

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

From: Shaokui Wei, MD, MPH
Epidemiologist, Analytic Epidemiology Branch
(AEB)
Division of Epidemiology (DE)
Office of Biostatistics and Epidemiology (OBE)

To: Wayne Hicks, PhD
Chair, Review Committee
Division of Blood Applications (DBA)
Office of Blood Research & Review (OBRR)

Through: Deepa Arya, MD, MPH, MBA
Chief, AEB/DE/OBE

Scott Proestel, MD
Director, DE/OBE

Subject: Pharmacovigilance Plan Review

Sponsor: Bio Products Laboratory (BPL)

Product: Albuminex 5% and Albuminex 25%

Proposed Indication: To restore and maintain circulating blood volume
for: Hypovolemia, Ascites, Burns, Nephrotic
Syndrome, Acute Respiratory Distress Syndrome
(ARDS), Cardiopulmonary Bypass

Submission Type/Number: BLA 125644/0

Submission Date: December 9, 2016

Action Due Date: June 18, 2018

1. Objective of the Review

The purpose of this review memo is to assess the adequacy of the sponsor's pharmacovigilance plan (PVP) for the proposed indications and determine if any additional post-marketing studies or risk evaluation and mitigation strategy (REMS) are required for Albuminex 5% and Albuminex 25%.

2. Product Information

2.1 Product description

Albuminex 5% and Albuminex 25% are sterile, ready-for-use, clear, slightly viscous, almost colorless, yellow, amber or slightly green aqueous solutions of human albumin for single dose intravenous infusion. They are prepared from the pooled plasma of US donors in FDA-licensed facilities in the US. The products also contain 130-160 mmol/L of sodium, less than 200 micrograms/L of aluminum and are stabilized with caprylate (0.08 mmol/g albumin) and acetyltryptophanate (0.08 mmol/g albumin) but do not contain any preservative. Albuminex 5% and Albuminex 25% contain 5g/dL and 25g/dL of total protein, respectively, of which at least 96% is human albumin. Compared to the normal range for serum albumin (35-50 g/L), Albuminex 5% is isooncotic to normal plasma and Albuminex 25% is hyperoncotic to normal human plasma. ALBUMINEX 5% and 25% are for intravenous administration only.

2.2 Proposed Indication

The proposed indication for Albuminex 5% and Albuminex 25% is to restore and maintain circulating blood volume for: Hypovolemia, Ascites, Burns, Nephrotic Syndrome, Acute Respiratory Distress Syndrome (ARDS), and Cardiopulmonary Bypass.

2.3 Proposed Dosing regimen

Albuminex 5% and Albuminex 25% contain 5 and 25 g of human albumin per dL, respectively. They may be diluted with 0.9% saline or 5% dextrose (glucose). The concentration of Albuminex 5% and Albuminex 25%, dosage, and infusion-rate should be adjusted to the patient's individual requirements and clinical indication.

3. Pertinent Regulatory History

Albuminex 5% and Albuminex 25% are new products and are not licensed in any country. However, Albuminex 5% and Albuminex 25% have similar formulations of Zenalb® 4.5% and 20%, which are currently licensed in many countries worldwide. The International Birth Dates for Zenalb® 4.5% and 20% are April 23, 1993 and April 27, 1993, respectively. The sponsor applied for the approval of a new product (instead of requesting approval for Zenalb) in the US to comply with the US Pharmacopeia (USP) and Code of Federal Regulations (CFR) requirements.

Albuminex 5% and Albuminex 25% are comparable to, and made from, the same (b) (4) as Zenalb® 4.5% and 20%, respectively. The primary

difference between Albuminex and Zenalb® is in the (b) (4), which are summarized in Table 1 below.

Table 1 Comparison of key specification parameters for Albuminex and Zenalb

	Zenalb® 4.5	Zenalb® 20	Albuminex 5%	Albuminex 25%
Active ingredient				
Albumin g/L	45	200	50	250
In-active ingredient				
Sodium (mmol/L)	100-160	50-120	130 -160	130 -160
Potassium (mmol/g of protein)	(b) (4)	(b) (4)	Not greater than 2	Not greater than 2
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium caprylate (sodium n-octanoate) (mmol/L)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sodium acetyltryptophanate (mmol/L)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Aluminum (µg/L)	No more than 200	No more than 200	No more than 200	No more than 200

Source: BLA 125644/0, Section 2.5 Clinical Overview, Table 1 in Page 12

Reviewer comment: “Potassium (mmol/g of protein)” is a typing error by the sponsor. The correct statement is “mmol/L” specified in Section 3.2.P.5.1 “Specifications” to conform to 21 CFR 640.82.

4. Materials Reviewed

Materials reviewed in support of this assessment include the following:

4.1 Pertinent sections of the licensing application in the Electronic Document Room (EDR)

- Section 1.16 Risk Management Plan (RMP), BLA 125644/0
- Section 1.14 Proposed Labeling, BLA 125644/0
- Section 2.5 Clinical Overview, BLA 125644/0

4.2 Input from the clinical reviewer

There were no safety concerns raised by the clinical review team that would require postmarketing studies or a risk evaluation and mitigation strategy for Albuminex 5% and Albuminex 25%.

5. Clinical Safety Database

The sponsor did not perform any clinical studies to investigate the pharmacokinetics, efficacy, and safety of Albuminex 5% and Albuminex 25%. This approach was discussed and agreed with FDA (CRMTS93II, PS002352 dated 30 April 2014: Written response to BPL Type C Meeting Request). The clinical data on which the safety of Albuminex 5% and Albuminex 25% is established comes from the published literature and BPL's post-marketing experience with albumin (Zenalb®) solutions.

5.1 Literature Review

The sponsor conducted a PubMed search in November 2015 to identify all randomized, controlled clinical trials (RCTs) and meta-analyses in which human serum albumin (HSA) was compared either with placebo/no treatment or a non-protein volume expander in disorders covered by the proposed indications.

According to the sponsor, adverse reactions to human albumin administration described in literature are rare. Von Hoegen and Waller¹ described a retrospective compilation of spontaneously reported serious adverse events (SAEs) for albumin. They combined records of SAEs received from 1990 to 1997 by nine major suppliers of therapeutic human albumin worldwide. The incidence of all SAEs was 1.29 per 10⁶ doses, including the non-fatal SAEs 1.04 per 10⁶ doses and the fatal SAEs 2.52 per 10⁷ doses. Vincent and coworkers² compiled all SAE reports received and the total number of doses of albumin distributed worldwide from the beginning of 1998 to the end of 2000 by ten major suppliers of therapeutic human albumin. The incidence of all reported SAEs was 5.28 per 10⁶ doses, including the non-fatal SAEs 4.65 per 10⁶ doses and the fatal SAEs 1.85 per 10⁷ doses. The major adverse events include: rigors, tremors, hypotension, pyrexia, feeling cold, blood pressure decreased/increased, body temperature increased and anaphylactic reactions.

The sponsor summarized the published safety data for HSA as follows:

- Mortality outcomes have been investigated in several studies and in several meta-analyses. The data documenting the safety of the administration of HSA in critically ill patients with a range of presenting pathologies is convincing.
- Although administration of HSA was shown to be associated with prolongation of Activated partial thromboplastin time (aPTT), clinical data overall suggest that HSA does not affect the blood coagulation profile, in contrast to Hydroxyethyl starch (HES) or gelatin.
- HSA does not affect the electrolyte/acid base balance.

1 Vincent JL, Wilkes MM, Navickis RJ. Safety of human albumin – serious adverse events reported worldwide in 1998 -2000. *Brit J Anaesthesia* 2003b; 91(5): 625-30.

2 Vincent JL, Wilkes MM, Navickis RJ. Safety of human albumin – serious adverse events reported worldwide in 1998 -2000. *Brit J Anaesthesia* 2003; 91(5): 625-30.

- Histamine release is a known adverse event of HSA administration. However, HES infusions were found to be associated with more anaphylactoid reactions compared with HSA administration.
- Excessive input of HSA, producing an intravascular and a general albumin overload, must be avoided. Dosage and the infusion-rate should be adjusted to the patient's individual requirements by clinical, hemodynamic and other physiological measurements.

The sponsor also stated that the results of virus validation studies have shown that the manufacturing process eliminates enveloped and non-enveloped viruses. According to the respective EU Guideline, there are no reports of virus transmission (including HAV, HBV, HCV, HIV or Parvovirus B19) with HSA products manufactured according to (b) (4) specifications by established processes.

5.2 Post-marketing Experience

Since Albuminex 5% and Albuminex 25% are not currently licensed in any country, there are no post marketing exposures for these products. The sponsor used Zenalb's post-marketing data to establish the safety of Albuminex 5% and Albuminex 25%.

5.2.1 Post-marketing Experience with Zenalb

The sponsor has stated that from 01 April 1991 to 31 July 2009, total product distributions of Zenalb® 4.5% amounted to approximately (b) (4) of albumin, equivalent to approximately (b) (4). For Zenalb® 20%, total product distributions amounted to approximately (b) (4) of albumin, equivalent to approximately (b) (4). During the period mentioned above, BPL received reports on a total of 116 adverse events which were possibly or probably related to Zenalb® 4.5% and seven adverse events which were possibly or probably related to Zenalb® 20%. Two fatal product-related adverse events were reported, one involving Zenalb® 4.5% and the other involving Zenalb® 20%. In one of these case reports, a 68 years old patient undergoing plasma exchange with Zenalb® 4.5% developed shivering, pyrexia, signs of fluid overload, pulmonary hemorrhage, hypotension, anemia and evidence of coagulopathy. The sponsor stated it was possible that during the course of the plasma exchange, the patient inadvertently received an excessive volume of Zenalb® 4.5%, resulting in dilution of blood clotting factors and ultimately to pulmonary hemorrhage, although this cannot be proven. The second fatal product-related adverse event report involved an 84 years old patient who developed anaphylaxis and acute pulmonary edema shortly after administration of Zenalb® 20%.

Between April 2009 and January 2016, BPL distributed approximately (b) (4) of Zenalb® 4.5%, equivalent to approximately (b) (4). During the same period, approximately (b) (4) of Zenalb® 20% were distributed, equivalent to approximately (b) (4). From 01 August 2009 until 31 January 2016, BPL has received a total of 11 product-related spontaneous

reports. Three serious product-related adverse events were reported for Zenalb® 4.5%, one of which was considered life-threatening, and the remaining reported as "other medically important conditions." Seven of the adverse drug reactions (ADRs) were with Zenalb® 20%, of which 5 were considered serious (two hospitalizations and 3 other medically important conditions); and 3 were in children (range 1 to 10 years). The UK regulatory authority reported 1 serious case (anaphylactic shock) for Human Albumin. All Zenalb® product-related adverse reactions were resolved in 1 to 2 days.

Reviewer comment: The sponsor did not provide details of each adverse drug reaction mentioned in the report.

The sponsor stated that from 01 April 1991 to 06 June 2016, no cases of transmission of Creutzfeldt Jacob Disease (CJD) or other, "as yet unknown infectious agents" were reported for HSA. Also, from 01 April 1991 to 06 June 2016, no cases of viral transmission were reported for Zenalb® 4.5% and Zenalb® 20%. However, Albumin (Human) is derived from human blood, and therefore may carry a risk of transmitting infectious agents including the Creutzfeldt-Jakob disease (CJD) agent. Studies have shown that the "manufacturing process eliminates enveloped and non-enveloped viruses. Additionally, heat treatment at 60°C for a period of at least 10 hours efficiently inactivates viruses."

Reviewer comment: A theoretical risk of transmitting infectious agents exists and the comment "as yet unknown infectious agents" does not have any predictive value.

To date, marketing authorization applications for Zenalb® have not been rejected in any country, and Zenalb® has not been withdrawn from the market in any country for safety reasons. Because of concerns about the risk of transmission of variant CJD, BPL ceased to manufacture all products, including Zenalb®, from UK plasma in May 1998 and began to issue Zenalb® 4.5 and Zenalb® 20 manufactured from US plasma in January 1999.

5.2.2 Literature Search for Zenalb

PubMed literature search conducted on May 7, 2018, using the term "Zenalb" identified 2 articles. Of these two articles, only one article was relevant to adverse events or safety, and this article was included in the sponsor's literature review (discussed in section 5.1). There are no new safety concerns for Zenalb identified in the literature.

6. Pharmacovigilance Plan Review

Based on published clinical safety data in literature and post-licensure studies, the sponsor delineated the important identified safety risks, important potential safety risks, and the important missing information (shown in Table 2).

Table 2: Summary of Safety Concerns Proposed by the Sponsor [Albuminex 5% and Albuminex 25%]

Summary of safety concerns	
Important identified risks	<ul style="list-style-type: none"> • Hypersensitivity reactions, including anaphylactic or anaphylactoid reactions • Hypervolemia • Hemolysis
Important potential risks	<ul style="list-style-type: none"> • Transmission of infective agents such as viruses, emerging viruses, other unidentified infective agents or pathogens • Infusion of large volumes may have an adverse effect on coagulation or hematocrit.
Missing information	<ul style="list-style-type: none"> • No clinical trial experience in patients who are pregnant or lactating

Source: BLA 125644/0, Section 1.16 Risk Management Plan, Table 1, Page 9

The sponsor has proposed to use routine pharmacovigilance to monitor the safety of Albuminex 5% and Albuminex 25%. There are no ongoing or planned additional pharmacovigilance studies/activities. The proposed post-marketing pharmacovigilance actions for the identified safety concerns and missing information are summarized in Table 3.

Table 3: Summary of Safety Concerns and Planned Pharmacovigilance (PhV) Actions Proposed by the Sponsor

Safety concerns	Proposed routine and additional PhV activities	Objectives
<p>Important identified risks:</p> <ul style="list-style-type: none"> • Hypersensitivity reactions, including anaphylactic or anaphylactoid reactions • Hypervolemia • Hemolysis 	<p>Routine pharmacovigilance activities only. Important identified risk to be closely monitored and reports will be followed up by the sponsor</p>	<p>To achieve safe and effective use of ALBUMINEX 5% and ALBUMINEX 25%</p> <p>To ensure the Marketing Authorization Holder (MAH) collects data on patient demographics, risk factors, severity and nature and trends of the reported adverse events in Individual Clinical Safety Reports (ICSRs)</p>

<p>Important potential risks:</p> <ul style="list-style-type: none"> • Transmission of infective agents such as viruses, emerging viruses, other unidentified infective agents or pathogens • Infusion of large volumes may have an adverse effect on coagulation or hematocrit 	<p>Routine pharmacovigilance activities only. Important identified risk to be closely monitored and reports will be followed up by the sponsor</p>	<p>To achieve safe and effective use of ALBUMINEX 5% and ALBUMINEX 25%</p> <p>To ensure the MAH collects data on patient demographics, risk factors, severity and nature and trends of the reported adverse events in ICSRs</p>
<p>Missing information:</p> <ul style="list-style-type: none"> • No clinical trial experience in patients who are pregnant or lactating 	<p>Routine pharmacovigilance activities – literature will be analyzed and outcomes data on exposure will be collected</p>	<p>To achieve safe and effective use of ALBUMINEX 5% and ALBUMINEX 25%</p> <p>To increase BPL's current knowledge of this missing information by identifying and analyzing data on outcome based exposures in pregnant patients or lactating mothers</p>

Source: BLA 125644/0, Section 1.16 Risk Management Plan, Table 2, Page 11

Reviewer Assessment: The sponsor's proposed post-marketing pharmacovigilance activities are adequate for all safety concerns noted in Table 2. No safety signal has been identified that would justify further studies or a REMS. The risks noted above will be stated the Section 5, Warning and Precautions of the Package Insert.

7. Integrated Risk Assessment

- The sponsor's proposed PVP adequately defines and describes the identified risks, potential risks, and important missing information.
- Review of the sponsor's post-marketing safety data for its' Zenalb® 4.5% and Zenalb® 20% product reveals a low rate of reporting. No serious safety concerns for Albuminex 5% and Albuminex 25% were identified during this review.
- The sponsor's proposed PVP, which includes routine PV surveillance and adverse event reporting as required by FDA regulation is acceptable.

8. DE Recommendations

DE agrees with the sponsor's proposed PVP which outlines routine pharmacovigilance for the monitoring of identified safety risks for Albuminex 5% and Albuminex 25%. DE also agrees that

the important identified and potential risks should be noted under Section 5 Warnings and Precautions of the package insert.