose)

2.2 Administration

Intravenous administration only.

Inspect visually for particulate matter and discoloration prior to administration, whenever the solution and container permit.

Do not dilute with sterile water for injection as hemolysis may occur (5.3).

KEDBUMIN™ may be diluted with 5% glucose or 0.9% sodium chloride.

Adjust the infusion rate to the rate of removal in plasma exchange.

Warm the product to room temperature if large volumes are to be administered.

Do not begin administration > 4 hours after the container has been entered. Discard unused material.

Record the batch number every time KEDBUMIN™ is administered to a patient.

3. DOSAGE FORMS AND STRENGTHS

KEDBUMIN™ is a sterile, aqueous solution for single dose administration intravenously. The product contains 0.25 g per mL human albumin and is available in the following presentation [10]:

- 12.5 g albumin per 50 mL single dose vial

4. CONTRAINDICATIONS

KEDBUMIN™ is contraindicated in patients with a history of hypersensitivity to albumin, excipients used in its formulation, or components of the container [11].

KEDBUMIN™ is also contraindicated in severely anemic patients and in patients with heart failure.

5. WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity

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.

5.2 Hypovolemia

KEDBUMIN™ should be used with caution in conditions where hypervolemia and its consequences or hemodilution could represent 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 [12]. 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 as coagulation factors, electrolytes, platelets, and erythrocytes.

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 hydration of the patient. Carefully monitor to guard against circulatory overload (10).

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

Because KEDBUMIN™ is derived from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. No cases of transmission of viral diseases or CJD have ever been identified for KEDBUMIN.

ALL infections suspected by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider to Kedrion at 1-855-427-6378.

See also **PATIENT COUNSELING INFORMATION** (17).

6. ADVERSE REACTIONS

6.1 General

The most common adverse reactions include flushing, urticaria, fever, chills, nausea, vomiting, tachycardia and hypotension. These reactions normally disappear when the infusion rate is slowed or stopped.

If a severe reaction such as shock or anaphylaxis occurs, the infusion should be stopped and appropriate treatment initiated.

7. DRUG INTERACTION

KEDBUMIN™ 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.

KEDBUMIN™ should not be mixed with protein hydrolysates or solutions containing alcohol since these combinations may cause protein precipitation.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C. Animal reproductive studies using KEDBUMIN™ have not been conducted. It is also not known whether KEDBUMIN™ can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. KEDBUMIN™ should be given to a pregnant woman only if necessary.

8.4 Pediatric Use

The adult dose may be given in children 12-16 years of age. Use of KEDBUMIN™ in children less than 12 years of age has not been clinically evaluated. If administered to children the dosage will vary with the clinical state and body weight of the individual. Typically, a dose one-fourth to one-half the adult dose may be administered. The usual rate of administration in children should be one-fourth the adult rate. Physicians should weigh the risks and benefits of KEDBUMIN™ in the pediatric population.

10. OVERDOSE

Hypervolemia may occur if the dosage and rate of infusion are too high. At the first clinical sign of circulatory overload, e.g. headache, dyspnea, jugular venous congestion, increased blood pressure, raised central venous pressure, or pulmonary edema, the infusion should be stopped and hemodynamic parameters carefully monitored. Additionally, diuresis or cardiac output should be increased in accordance with the severity of the clinical situation (5.2).

11. DESCRIPTION

KEDBUMIN™ is a sterile, aqueous solution for single dose intravenous administration. The product contains 0.25 g per mL human albumin and is prepared by cold ethanol fractionation from pooled human plasma obtained from venous blood at FDA-licensed facilities located in the USA. Intermediate source material (albumin paste) is obtained from a U.S. licensed manufacturer. The colloid osmotic effect of KEDBUMIN™ is approximately four times that of blood plasma.

KEDBUMIN™ is a clear, slightly viscous liquid, with a yellow, amber, or green tint. The product is stabilized by the addition of 0.08 mmol sodium caprylate and 0.08 mmol sodium acetyltryptophan per gram of albumin. Additionally, each liter of material contains 130-160 mEq of sodium ion and ≤ 200 µg of aluminum. The product contains no preservatives.

KEDBUMIN™ is heated for ten hours at 60°C. The KEDBUMIN manufacturing process results in viral reduction in in vitro studies (see table below). These reductions are achieved through a combination of process steps including Cohn fractionation and final container heat treatment.

	Mean Reduction Factor (log10)						
	Enveloped viruses			**Non –enveloped viruses**			
Manufacturing Step	**HIV-1**	**BVDV**	**PRV**	**REO**	**PPV**	**HAV**	**EMCV**
Fractionation of Effluent I to Effluent II +III	3.4	3.5	3.9	2.1	1.0	1.4	
Fractionation of Effluent IV-1 to Effluent IV-4							3.7
Depth Filtration of Fraction V suspension	3.4		≥ 3.4	4.9	4.2	2.0	
Heat treatment	**≥ 6.06**	> 5.17	> 5.07	4.62		> 5.0	
Overall Reduction Factor	**≥ 12.86**	**> 8.67**	**≥ 12.37**	**11.62**	**5.2**	**> 8.4**	**3.7**

HIV-1: Human Immunodeficiency Virus Type 1
BVDV: Bovine Viral Diarrhoea Virus
PRV: Pseudorabies Virus
REO: Reovirus Type 3
PPV: Porcine Parvovirus
HAV: Hepatitis A Virus
EMCV: Encephalomyocarditis virus

12. CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Human albumin is not a glycoprotein. It has the lowest molecular weight (66,241 Daltons) of all plasma proteins. Because of its three dimensional structure, solutions of albumin have a lower viscosity than solutions of other plasma proteins. This is important since work performed by the heart depends in part on the viscosity of blood. Human albumin accounts quantitatively for more than half of the total proteins in the circulation (by weight) and represents approximately 10 % of the protein synthesized in the liver.

Approximately 40% of albumin is contained in the circulation. The remainder is located in the extravascular space of tissues, principally muscle, skin, and intestine.

KEDBUMIN 25% has a hyperoncotic effect.

A major function of albumin is its role in osmotic regulation. Albumin is responsible for 75% of normal oncotic pressure within the intravascular space [13, 14]. Other physiological functions include binding and transport of molecules (hormones, enzymes, drugs and toxins); free radical scavenging; hemostatic effects (platelet function inhibition and antithrombotic effects); and capillary membrane permeability [14].

12.3 Pharmacokinetics

Under normal conditions, the total exchangeable albumin pool is 4-5 g per kg body weight, of which 40-45% is present intravascularly and 55-60% is in the extravascular space. Increased capillary permeability will alter albumin kinetics and abnormal distribution may occur in conditions such as severe burns or septic shock.

Under normal conditions, the half-life of albumin is approximately 19 days. The balance between synthesis and breakdown is normally achieved by feed-back regulation. Elimination is predominantly intracellular and due to lysosomal proteases. In healthy subjects, less than 10% of infused albumin leaves the intravascular compartment during the first two hours following infusion. There is considerable individual variation in the effect on plasma volume. In some patients plasma volume can remain elevated for several hours. However, in critically ill patients, albumin can leak out of the vascular space in substantial amounts at an unpredictable rate.

15. REFERENCES

1. Vermeulen LC, Jr., Ratko TA, Erstad BL, Brecher ME, Matuszewski KA. A paradigm for consensus. The University Hospital Consortium guidelines for the use of albumin, nonprotein colloid, and crystalloid solutions. *Arch Intern Med.* Feb 27 1995;155(4):373-379.
2. Gines A, Fernandez-Esparrach G, Monescillo A, et al. Randomized trial comparing albumin, dextran 70, and polygeline in cirrhotic patients with ascites treated by paracentesis. *Gastroenterology.* Oct 1996;111(4):1002-1010.
3. Aboulghar M, Evers JH, Al-Inany H. Intravenous albumin for preventing severe ovarian hyperstimulation syndrome: a Cochrane review. *Hum Reprod.* Dec 2002;17(12):3027-3032.
4. Medicine PCotASfR. Ovarian Hyperstimulation Syndrome. *Fertility and Sterility.* 2000;86(5 Suppl 1):S178-S183. .
5. Martin GS, Moss M, Wheeler AP, Mealer M, Morris JA, Bernard GR. A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. *Crit Care Med.* Aug 2005;33(8):1681-1687.
6. Manelli JC. [Is albumin administration useful in critical care for burnt patients?]. *Ann Fr Anesth Reanim.* 1996;15(4):507-513.
7. Tullis JL. Albumin. 2. Guidelines for clinical use. *JAMA.* Jan 31 1977;237(5):460-463 concl.
8. Schiff P. Albumin-containing plasma volume expanders. *Aust N Z J Surg.* Dec 1977;47(6):783-786.
9. Wilkes MM, Navickis RJ, Sibbald WJ. Albumin versus hydroxyethyl starch in cardiopulmonary bypass surgery: a meta-analysis of postoperative bleeding. *Ann Thorac Surg.* Aug 2001;72(2):527-533; discussion 534.
10. Gerety RJ, Aronson DL. Plasma derivatives and viral hepatitis. *Transfusion.* Sep-Oct 1982;22(5):347-351.
11. Gellis SS, Neefe JR, et al. Chemical, clinical, and immunological studies on the products of human plasma fractionation; inactivation of the virus of homologous serum hepatitis in solutions of normal human serum albumin by means of heat. *J Clin Invest.* Mar 1948;27(2):239-244.
12. Pierce LR, Gaines A, Finlayson JS, Varricchio F, Epstein JS. Hemolysis and acute renal failure due to the administration of albumin diluted in sterile water. *Transfusion.* Jan 1999;39(1):110-111.
13. Doweiko JP, Nompleggi DJ. Role of albumin in human physiology and pathophysiology. *Jpen.* Mar-Apr 1991;15(2):207-211.
14. Mendez CM, McClain CJ, Marsano LS. Albumin therapy in clinical practice. *Nutr Clin Pract.* Jun 2005;20(3):314-320.

16. HOW SUPPLIED/STORAGE AND HANDLING

KEDBUMIN™ is supplied as a sterile, aqueous solution for single dose intravenous administration containing 0.25 g per mL human albumin. It is available in the following glass vial size:

50 mL vial 25% (NDC X)

Storage

Do not use KEDBUMIN™ after the expiration date which is stated on the carton and label after "EXP." The expiration date refers to the last day of that month.

Do not store above 30°C.

Keep the vial stored in the outer carton in order to protect from light.

Do not freeze.

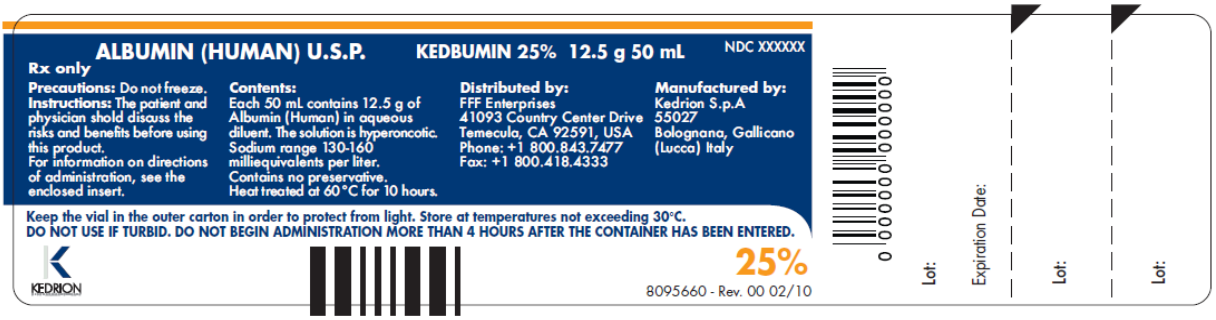
17. PATIENT COUNSELING INFORMATION

Inform patients being treated with KEDBUMIN about the potential risks and benefits with its use (6). Discontinue immediately if allergic symptoms or circulatory overload occur (e.g. skin rashes, hives, itching, breathing difficulties, coughing, nausea, vomiting, fall in blood pressure, increased heart rate).

Inform patients that KEDBUMIN is a derivative of human plasma and may contain infectious agents that cause disease (e.g., viruses, and theoretically, CJD agent). Inform patients that the risk that KEDBUMIN may transmit an infectious agent has been reduced by screening plasma donors for prior exposure for certain viruses, by testing the donated plasma for certain virus infections, and by inactivating and/or removing certain viruses during manufacturing (5).

Distributed by:
FFF Enterprises
41093 County Center Drive
Temecula, CA 92591
USA
Phone: +1 800.843.7477
Fax: +1 800.418.4333
Manufactured by:
Kedrion S.p.A.
Via Provinciale Loc. Bolognana
55027 Gallicano (Lucca)
Italy
Phone: +39 0583 1969 1
Fax: +39 0583 1969 981

PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – 50 ML VIAL



PACKAGE LABEL – PRINCIPAL DISPLAY PANEL – 50 ML CARTON