



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Albumin (human)

Proprietary Product Name: Albumex 20/Albumex
5/Albumex 4

Sponsor: CSL Ltd

July 2011

TGA Health Safety
Regulation

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- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
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- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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I. Introduction to Product Submission

Submission Details

<i>Type of Submission</i>	Extension of Indications
<i>Decision:</i>	Withdrawn
<i>Date of Decision:</i>	14 June 2011
<i>Active ingredient(s):</i>	Albumin (human)
<i>Product Name(s):</i>	Albumex 20, Albumex 5 and Albumex 4
<i>Sponsor's Name and Address:</i>	CSL Ltd, 189-209 Camp Rd, Broadmeadows, VIC 3047
<i>Dose form(s):</i>	Solution for injection
<i>Strength(s):</i>	2 g/10 mL, 20 g/100 mL, 2.5 g/50 mL, 25 g/500 mL, 2 g/50 mL, 20 g/500 mL, 10 g/250 mL and 12.5 g/250 mL
<i>Container(s):</i>	Glass vial
<i>Approved Therapeutic use:</i>	Not applicable.
<i>Route(s) of administration:</i>	Intravenous (IV)
<i>Dosage:</i>	See attached Product Information document.
<i>ARTG Number (s):</i>	31820, 46283, 50595, 50620, 59154, 59155, 72895 and 72896

Published references cited in this document are listed under *References* at the end of the document.

Product Background

Albumin is the most abundant plasma protein. Albumex is produced from pooled human plasma, now prepared by predominantly chromatographic techniques. From 1995-2000 there was a single viral inactivation step. An additional viral inactivation step has been included in products manufactured since 2000.

As a therapeutic product albumin has a perceived primary role in contributing to plasma colloid oncotic pressure. Albumin's physiological role is not restricted to this as it also acts as a carrier for various solutes in plasma. It may also act as a free radical scavenger. These latter two aspects of are not generally assessed in clinical trials.

Type, timing and quantity of fluid resuscitation may have a bearing on mortality and morbidity in hypovolaemia. Albumin was widely used until a Cochrane review¹ questioned the safety and efficacy of albumin in fluid resuscitation. The reviewers concluded that there was an increase in the absolute risk of death with use of albumin when compared with use of crystalloids (such as normal saline).

In response to this and a meta-analysis with contradictory conclusions (Wilkes *et al*, 2001), the SAFE investigators (Finfer *et al*, 2004) conducted a large, randomised study of albumin versus normal saline in the Australian and New Zealand intensive care unit (ICU) setting. By virtue especially of its size, this study currently dominates the landscape of

¹ Cochrane Injuries Group Albumin Reviewers [CIGAR], 1998

evidence regarding use of albumin for fluid resuscitation. The meta-analyses and the SAFE study are evaluated below under *Clinical Findings, Efficacy*.

This AusPAR describes the evaluation of an application by CSL Limited (the sponsor) which proposes a change in the Product Information (PI) for the albumen products, Albumex, which constitutes an extension of indications for Albumex 4² and somewhat more than editorial changes for Albumex 20. Albumex 4, Albumex 5, Albumex 20 contain human albumin, sodium, chloride and octanoate in varying amounts. The purpose of the current Australian application is to update and simplify the hypovolaemia / shock indication in the approved PI and in the process, extend the current indication to include unrestricted "first line use".

- To make the indication wording simple and direct.
- To remove text that is instructional beyond the scope of the product and to remove text that recommends use of crystalloids and synthetic products for which CSL has no safety or efficacy data.

Basic to the practice of intravenous (IV) fluid resuscitation is the concept that total fluid intake must balance initial fluid deficit, ongoing losses and maintenance requirements. The proposed new indication (*Albumex 4 is indicated for the restoration of circulating blood volume*) does not cover use in maintenance fluid therapy. The text proposed for deletion appears to cover maintenance use in some contexts:

Albumex 4 may also be useful following initial resuscitation with crystalloid or synthetic colloid solutions in patients in whom extended support of the intravascular volume is required, such as seriously ill patients with multiple organ failure or the systemic capillary leak syndrome.

The sponsor states that:

The restrictions on "first line use" were not based on patient safety concerns but rather had their origins in 1990s Government public health policy and published guidelines, when blood stocks were at low level. CSL can confirm blood stocks are no longer at levels sufficiently low to dictate restrictions for patients who might otherwise benefit from the use of Albumex.

No significant changes to the dosage are proposed. Advice about warming to room temperature prior to infusion has been proposed for removal.

Regulatory Status

The sponsor states that no similar application has been submitted in any other country and that aspects of the PI requiring updating are not present in Product Information (PI) documents of other human plasma derived albumin products manufactured by CSL's companies (CSL Behring) or competitor products. However, the sponsor also notes that in New Zealand, wording in the hypovolaemia/shock indication was amended in 2005:

Medsafe agreed that restrictions based on supply issues in the late 1980's should not be the basis for a restriction of the product to second line use...

The wording of the NZ hypovolaemia/shock indication is as follows:

Hypovolaemia/shock. Preservation of an adequate circulating volume should be the primary aim of therapy. Albumex 4 may, however, be the initial plasma expander of choice if shock is associated with significant hypoalbuminaemia (albumin concentration less than 25 g/Litre), or if it is clinically desirable to avoid the infusion of large volumes of crystalloid solutions.

² The same textual addition proposed for Albumex 4 is implied in the application form relating to Albumex 5. Albumex 5 is not supplied in Australia.

Albumex 4 may also be useful following initial resuscitation with crystalloid or synthetic colloid solutions in patients in whom extended support of the intravascular volume is required, such as seriously ill patients with multiple organ failure or the systemic capillary leak syndrome.

The implication is that first line use should only be considered in limited circumstances (significant hypoalbuminaemia or avoidance of massive infusion of crystalloid).

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical Findings

No new nonclinical data were submitted.

IV. Clinical Findings

Introduction

In 1998 a Cochrane review suggested increased mortality associated with the use of intravenous albumin.

As noted in a previous TGA evaluation report:

“Cochrane Database of Systematic Reviews 2004 Issue 4:

In the 32 randomised controlled trials described in the 2004 Cochrane review there were 1632 deaths among 8452 trial participants (19.3%) (10).

For hypovolaemia, the pooled relative risk of death following albumin or plasma protein fraction (PPF) administration versus no albumin/PPF or a crystalloid solution was 1.01 (95% confidence interval (CI) 0.92-1.10). This estimate was heavily influenced by the results of the SAFE trial, which received 91% of the weight of the meta-analysis in the most recent Cochrane review.

For trials where subjects had burns as the indication for albumin, the relative risk of death from all causes for the albumin/PPF groups was 2.40 (1.11-5.19).

For the indication hypoalbuminaemia, the relative risk of death for albumin/PPF vs. no albumin or a crystalloid was 1.38 (0.94-2.03)

It is notable that the synopsis conclusion in this updated review is

“There is no evidence that giving human albumin to replace lost blood in critically ill or injured people improves survival when compared to giving saline.”

The SAFE study, published in 2004, showed no excess 28 day mortality in ICU patients overall. As noted by the previous TGA evaluator of this study:

“The SAFE Study was a multi-centre double blind randomised parallel group controlled trial in patients who had been admitted to the closed, multidisciplinary intensive care units of 16 academic tertiary hospitals in Australia and New Zealand between November 2001 and June 2003.

Randomisation of eligible patients on admission to ICU was achieved centrally via a secure website, and stratified according to institution and trauma diagnosis on admission to ICU. Patients 18 years and older who fulfilled the objective criteria for requirements for fluid administration to maintain or increase intravascular volume were randomised 1:1 to receive either CSL 4% albumin or normal saline as fluid resuscitation in the ICU, until death, discharge from the ICU, or 28 days after randomisation, when fluid was required for hypovolaemia, a decision made by the treating physician. The primary outcome variable was 28 day survival. Original data were not presented.

Important exclusions from the study were patients admitted to the ICU after cardiac surgery or liver transplantation, patients admitted to the ICU for treatment of burns, and patients requiring plasmapheresis during the admission to ICU.

The statistical section of the publication, and the synopsis, state that the trial was designed to enrol 7000 patients, to provide a power of 90% to detect a 3% difference in absolute mortality rates between the two groups from an estimated baseline mortality rate of 15%. All analyses were on an intention to treat basis using available observations. The study population comprised 6997 patients, n=3497 assigned to albumin and n=3500 assigned to normal saline. However, numbers exposed were 3490 and 3394 for albumin and saline respectively.

The SAFE study suggests no overall difference in 28 day survival between 4% albumin and normal saline when used for correction of hypovolaemia in patients transferred into an ICU."

"There were 22 AEs reported in 3409 patients exposed to albumin, vs. 14 in the 3394 exposed to saline.

Most frequently reported were:

pulmonary oedema (albumin n=12, 0.4% vs. saline n=3, 0.09%)

hypoxia (albumin n=7, 0.2% vs. saline n=1, 0.03%)

hyperchloraemic acidosis (albumin n=1, 0.03%, vs. saline n=4, 0.1%)"

"No information on withdrawals due to adverse events in the SAFE study is available."

"Although not stated, it appears that the adverse event report summary data have been provided to CSL by the ANZICS trial group."

Literature based submission-Search strategy

The current Australian submission was a literature based submission. Many studies captured in the literature based submission were conducted in the era before Good Clinical Practice (GCP) was formalised and indeed before reporting of informed consent was expected in published papers. The pivotal study in the application (SAFE) has appropriate statements regarding informed consent in the ICU patient population it studied. The study protocol was accepted by relevant ethics committees.

The sponsor justified its search methodology for the literature search used in their submission. The search strategy used was subsequently approved by TGA.

Searches were conducted for the entire period of establishment of the databases. Although the sponsor extended its search to include pre-1990 clinical studies, the sponsor noted that:

...clinical studies prior to 1990 used albumin formulations that have been superseded by recent formulations arising from improved manufacturing processes with higher purity

and viral safety. These early studies are therefore not considered relevant for supportive safety data for the current Albumex 4 formulation.

The sponsor's Clinical Expert noted that most retrieved studies were not of CSL's Albumex, and noted that "trials conducted on other human albumin products are not directly applicable to the Albumex range in terms of safety but are included for efficacy data". Additional viral inactivation steps in the process of manufacturing Albumex might increase the safety of the product from the perspective of blood borne pathogen contamination, and it may be that the purity of Albumex differs from the purity of albumin products manufactured using Cohn fractionation or modifications. Nevertheless, some safety issues with albumin must be intrinsic to albumin in the context of its indications for use and extrinsic to viral or other impurities.

Pharmacokinetics

There were not new data submitted under this heading.

Pharmacodynamics

Many smaller clinical studies used as their primary endpoint a variety of physiological variables (such as left ventricular stroke work index) that could be seen in the context of this submission as pharmacodynamic endpoints. There is some blurring of the distinction between such variables and efficacy variables since they are generally presented as surrogates for efficacy. These studies are therefore evaluated in the section on *Efficacy* below.

Efficacy

Introduction

In the following clinical evaluation, classification as a pivotal study requires that the study directly addresses an issue related to the current submission (the primary issue being efficacy and safety of use of Albumex 4% or 5% as 'first-line therapy' instead of 'second-line therapy' in hypovolaemia). In addition, characteristic design features and conduct of a pivotal study are required: use of the product in question (Albumex 4% or Albumex 5%); randomisation against a relevant comparator (one currently registered in Australia for the same or comparable indications); reasonable sample size (the exact threshold depending on the study question being posed). More emphasis is placed on evaluation of the one pivotal study identified, which was the SAFE study. Some other studies can be considered supportive. Other studies have critical deficiencies in design or conduct and are not evaluated in detail. In the opinion of the clinical evaluator, guideline documents are not as useful as primary data in support of the current submission. The guideline documents are presumably based on primary data and any relevant primary data should be available in the data submission for direct evaluation.

Pivotal efficacy studies

SAFE

The SAFE Study Investigators. A comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit. NEJM 2004; 350: 2247-56.

This study has been reviewed by TGA previously. The clinical evaluator for that submission commented that SAFE was...

...a multi-centre double blind randomised parallel group controlled trial in patients who had been admitted to the closed, multidisciplinary intensive care units of 16 academic tertiary hospitals in Australia and New Zealand between November 2001 and June 2003.

Randomisation of eligible patients on admission to ICU was achieved centrally via a secure website, and stratified according to institution and trauma diagnosis on admission to ICU. Patients 18 years and older who fulfilled the objective criteria for requirements for fluid administration to maintain or increase intravascular volume were randomised 1:1 to receive either CSL 4% albumin or normal saline as fluid resuscitation in the ICU, until death, discharge from the ICU, or 28 days after randomisation, when fluid was required for hypovolaemia, a decision made by the treating physician. The primary outcome variable was 28 day survival. Original data were not presented.

Important exclusions from the study were patients admitted to the ICU after cardiac surgery or liver transplantation, patients admitted to the ICU for treatment of burns, and patients requiring plasmapheresis during the admission to ICU.

The statistical section of the publication, and the synopsis, state that the trial was designed to enrol 7000 patients, to provide a power of 90% to detect a 3% difference in absolute mortality rates between the two groups from an estimated baseline mortality rate of 15%. All analyses were on an intention to treat basis using available observations. The study population comprised 6997 patients, n=3497 assigned to albumin and n=3500 assigned to normal saline. However, numbers exposed were 3490 and 3394 for albumin and saline respectively.

The SAFE study suggests no overall difference in 28 day survival between 4% albumin and normal saline when used for correction of hypovolaemia in patients transferred into an ICU.

SAFE was a study of patients admitted to ICU with trauma, severe sepsis or acute respiratory disorder syndrome. It was a large, simple trial, focusing on mortality at 28 days rather than surrogates such as haemodynamic endpoints. The relative risk of death in the albumin arm at 28 days was 0.99 (95% CI 0.91-1.09). Key secondary endpoints are set out in Table 1 below (*VI. Overall Conclusion and Risk/Benefit Assessment, Clinical*).

The observation was also made that saline subjects received only 1.4-fold more fluid for resuscitation in ICU over the first four days than albumin patients. Traditionally it had been thought that approximately three fold more crystalloid was required than colloid in the context of fluid resuscitation, though the evidence for this is somewhat unclear. The finding that volume of study fluid required was only fractionally higher in the saline arm than the albumin arm runs contrary to findings of many other published studies that built tighter haemodynamic monitoring into the study protocol. SAFE, however, might mirror actual practice better.

Albumin patients were transfused with statistically significantly more red blood cells than saline patients on Days 1-2, though this amounted to a mean difference of only slightly over 70 mL over Days 1 and 2 combined. This difference was accounted for, according to the principal investigator, by albumin patients having a “better and quicker intravascular volume expansion” that tipped them over the threshold for transfusion (presumably due to dilutional anaemia, higher in the albumin arm despite lower overall infused volumes because the saline volume tends to extravasate quickly). Haemoglobin (Hb) or haematocrit values themselves were not assessed, so chance baseline differences in Hb cannot be discounted, except by reference to the large sample size. The other obvious possibility is that albumin affects coagulation (see discussion below under *Safety*).

The SAFE study is reasonably described as pivotal for this submission. Firstly, one treatment arm received Albumex 4%, and the comparator arm was normal saline which is appropriate in the Australian context (indeed, the study was conducted in Australia and NZ). Secondly, the study was very large (almost 7000 subjects), generally well designed and well conducted (see also discussion below). Thirdly, the study enrolled hypovolaemic

patients, and offered use of albumin (in subjects randomised to that arm) as a “first line” agent for reversal of intravascular volume depletion, which aligns with the purpose of the current submission. Fourthly, the study included clinically relevant endpoints such as mortality at 28 days (see discussion below). Fifthly, for the duration of a subject’s stay in ICU the subject received the randomised study drug when fluid resuscitation was required. This is in contrast to many other studies in the current Australian submission that restricted the randomisation of study drug to a particular period such as the first postoperative morning.

The study was presented as an efficacy study. The primary endpoint was mortality at 28 days. In the context of the use of fluid resuscitation in hypovolaemic ICU patients, mortality is a potentially reasonable primary efficacy endpoint. Its indisputable relevance balances its generally indirect relationship with drug action. However, cause of death was not analysed. It is difficult to distinguish between mortality from inefficacy and mortality from problems with drug safety *per se*, which theoretically might cloud interpretation of ‘efficacy’ results.

More importantly, using the 28 day mortality endpoint would require a strong difference in drug effect, one way or the other (in efficacy, inefficacy, absence or presence of adverse drug reactions), to allow demonstration of a treatment difference given the multitudinous causes of mortality in an ICU patient up to Day 28. In this sense, the trial is biased towards not detecting a difference in mortality. There was 90% power to detect a 3% difference in mortality between arms (based on estimated baseline mortality rates of 15%).

From the published paper, it is unclear whether the study was set up as an equivalence trial. The authors state a hypothesis of ‘no difference in 28 day rate of death from any cause’ but power calculations suggest an attempt to show superiority (power of 90% to detect a 3% difference in absolute mortality rates) and nowhere was any delta nominated (threshold for clinically relevant difference, within which the limits of the 95% CI around the difference in treatment effect should reside in order to establish equivalence). In general terms, an inability to establish superiority (a statistically significant difference in mortality rates) is not the same as the demonstration of equivalence.

It is far from ideal to choose a delta value once study results are known (see EU guideline³). Having said that, the absolute difference in 28-day mortality turned out to be small; -0.2% (albumin minus saline), with a 95% CI of -2.1% to 1.8%. Whether a particularly small delta value should be applied to the assessment of mortality in a treatment as ubiquitous as IV fluid for volume resuscitation is arguable; but a delta of <2.0% would be unusually small so it is reasonable to accept that the study showed equivalence.

Some caveats apply to this conclusion of therapeutic equivalence between arms. Subgroup analysis suggested unfavourable outcomes in the albumin arm in patients with traumatic brain injury (24.5% [albumin] versus 15.1% [saline] 28 day mortality, $p=0.009$). Only ‘patients with trauma’ were a pre-defined subgroup. Analysis of traumatic brain injury was *post hoc*. Follow up to 24 months produced consistent findings in a linked study of the same patients (SAFE-TBI; Myburgh *et al*, 2007). Also, the conclusion drawn is broadly consistent with that of a crystalloid versus colloid meta-analysis by Choi *et al* (1999), where subgroup analysis found a difference in mortality in favour of crystalloid in trauma (relative risk (RR) 0.39, 95% CI 0.17-0.89). These are fairly strong grounds to

³ TGA-adopted European Union guideline CPMP/EWP/482/99 Points to consider when switching between inferiority and non-inferiority. page 4, Section III, ‘Relevance of Pre-definition’ www.tga.gov.au/docs/pdf/euguide/ewp/048299en.pdf.

recommend against use of albumin in fluid resuscitation where traumatic brain injury exists.

Subgroup results in SAFE also suggested that further study should be conducted of albumin versus saline in severe sepsis, to confirm a possible benefit of albumin use.

The study excluded children <18 years of age. Also excluded were patients admitted to ICU after burns, cardiac surgery or liver transplantation and the results should therefore not be generalised to such patient groups without caution.

Deviations from protocol (such as the contamination by use of other resuscitation fluids, in about 10% per arm) would have the general effect of biasing towards equivalent outcomes across arms.

Use of resuscitation fluids once the patient had left ICU was not per protocol or subject to the initial randomisation step. This would bias towards equivalence but to what extent is unclear. While most ICU patients with trauma, severe sepsis or acute respiratory distress syndrome (ARDS) would not spend 28 days in ICU, it is fair to say that most fluid resuscitation would be in the initial days of hospitalisation within the ICU setting.

All analyses were the “intent to treat” group (ITT) yet in equivalence trials it is important to demonstrate that both the ITT and the “per protocol” (PP) cohorts show comparable outcomes. This was not done.

Though perhaps a minor issue, it is notable that in analysis of duration of renal replacement therapy, mean duration in the albumin arm was 0.48 days and 0.39 days in the saline arm. While the p-value for this comparison was stated to be 0.41, the 95% CI around the difference of 0.09 days was stated to be ‘-0.0 to 0.19’ days. It would be an unusual distribution of values that could produce these discordant results.

Overall, the study results support the application, except that it may be reasonable to consider a precaution regarding use of albumin in traumatic brain injury. In particular since the follow up study confirmed long term negative outcomes in this subgroup given albumin. In the current PI, there is no contraindication or even precaution for use in traumatic brain injury, only a carefully worded description of the *post hoc* follow up study that emphasises the possibility that the results represent a chance finding.

Supportive studies

In a study by Boldt *et al* (2006) 50 patients older than 70 years undergoing major abdominal surgery were randomised to receive either 5% albumin or 6% hydroxyethyl starch (HES) (130/0.4) if mean arterial pressure was <60 mmHg or central venous pressure (CVP) was <10 mmHg during surgery and within 24 hours post-surgery. Choice of comparator was appropriate; for example, Fresenius Kabi’s Voluven has the indication “*Voluven is indicated for the therapy and prophylaxis of hypovolaemia*”.

Patients with significant baseline organ dysfunction (such as NYHA Class III-IV heart failure⁴) were not included. Outcomes in the ICU and in the period until hospital discharge

⁴ In order to determine the best course of therapy, physicians often assess the stage of heart failure according to the New York Heart Association (NYHA) functional classification system. This system relates symptoms to everyday activities and the patient's quality of life. Class I (Mild): No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnoea (shortness of breath). Class II (Mild): Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnoea. Class III (Moderate): Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnoea. Class IV (Severe): Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

were reported and were broadly similar. However, the study was not powered to detect significant differences in many of these outcomes, including mortality. In fact, the study was powered to detect a difference in the circulating levels of interleukin-6 (IL-6), a pro-inflammatory cytokine. IL-6 was higher to the first post-operative day in the albumin arm. Perhaps of more relevance, patient haemodynamics were similar in both treatment arms, although slightly more albumin was required to maintain mean arterial pressure and CVP at desired levels (3960 mL albumin versus 3500 mL HES; $p > 0.05$). In summary, the study was somewhat supportive of a role for albumin 5% in 'first line' treatment of surgical/post-surgical hypovolaemia, with the caveats that (a) the study was not powered to detect differences in some important clinical outcomes, and (b) Albumex 5% was not used.

In a study by Boldt *et al* (2008) 50 hypoalbuminaemic (< 3.5 g/dL = < 35 g/L) patients older than 80 years undergoing cardiac surgery were randomised to either 5% albumin (n=25) or HES 6% (130/0.4) (n=25). The study drug was used for bypass pump priming and given until the morning of the second post-operative day to target pulmonary capillary wedge pressure or CVP between 12-14 mmHg (10-14 mmHg post-operatively). There was little difference between arms in volume of study drug given, or in haemodynamic endpoints. ICU and in-hospital mortality did not differ across arms. The actual primary endpoint was serum IL-6 level, which did not differ across the two treatment arms. The authors concluded that use of albumin lacked advantages compared to use of HES in the studied population.

Kuitunen *et al* (2007) randomised 45 cardiac surgery patients to receive 4% succinylated gelatin, 6% HES (200/0.5) or albumin 4% after surgery. The treatment was given as a fixed dose (15 mL/kg) over a median of 95-100 minutes which may not mirror usual practice of fluid resuscitation. In Australia, Gelofusine (succinylated gelatin 40 g/L) is a registered product with relevant indications. It was concluded that in the early post-operative period after cardiac surgery, HES and albumin infusions improve haemodynamics more than succinylated gelatin.

In another study (Niemi *et al* 2008) 45 elective cardiac surgical patients were randomised to receive 6% HES 200/0.5 (n=15), 6% HES 130/0.4 (n=15) or albumin 4% (n=15) post-surgically in ICU. Volume deficit in this context is due to cardiopulmonary bypass (CPB) related alterations in the endothelium, vasodilatation due to re-warming and fluid loss via chest tube drainage. A fixed dose of 15 mL/kg was given, which may not mirror usual practice of fluid resuscitation. Haemodynamics did not differ substantially across the two treatment arms at 2 and 18 hours (last measurement was on the first post-operative morning) although initially heart rate fell slightly in the albumin arm but tended to rise in the HES 130/0.4 arm. Acid base balance investigations showed that pH did not differ across the treatment arms but base excess decreased less in HES groups than in the albumin group (that is, base excess was most negative in the albumin arm).

Rackow *et al* (1983) randomised 26 patients in hypovolaemic shock to fluid challenge with 5% albumin (manufactured by Cutter), 6% hetastarch or 0.9% saline solutions. Subjects ranged in age from 54 to 97 years (median 79 years). Of these patients, 69% had septic shock and 31% had hypovolaemic shock. Perfusion failure was substantiated by elevated lactate levels. Fluid challenge was 250 mL every 15 minutes until pulmonary artery wedge pressure (WP; indicative of pulmonary intravascular hydrostatic pressure) reached 15 mmHg. WP was then maintained at this level with test fluid for 24 hours. Two to four times the volume of saline as colloid was required to achieve similar haemodynamic endpoints.

There was a greater incidence of pulmonary oedema in the saline resuscitated group (87.5%) than in the colloid groups (22%) as measured by chest x-ray (CXR) at 24 hours.

This large disparity was not reported in the SAFE study (perhaps due to the generally younger population under study in SAFE). In fact, in the previous TGA evaluation of SAFE it was noted that there were more cases of pulmonary oedema in the albumin arm (0.4%) than the saline arm (0.09%) but a suspicion of under-reporting exists given that only 36 Adverse events (AEs) were reported in total (and these were not discussed in the published paper, implying that CSL obtained these data directly from the investigators).

Results of this relatively old study support use of albumin in first line treatment of shock. However it should be noted that Albumex was not used, the study was relatively small and endpoints chosen for analysis focused more on haemodynamics than clinical outcome (even reports of pulmonary oedema were not correlated with symptoms or need for treatment).

Saxena *et al* (1997) randomised 75 patients undergoing coronary artery bypass surgery (CABG) to receive hetastarch 6% (10 mL/kg), albumin 5% (10 mL/kg) or Ringer's lactate (30 mL/kg) to restore normovolaemia after removal of 10 mL/kg blood before institution of CPB. Those receiving crystalloid had an increase in heart rate relative to those receiving colloid. Although to the first post-operative day, haemodynamic parameters were similar across arms it should be noted that pulmonary capillary wedge pressure was not measured and cardiac index was not calculable.

Verheij *et al* (2006) reported a study of ICU (immediately post-elective cardiac or vascular surgery) patients randomised to receive fluid loading post-surgery of saline, gelatin 4%, HES 6% or albumin 5% (n=16-18 per arm; median ages 62-66 years). The 90 minute fluid loading followed a fluid challenge protocol based on CVP and pulmonary capillary wedge pressure. There was greater improvement in cardiac index with colloids than with saline loading but no major difference across colloid groups. This was attributed to differing cardiac filling rather than cardiac function. Paradoxically, there was a decrease in heart rate in the saline arm over the 90 minutes but not in the colloid arms (in fact there was an increase in the albumin arm). However, the short term haemodynamic and pulmonary endpoints measured were not correlated with clinical outcomes, limiting the value of the study in the context of the current submission. The study did not report adverse events.

Wahba *et al* (1996) randomised 20 post-cardiac surgery patients to receive either Haemaccel (a polygeline solution) or albumin 5% for fluid resuscitation. Dose was titrated to haemodynamic response. In both treatment arms, haemodynamic stability was achieved, with no statistically significant differences between treatment groups, using very similar amounts of colloid. Safety was not evaluated.

The following studies were not considered to be supportive of the efficacy of Albumex 4% or Albumex 5% in first line as opposed to second line fluid resuscitation. The principle reason(s) for discounting them are given below:

- Abraham *et al* (2005). The study examined preloading after induction of anaesthesia, in a narrow population of patients undergoing neurosurgery in the sitting position. The study does not strictly address restoration of blood volume in hypovolaemia by albumin and falls in mean arterial pressure (MAP) of $\geq 20\%$ from baseline were treated with normal saline in all groups. The authors did however conclude that preloading with HES and saline is superior to 5% albumin and saline or saline alone for maintaining cardiovascular stability in sitting neurosurgery.
- Friedman *et al* (2008). The chosen comparators (HES 200/0.5 solutions) are not registered on the Australian Register of Therapeutic Goods (ARTG). Just as different colloids are considered quite different entities with different risk benefit profiles, so are HES products with different average weights and molar substitutions.

- Grundmann *et al* (1985). Randomisation was by timing of albumin treatment rather than between albumin and a comparator agent.
- Lazrove *et al* (1980). The study was too small, with a sample size of 10 per arm in a crossover design; molar substitution of the comparator HES was not specified.
- Lennihan *et al* (2000). Randomisation was to maintain normal or elevated cardiac filling pressures in the context of subarachnoid haemorrhage patient aneurysm clipping surgery.
- London *et al* (1988) and Mastroianni *et al* (1994). The comparator agent (pentastarch) is not currently registered in Australia.
- Moggio *et al* (1983). The comparator agent (Hespan; HES 6%) was not adequately characterised. Given the publication year and the changes in the formulation of HES products that have occurred since the publication of this paper, the agent used is unlikely to be one that is currently registered in Australia.
- Puri *et al* (1983). It is not specified that subjects were randomised between treatment arms. Baseline differences were (from interpretation of available data) marked for heart rate and urine output. It is unclear what species of HES was used as a comparator.
- Rackow *et al* (1989). The chosen comparator (pentastarch) is not on the ARTG.
- Salinas *et al* (2006). The study examined rapid preloading of 5% albumin (5 mL/kg) or Ringer's solution (25 mL/kg) over 15 minutes after induction of anaesthesia, at the time of incision in cardiac surgery patients. The study does not strictly address restoration of blood volume in hypovolaemia by albumin. There was only a 30 minute follow-up in which cardiac haemodynamic endpoints were assessed.
- Trof *et al* (2010). Results for the colloid arms (gelatine 4%, HES 6% or albumin 5%) were presented in aggregate, making conclusions regarding albumin difficult to draw.
- Vogt *et al* (1996). The comparator agent (HES 200/0.5) is not currently registered in Australia.
- Vogt *et al* (1999). The comparator agent (HES 200/0.5) is not currently registered in Australia.

Meta-analyses

The clinical evaluator considered that meta-analyses from before the SAFE study publication are not sufficiently up to date to be pivotal. However, the influential Roberts *et al* (1998) meta-analysis is discussed briefly to provide historical perspective.

The Cochrane Injuries Group Albumin Reviewers (Roberts *et al*, 1998) examined the effect on mortality of administering human albumin or plasma protein fraction (all doses and concentrations [2.5-25%]) during management of critically ill patients with (a) hypovolaemia, (b) burns or (c) hypoalbuminaemia. These indications do not align exactly with the indication under review in the current submission (that is, second versus first line treatment of hypovolaemia). However, risk of death was analysed by indication. For hypovolaemia, the relative risk of death after albumin administration was 1.46 (95% CI 0.97-2.22). Notably, the increased relative risk of death was not statistically significant in the subgroup of hypovolaemic patients. The method of categorisation of patients into each of these groups was not always transparent at the level of the individual study.

A fixed effects model was used to arrive at this relative risk on the basis that statistical evidence of heterogeneity between trials was not found. However, it appears that

heterogeneity was tested based on the chi-square test. There may be low power to detect heterogeneity based on this test. No I^2 statistic was stated to help quantify heterogeneity. On the other hand, visual inspection of the Forest plot for results in hypovolaemia studies does not suggest massive heterogeneity at least of results (this obviously does not address heterogeneity of study design and conduct). In general, a random effects model would be a more conservative method, in that it calculates a larger p-value. When studies are heterogeneous in design and conduct, heterogeneity of actual results looms even larger as an issue in interpretation of summary estimates in meta-analyses.

The authors comment on use of the mortality endpoint. They note that “in the context of critical illness, death or survival is a clinically relevant outcome that is of immediate importance to patients” and that “mortality data would be less prone to measurement error or biased reporting than would data on pathophysiological outcomes”. Further, “use of a pathophysiological endpoint as a surrogate for an adverse outcome assumes a direct relationship between the two”. Use of all cause mortality was justified because “the attribution of cause of death in critically ill patients, many of whom may have multiorgan failure, can be problematic and may be prone to bias”.

The meta-analysis was criticised following publication for exclusion of relevant randomised controlled trials and for its dealing with study heterogeneity.

Following this meta-analysis, a paper by Wilkes and Navickis (2001) was published which found no statistically significant effect of albumin on mortality although point estimates still suggested harm (RR 1.12 for surgery or trauma studies). This review was supported by industry.

The Albumin Reviewers (Alderson *et al*, 2009) updated the work of the Cochrane Injuries Group Albumin Reviewers discussed above. The search was last updated in June 2008. The update was heavily influenced by the SAFE study and produced a relative risk for mortality following albumin of 1.01 (95% CI 0.93-1.11). The SAFE study contributed 88.2% of information based on weighted values used in the meta-analysis and an even higher proportion of information for hypovolaemia mortality. Whether the SAFE study should have been included in the hypovolaemia group of this meta-analysis is open to question.

Perel and Roberts (2007) conducted a meta-analysis of colloids versus crystalloids for fluid resuscitation in critically ill patients. Results for albumin or plasma protein fraction were separated from results for other colloids. Results for albumin or plasma protein fraction were largely influenced by the SAFE study, with a pooled relative risk of mortality of 1.01 (95% CI 0.92-1.10).

Vincent *et al* (2004) published a meta-analysis of randomised controlled trials (RCTs) which assessed morbidity in hospitalised patients receiving human albumin. The primary endpoint was incidence of complications and included death. However, subjects were not included due to presence of hypovolaemia *per se*. The closest approximation would be subjects included due to ‘surgery or trauma’. The meta-analysis concluded that there was no significant difference in morbidity between ‘surgery or trauma’ subjects given albumin and those in the control arm (RR 1.00, 95% CI 0.89-1.11). This finding of no difference would be somewhat influenced by the receipt in the control arm of some albumin as part of the study fluid regimen.

Bunn *et al* (2008) meta-analysed the mortality associated with the use of various colloids including albumin. Their analysis did not include interaction with indication (such as hypovolaemia) and this negated the relevance of this publication.

The clinical evaluator's conclusions on clinical efficacy

The SAFE study is the only pivotal study identified by the sponsor. It supports use of Albumex 4% as first line treatment of hypovolaemia as no mortality differences at 28 days were found between the albumin and saline treatment arms. Various aspects of the study design and conduct biased towards a finding of equivalence. Most notably, only a strong differential drug effect on efficacy or safety would influence mortality at 28 days, given the various other influences on mortality in this particular group of subjects.

Other studies were supportive of the proposed change only in that they provided no categorical evidence that the proposed change would be dangerous.

There is sufficient efficacy evidence from the SAFE study to support the proposed change in indication.

Safety

As noted, the SAFE study used 28 day mortality as its primary endpoint. The value of this outcome for safety as opposed to efficacy of albumin has already been discussed. Similar arguments apply to the secondary endpoints used in the study, such as new organ failure or duration of renal replacement therapy. There was no reporting of adverse drug reactions (ADRs) to albumin. Hypotension is an important ADR for albumin and in a large, pragmatic study such as SAFE it is possible that hypotension and similar ADRs were under-reported.

In general across the submitted RCTs, adverse events following albumin administration were very poorly reported. Where reporting was made, it was typical for details of monitoring procedures to be absent. For example, Kuitunen *et al* (2006) noted no AEs for albumin but did not describe how AEs were monitored. In the SAFE study, the published article made no mention of pulmonary oedema yet the sponsor has access to data indicating pulmonary oedema was reported as an AE in some patients.

Niemi *et al* (2006) in their study of cardiac surgical patients examined the influence of albumin on coagulation, using an *in vitro* diagnostic kit (ROTEM; thromboelastometry) that assessed thrombus stability and measures such as chest tube drainage. Albumin did not induce a hypocoagulable state and the study authors concluded that its haemostatic effects were limited to haemodilution. This is relevant when interpreting the SAFE study finding of slightly higher red blood cell transfusion requirements in the albumin arm than the saline arm and is consistent with the interpretation that such a difference in transfusion requirements can be attributed to differential timing and the amount of haemodilution. Schramko *et al* (2009) also concluded that albumin did not change coagulation status according to thromboelastometry.

The clinical evaluator's conclusions on clinical safety

Most of the submitted published studies did not address the type and frequency of adverse reactions to albumin administration. Broadening of albumin's hypovolaemia indication to include first-line use may change the profile of patients receiving the product. It would therefore have been better to have safety data in a sample of such subjects from studies with appropriate adverse event monitoring. It can be argued that analysis of mortality data (for example from SAFE) or morbidity data (for example from Vincent *et al*, 2004) integrates efficacy and safety to indicate net benefit or harm but it would have been ideal to have distinct adverse event data for analysis.

Clinical Summary and Conclusions

Product Information – Evaluation and Recommendations

Albumex 4 and Albumex 5

INDICATIONS

The change to the ‘hypovolaemia/shock’ indication is discussed elsewhere in this AusPAR.

A new sentence is proposed for the ‘cardiopulmonary bypass’ indication, namely:

Albumex 4 is indicated for cardiopulmonary bypass.

This is a broadening of indication from the narrower indication in the current PI document which limits intra-operative use of Albumex 4 to priming the pump for patients with poor left ventricular function and other complicating factors. On the other hand, indications in the ARTG are slightly divergent from the current PI indications in that they include the statement: “Albumex 4 may be used for priming the pump for cardiopulmonary bypass surgery”. It would be acceptable to include this sentence in the PI, since it is already in the ARTG. The sponsor’s proposed sentence is rather vague in that it is not clear what aspect of cardiopulmonary bypass albumin could be used for. In this sense it is a potential broadening of indication. If the sponsor wants to go beyond the sentence already in the ARTG concerning CPB, it should provide adequate justification and/or clinical trial evidence.

Albumex 20

INDICATIONS

There is a proposal to add text under the ‘Hypoproteinaemia in the acutely ill patient’ heading as follows:

Albumex 20 is indicated for hypoproteinaemia in acutely ill patients.

Given the existing heading for this indication, this seems reasonable. It should be noted that in the current PI, the text under the heading ‘Hypoproteinaemia in acutely ill patients’ does not align exactly with the heading in that subjects with hypoproteinaemia (typically, hypoalbuminaemia) may not necessarily have “existing or anticipated clinical problems or complications from reduced oncotic pressure” but that problems stemming from reduced oncotic pressure could at least be anticipated in most such subjects.

The proposed synthesis of the shock indication text as “Albumex 20 is indicated for shock” is a broadening of indication, since various types of shock exist and the current PI provides an indication only for shock due to acute loss of blood or plasma. Thus, without further evidence, this proposed change should be rejected. Not all patients requiring fluid resuscitation are in shock. The SAFE study did not break down results according to whether the patient was in shock or not and therefore the results of this study cannot be used to justify this proposed change. The sponsor may wish to pinpoint the good quality publications that support this broadening of indication for Albumex 20.

The proposal to state that “Albumex 20 is indicated for plasma exchange” should be modified to “Albumex 20 is indicated for plasma exchange if serum albumin is not maintained with iso-oncotic albumin solutions”.

Summary and Discussion

This submission was to amend various aspects of the Product Information for Albumex 4, Albumex 5 and Albumex 20. Almost all evidence in support of the proposed changes amassed by the sponsor was in support of one change, regarding broadening of the Albumex 4 and Albumex 5 ‘hypovolaemia/shock’ indication from second line to first line

treatment. This evidence took the form of published papers gathered using a TGA-approved literature search process. Despite the collection of numerous papers, only one published paper can be regarded as pivotal; the publication of the SAFE study by Finfer *et al* 2004⁵. Although there are reservations regarding possible biases towards therapeutic equivalence in the design and conduct of the study, overall the study results do support the proposed change in the 'hypovolaemia/shock' indication to include first line treatment. A caveat is that first- or second-line treatment with albumin solutions for fluid resuscitation of patients with traumatic brain injury cannot be recommended. The numerous other published studies, meta-analyses and guidelines provided by the sponsor are either supportive in that they do not identify net harm from use of albumin solutions as first line agents in fluid resuscitation or are considered to be irrelevant for the purpose of this submission.

The sponsor's clinical expert states that "supply and costs are not issues in the current supply of albumin products to the Australian market and are not considerations when considering the efficacy and safety of a product for use in a particular indication". In agreement with the second part of the expert's statement, the evaluator did not consider supply or cost in arriving at a recommendation.

Recommendations

The clinical evaluator recommended approval of the extension of the Albumex 4 and Albumex 5 'hypovolaemia/shock' indication as proposed by the sponsor.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

No new quality data were submitted with this application.

Nonclinical

No new nonclinical data were submitted.

Clinical

The clinical evaluator noted that there was an application to Medsafe some years ago to amend the indication in New Zealand. The amended indication [with underscoring added] is:

"Hypovolaemia / shock. Preservation of an adequate circulating volume should be the primary aim of therapy. Albumex 4 may, however, be the initial plasma expander of choice if shock is associated with significant hypoalbuminaemia (albumin concentration less than 25 g/Litre), or if it is clinically desirable to avoid the infusion of large volumes of crystalloid solutions. Albumex 4 may also be useful following initial resuscitation with crystalloid or synthetic colloid solutions in patients in whom extended support of the intravascular volume is required, such as seriously ill patients with multiple organ failure or the systemic capillary leak syndrome."

In regard to the extent of the literature search, the clinical evaluator was reasonably satisfied. The pivotal study of the submission was the SAFE study⁵ and it also was dominant in any meta-analysis. The clinical evaluator added, "It was a large, simple trial, focusing on mortality at 28 days rather than surrogates such as haemodynamic endpoints. The relative risk of death in the albumin arm at 28 days was 0.99 (95% CI 0.91-1.09)." There was 90% power to detect a 3% difference in mortality between treatment arms (based on estimated baseline mortality rates of 15%). The clinical evaluator considered SAFE to be the pivotal study of the submission by reason of the treatments used, the indication, the use of a relevant end point (death but without causality) and its size. The clinical evaluator was not clear if the study was originally intended to be a superiority study. However, any difference in mortality between study arms is small, except in some subgroups; "Subgroup analysis suggested unfavourable outcomes in the albumin arm in patients with traumatic brain injury (24.5% [albumin] versus 15.1% [saline] 28 day mortality, $p=0.009$)." This result was reported in a further analysis to 24 months post-study (SAFE-TBI).

The secondary outcomes are listed below (Table 1):

Table 1. Secondary outcomes in the SAFE study

- Survival time during the first 28 days
- Proportion of patients who had 1, 2, 3, 4 or 5 new organ failures
- Duration of mechanical ventilation
- Duration of renal-replacement therapy
- Duration of the ICU and hospital stay.

Death from any cause within 28 days was also examined in 6 pre-defined subgroups according to the presence or absence of: trauma, presence or absence of severe sepsis and presence or absence of ARDS.

The Delegate noted that these do not include adverse events attributable to saline (but as noted in the previous evaluation report, hyperchloraemic acidosis as an adverse event was rarely reported: "hyperchloraemic acidosis (albumin $n=1$, 0.03%, vs. saline $n=4$, 0.1%)") or benefits attributable to colloids (sparing of volume of infusion). The study was conducted in adults.

The clinical evaluator observed in regard to the sparing of infusion volumes that "The observation was also made that saline subjects received only 1.4-fold more fluid for resuscitation in ICU over the first four days than albumin patients. Traditionally it had been thought that approximately three fold more crystalloid was required than colloid in the context of fluid resuscitation, though the evidence for this tradition is somewhat unclear. The finding that volume of study fluid required was only fractionally higher in the saline arm than the albumin arm runs contrary to findings of many other published studies that built tighter haemodynamic monitoring into the study protocol. SAFE, however, might mirror actual practice better." The Delegate noted that the last statement was speculative.

If the study was intended to be an equivalence study, then the ITT analysis would not be sufficient ("All analyses were ITT yet in equivalence trials it is important to demonstrate that both ITT and PP cohorts show comparable outcomes. This was not done.")

Overall, the clinical evaluator considered that the SAFE study was supportive of the application; "...in that no mortality differences at 28 days were found between albumin and saline arms" but that, "Various aspects of the study design and conduct biased towards a finding of equivalence; most notably, only a strong differential drug effect on

⁵ The SAFE Study Investigators. A comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit. *NEJM* 2004; 350: 2247-56.

efficacy or safety would influence mortality at 28 days, given the various other influences on mortality in this group of subjects”.

Several other studies were described. These are of interest but lacked direct comparisons to Albumex and their meta-analyses were considered to be out of date.

Safety

In regard to safety, the clinical evaluator remarked that the reporting of adverse events following albumin treatment was poor and the reporting methods were not described. SAFE reported a mixed primary outcome (mortality may reflect efficacy and adverse effects).

Recommendations of Clinical Evaluator

The product information changes are not all uniformly supported, including the suggestion of broadening the indications of Albumex 20.

Taking the best possible view of SAFE, the clinical evaluator suggested: “Although there are reservations regarding possible biases towards therapeutic equivalence in the design and conduct of the study, overall the study results do support the proposed change in ‘hypovolaemia/shock’ indication to include first line treatment. A caveat is that first or second line treatment with albumin solutions for fluid resuscitation of patients with traumatic brain injury cannot be recommended.”

Risk Management Plan

None was provided. For a long registered product, this was considered acceptable by the Office of Product Review.

Risk Benefit Analysis

Delegate Considerations

1. The SAFE study may have been an exploratory study to exclude elevated mortality and may not have been intended to show superiority but to detect a real mortality difference of at least 3%⁶:

“The Saline versus Albumin Fluid Evaluation (SAFE) study is a randomised, controlled, blinded trial comparing intravenous albumin with saline for fluid resuscitation in critically ill patients. The study intends to recruit 7,000 patients over 18 years of age from 16 ICUs throughout Australia and New Zealand over 18 months. Eligible ICU patients who require fluid resuscitation will be randomised to receive either 4% human albumin solution (Albumex) or 0.9% sodium chloride (saline). The primary study outcome measure is 28-day all-cause mortality. Secondary outcomes include length of stay in the ICU, length of hospital stay, organ dysfunction as measured by the components of the Sepsis-related/Sequential Organ Failure Assessment (SOFA) score, and other physiological measures of response to fluid therapy.”

⁶ Efficacy of albumin in critically ill patients. The Saline vs. Albumin Fluid Evaluation (SAFE) Study (ISRCTN76588266): Design and conduct of a multi-centre, blinded randomised controlled trial of intravenous fluid resuscitation in critically ill patients. Authors: ANZICS Clinical Trials Group and Institute for International Health SAFE Study Investigators (Finfer *et al*). <http://www.bmj.com/content/326/7389/559/suppl/DC1>.

“Patients who satisfy the diagnostic criteria for severe sepsis and the acute respiratory distress syndrome at study entry are identified to allow *a priori* subgroup analysis.”

“Based on a 15% mortality rate in the control group, at 90% power, 7,000 patients will be required to detect a 3% or larger difference in the absolute risk of death between the two treatment groups. An absolute risk reduction of this magnitude is based upon the approximate minimal effect suggested by the lower confidence interval in the Cochrane Injury Group Albumin Reviewers Paper.”

The investigators have not stated that equivalence might be declared if a difference of <3% in the absolute death rate were not found.

2. The available data do not provide a firm suggestion that Albumex is harmful when used as a therapeutic alternative to normal saline in hypovolaemic patients. The detection of a signal in respect of traumatic brain injury suggests some sensitivity to detect an expected adverse effect. On the other hand, Albumex offered no particular advantages over a crystalloid infusion. It would seem unusual, based on SAFE, to select, as a therapeutic alternative to a crystalloid infusion, a colloid that may be associated with some risk of hypotension and with a low but not zero risk of transmission of adventitious infectious agents.

3. It is notable that Medsafe considered a narrower indication that is not quite first line but which does allow some discretion to prescribers, “*...Albumex 4 may, however, be the initial plasma expander of choice if shock is associated with significant hypoalbuminaemia (albumin concentration less than 25 g/Litre), or if it is clinically desirable to avoid the infusion of large volumes of crystalloid solutions. ...*” In practice, however, SAFE did not show a sparing effect in terms of the infusion of crystalloids, so this would have to be modified to, “*Albumex 4 may, however, be the initial plasma expander of choice if shock is associated with significant hypoalbuminaemia (albumin concentration less than 25 g/Litre...*” and that such discretion is exercised in the knowledge that this biological substance adds certain potential risks.

4. The clinical evaluator’s suggestions for the PI were otherwise supported. The PI should make it plain that SAFE did not show significant crystalloid sparing effects and that some risks (hypotension, infection) are associated with the selection of a biological substance.

The Delegate proposed that the application should be approved.

The registered indication should be,

Albumex 4 is indicated for the restoration of circulating blood volume in hypovolaemia/shock associated with significant hypoalbuminaemia (albumin concentration less than 25 g/Litre) and in other circumstances where a blood derived colloid infusion solution is clinically desirable. Albumex 4 may be useful following initial resuscitation with crystalloid or synthetic colloid solutions in patients in whom extended support of the intravascular volume is required, such as seriously ill patients with multiple organ failure or the systemic capillary leak syndrome.”

Response from Sponsor

The sponsor noted that the Delegate feels the changes to the Albumex 20 indications are more than “editorial changes”. CSL accept this.

Changes raised by the clinical evaluator were addressed in the sponsor’s response to the clinical evaluation report (CER).

The Delegate has commented on a range of aspects of the CER:

- The Delegate stated that the clinical evaluator noted the indication approved by Medsafe, this indication was based on a separate application approved in New Zealand in 2004.
- The Delegate noted that the clinical evaluator was satisfied with the SAFE study as the pivotal study of the submission. As clarified in the response to the CER the SAFE study was intended to be an equivalence study.
- The Delegate has noted that the key secondary outcomes do not include the adverse events attributable to saline or the potential benefits attributable to colloids (sparing of volume of infusion), this is correct. Neither the SAFE publication nor CSL has claimed that either of these endpoints is significant for Albumex.
- The Delegate also notes that the Evaluator found that the ratio of albumin to saline (over four days 1:1.4) is quite different to the “traditional” 1:3 ratio. CSL has not claimed a crystalloid sparing effect in the Albumex PI.

Safety

In regard to safety, CSL agreed that the methods for reporting adverse events in the SAFE study were not described and that adverse events reported were not detailed. It is also agreed that the primary outcome, mortality, may reflect efficacy and adverse effects.

Recommendations of clinical evaluator

CSL agreed with the assessments of the clinical evaluator that the overall study results support the proposed change in ‘Hypovolaemia/shock’ indication to support first line treatment. Furthermore, CSL has agreed (in response to the CER) to include a precaution relating to use of albumin in patients with traumatic brain injury.

Response to Delegate’s Comments

Comment 1:

The SAFE study may have been an exploratory study to exclude elevated mortality, that is, it was not intended to show superiority but to detect a real mortality difference of at least 3%. The investigators have not stated that equivalence might be declared if a difference of <3% in the absolute death rate were not found.

The introduction to the SAFE publication states that the hypothesis was that “..there is no difference in the 28-day rate of death from any cause” thus the study was intended as an equivalence trial based on a clinically significant difference in absolute mortality being 3%.

Since CSL has made no claims about superiority, the importance and relevance of the Delegate’s comment was not clear.

Comment 2:

The available data do not provide a firm suggestion that Albumex is harmful when used as a therapeutic alternative to normal saline in hypovolaemic patients. The detection of a signal in respect of traumatic brain injury suggests some sensitivity to detect an expected adverse effect. On the other hand, Albumex offered no particular advantages over a crystalloid infusion. It would seem unusual, based on SAFE, to select as a therapeutic alternative to a crystalloid infusion, a colloid that may be associated with some risks of hypotension and with a low but not zero risk of transmission of adventitious infectious agents.

CSL agreed with the Delegate’s statement:

- that the data do not suggest that Albumex is harmful when used as a therapeutic alternative to saline for hypovolaemia, and
- that the detection of a signal in respect of traumatic brain injury suggests some sensitivity to detect an expected adverse event.

The Delegate stated that Albumex offered no particular advantages over a crystalloid infusion. CSL noted, however, that the study did identify a potential benefit for albumin patients with sepsis, this is a signal that requires further consideration. Additionally, the Delegate's opinion on therapeutic alternatives was noted.

Comment 3

It is notable that Medsafe considered a narrower indication that is not quite first line but which does allow some discretion to prescribers, "...Albumex 4 may, however, be the initial plasma expander of choice if shock is associated with significant hypoalbuminaemia (albumin concentration less than 25g/Litre), or if it is clinically desirable to avoid the infusion of large volumes of crystalloid solutions..." In practice, however, SAFE did not show a sparing effect in terms of the infusion of crystalloids, so this would have to be modified to, "Albumex 4 may, however, if shock is associated with significant hypoalbuminaemia (albumin concentration less than 25g/Litre)..." and that such discretion is exercised in the knowledge that this biological substance adds certain potential risks.

CSL acknowledged that the Albumex hypovolaemia indication approved by Medsafe has been considered by the clinical evaluator and Delegate during this evaluation. Medsafe's own evaluation and conclusions were based on the information available/provided at the time of submission. The SAFE publication was the sole clinical data provided to Medsafe.

Comment 4

The evaluator's suggestions for the PI are otherwise supported. The PI should make it plain that SAFE did not show significant crystalloid-sparing effects and that some risks (hypotension, infection) are associated with the selection of a biological substance.

CSL has agreed with the majority of the evaluator's suggestions for the PI.

In response to the Delegate's concerns, relating to crystalloid sparing effects, CSL has included an amendment to the Clinical Trials section of the Albumex 4 PI to refer to the relative amounts of Albumex and saline delivered to patients in the SAFE study. No claim for crystalloid sparing has been made in the PI – nor has one been considered. The Albumex product information already includes a discussion of viral safety (and possible transmission of infection) and the risk of hypotension in the Precautions section. Also the Adverse Effects section of the PI contains additional information on the occurrence of hypotension, including prevalence in clinical trials and during post-marketing surveillance.

Proposed Actions

CSL welcomed the Delegate's initial decision to recommend approval of the extension of indications application and will work promptly with the Delegate to finalise the wording in product information.

However, with regard to the Delegate's proposed indication for Hypovolaemia/shock for Albumex 4, CSL wished to make minor modifications.

In the first sentence:

- circumstances where a plasma derived colloid infusion is clinically desirable would include situations of significant hypoalbuminaemia.
- the word “blood” has been replaced with “plasma” as it is more usual to use the statement “Albumex is a plasma derived product.”

In the second sentence:

- as this is a second area in which fluid resuscitation is described, the sponsor included the word “also”.
- deletion of the adjective “synthetic” to retain the maintenance indication

CSL proposed the following Hypovolaemia/Shock indication:

Albumex® 4 is indicated for the restoration of circulating blood volume in hypovolaemia/shock in circumstances where a plasma derived colloid infusion is clinically desirable. Albumex® 4 may also be useful following initial resuscitation with crystalloid or colloid solutions in patients in whom extended support of the intravascular volume is required, such as seriously ill patients with multiple organ failure or the systemic capillary leak syndrome.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate’s overview, as well as the sponsor’s response to these documents, recommended rejection of the application for registration of albumin (human) (Albumex) for a broadening of the indication to the restoration of circulating blood volume and amendment to PI.

In making this recommendation, the committee considered that there was insufficient evidence provided to support the broadening of the indication or for the PI amendments. In regard to the study that is known as SAFE, there was no evidence of superiority to the comparator (saline solution) provided and evidence of equivalence was not convincing.

The ACPM advised that there were safety concerns, in particular, the rate and severity of adverse events surrounding patients with brain injury treated with h-albumin was significantly higher. There is also a concern regarding the effect in liver disease as no data were supplied.

Outcome

The application was withdrawn by the sponsor. Negotiations concerning the text of the product information document are continuing. The sponsor was not able to provide a copy of the original, approved version of the independent investigator led study protocol, or a “per protocol” analysis of the SAFE study.

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Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Albumex[®] 4

Human Albumin 4 % (40 g/L)

Australia

NAME OF THE MEDICINE

Human albumin, solution for intravenous infusion.

DESCRIPTION

Albumex[®] 4 is prepared from pooled human plasma donated by Australia's voluntary non-remunerated donors. Albumex[®] 4 is a clear, slightly viscous liquid; it is almost colourless, yellow, amber or green. It is prepared using predominantly chromatographic techniques. It is a 4 % w/v protein solution which is iso-osmotic and iso-oncotic with human serum. It has a nominal osmolality of 250 mOsm/kg, is approximately isotonic and the pH is approximately 7. Albumex[®] 4 is heated at 60° C for 10 hours and incubated at low pH to inactivate viruses. The composition of Albumex[®] 4 is as follows:

Human Albumin 40 g/L
Sodium 140 mmol/L
Chloride 128 mmol/L
Octanoate 6.4 mmol/L

PHARMACOLOGY

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. The metabolic half-life of albumin *in vivo* is about 20 days and the turnover in an adult is approximately 15 g per day. There is rapid interchange of albumin between the intra- and extravascular spaces. Albumex[®] 4 has two main functions: maintenance of plasma colloid osmotic pressure and carriage of intermediate products in the transport and exchange of tissue metabolites.

The beneficial effect of albumin human for fluid resuscitation is thought to result principally from its contribution to colloid osmotic pressure (i.e. oncotic pressure).

Albumex[®] 4 is iso-oncotic with human serum. When infused into adequately hydrated patients its effect is to expand the circulating blood volume by an amount approximately equal to the volume of Albumex[®] 4 infused.

Pharmacokinetics

There is no specific pharmacokinetic information on Albumex[®] 4. The general information provided is based on published data for albumin.

Under normal conditions, the total exchangeable albumin pool is 4-5 g/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 average half-life of albumin is about 19 days. The balance between synthesis and breakdown is normally achieved by feedback regulation. Elimination is predominantly intracellular and due to lysosome proteases.

In healthy subjects, less than 10 % of infused albumin leaves the intravascular compartment during the first 2 hours following infusion. There is considerable individual variation in the effect on plasma volume. In some patients the plasma volume can remain increased for some hours. However, in critically ill patients, albumin can leak out of the vascular space in substantial amounts at an unpredictable rate.

CLINICAL TRIALS

The Saline versus Albumin Fluid Evaluation Study

The Saline versus Albumin Fluid Evaluation (SAFE) study was conducted by the Australian and New Zealand Intensive Care Society Clinical Trials Group. This large multicentre, double blind, prospective randomised controlled trial was conducted to determine the effect of fluid resuscitation with either albumin or saline on mortality in a heterogeneous population of patients in the Intensive Care Unit (ICU). The SAFE study randomised 6997 patients to receive either albumin 4 % (Albumex[®] 4 in blinded labelling, n=3497) or saline (n=3500). The two groups had similar baseline characteristics. No predetermined clinical margin of superiority or non-inferiority was made. The study was intended to detect a real mortality difference of at least 3% between the treatment groups, based on an enrolment of 7,000 patients and an estimated baseline mortality rate of 15%.

Randomisation was stratified at each centre when the patients were admitted to ICU to ensure that each institution treated equal numbers of patients for each treatment. Patients with burns or those requiring plasmapheresis and those patients admitted to ICU after cardiac bypass surgery and liver transplant were excluded from the study. The statistical results presented derived from an intention to treat analysis. The study was not explicitly a superiority study and no “per protocol” analysis is available. It is not known to what extent the statistical results of a “per protocol” analysis would agree with, or differ from, the results of the intention to treat analysis.

Death from any cause during the 28 days after randomisation was the primary outcome measure. There were 726/3473 (20.9 %) deaths in the albumin group and 729/3460 (21.1 %) deaths in the saline group (relative risk of death 0.99, 95 % confidence interval 0.91 to 1.09, p=0.87).

There were no statistically significant differences between the two groups in the secondary outcomes measured: mean (\pm SD) number of days spent in ICU (6.5 ± 6.6 in the albumin group and 6.2 ± 6.2 in the saline group, $p=0.44$), days spent in hospital (15.3 ± 9.6 and 15.6 ± 9.6 respectively, $p=0.30$), days of mechanical ventilation (4.5 ± 6.1 and 4.3 ± 5.7 , respectively, $p=0.74$) or days of renal replacement therapy (0.5 ± 2.3 and 0.4 ± 2.0 , respectively, $p=0.41$). The proportion of patients with new single or multiple organ failure was similar in the two groups ($p=0.85$). There was no significant difference in survival times during the first 28 days between the two groups ($p=0.96$).

On each of the first three study days, the patients who had been randomly assigned to receive albumin received less study fluid than did those assigned to saline, resulting in a greater net positive fluid balance in the saline group on each of those days. The ratios of the volume of albumin to the volume of saline administered during the first four days were as follows: 1:1.3 on day 1, 1:1.6 on day 2, 1:1.3 on day 3, and 1:1.2 on day 4. Overall during the first four days the study showed a ratio of 1.4:1 in the volume of saline used to compare albumin.

This study concluded that in a heterogeneous group of patients in the ICU, use of either 4 % albumin or normal (0.9 %) saline for fluid resuscitation results in similar mortality at 28 days. The trial did not examine the comparative safety of albumin use as an initial resuscitation fluid in pre-hospital, surgery or emergency department settings.

Predefined sub-group analyses were performed for patients with trauma, severe sepsis and acute respiratory distress syndrome as part of the SAFE study. There was a trend towards increased mortality in patients with trauma treated with albumin, which was due to a worse outcome in those patients with trauma and associated brain injury. Conversely, there was a trend towards a better outcome with albumin in patients with severe sepsis. Both these trends should be interpreted with caution. Specifically designed and appropriately powered studies are needed to establish whether these are real treatment effects or due to chance.

A post hoc, follow-up study of patients with traumatic brain injury enrolled in the SAFE Study was published in 2007. This post hoc analysis found that, when comparing albumin with saline for intravascular fluid resuscitation in the ICU, higher mortality rates were observed among patients with severe traumatic brain injury (Glasgow Coma Score, 3 to 8) who received 4 % albumin than among those who received saline. The authors note the study was designed post hoc, and some data were collected retrospectively. The authors add it remains possible that the results represent a chance subgroup finding and that the biologic mechanisms for the observed differences in mortality are unclear such that further detailed analyses of biologic mechanisms associated with intracranial hypertension are required.

INDICATIONS

Hypovolaemia/shock

Preservation of an adequate circulating blood volume should be the primary aim of therapy. The initial resuscitating fluid should not be a human blood product, but rather an alternative plasma volume expander should be used as first-line replacement. Albumex[®] 4 may, however, be the initial plasma expander of choice if shock is associated with significant hypoalbuminaemia (albumin concentration

less than 25 g/L), or if it is clinically desirable to avoid the infusion of large volumes of crystalloid solutions.

Albumex[®] 4 may also be useful following initial resuscitation with crystalloid or synthetic colloid solutions in patients in whom extended support of the intravascular volume is required, such as seriously ill patients with multiple organ failure or the systemic capillary leak syndrome.

Cardiopulmonary bypass

Albumex[®] 4 may be used for priming the pump for cardiopulmonary bypass surgery for patients with poor left ventricular function, and other complicating factors such as long bypass time, anaemia or repeat surgery. For post-operative hypovolaemia Albumex[®] 4 may be used if further colloid is required after a moderate amount of synthetic colloid (1-2 L) has been given, or there is ongoing bleeding or anaemia, until cross-matched blood is available.

Plasma exchange

Albumex[®] 4 is indicated as a replacement solution in plasma exchange procedures particularly when the volume exchanged exceeds 20 mL/kg body weight. In patients with thrombotic thrombocytopenic purpura, fresh frozen plasma may be a preferred replacement.

CONTRAINDICATIONS

Albumex[®] 4 must not be used if there is a history of allergy to this product. Albumin is contraindicated in patients with cardiac failure, pulmonary oedema or severe anaemia.

PRECAUTIONS

Allergic reactions: Hypersensitivity reactions occur rarely when human albumin solutions are administered because of the human origin of the product. Should an anaphylactic reaction to Albumex[®] 4 develop, the infusion should be stopped and treatment instituted with adrenaline, hydrocortisone and anti-histamines as appropriate.

Hypotension: Hypotension has been associated with human albumin solutions. Hypotension following administration of albumin can aggravate myocardial depression when present in patients with shock.

Circulatory overload: Patients with a history of cardiac failure or pulmonary oedema or who have renal insufficiency, severe or stabilised chronic anaemia or are on cardiopulmonary bypass are at special risk of developing circulatory overload if the dosage and rate of infusion are not adjusted to the patients circulatory situation. When being infused with Albumex[®] 4 they should be carefully monitored for this potential complication. At the first clinical signs of circulatory overload (headache, dyspnoea, jugular vein congestion), or increased blood pressure or raised venous pressure associated with pulmonary oedema, the infusion is to be stopped immediately.

The rise in blood pressure which may follow rapid administration of albumin necessitates observation of the injured patient to detect bleeding points which failed to bleed at the lower blood pressure; otherwise, new haemorrhage and shock may occur.

The use of albumin for fluid resuscitation of patients with traumatic brain injury is not recommended.

Albumex[®] 4 contains trace amounts of aluminium ($\leq 200 \mu\text{g/L}$). Accumulation of aluminium in patients with chronic renal insufficiency has led to toxic manifestations such as hypercalcaemia, vitamin D-refractory osteodystrophy, anaemia and severe progressive encephalopathy. Therefore, when large volumes of albumin are contemplated for administration to such patients, serious consideration of these potential risks relative to the anticipated benefits should be given.

Pathogen safety

This product is made from human plasma. Products made from human plasma may contain infectious agents such as viruses and theoretically Creutzfeldt-Jakob Disease (CJD) agents, that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain infectious agents and by testing for the presence of certain viral markers.

In addition, virus inactivation/removal procedures are included in the manufacturing process. The current process and procedures applied in the manufacture of this product are effective against enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and the non-enveloped virus, hepatitis A (HAV). These procedures contribute significantly to ensure freedom from parvovirus B19.

Despite these measures, such products may still potentially transmit disease. There is also the possibility that other known or unknown infectious agents may be present in such products.

Vaccination for patients in receipt of medicinal products from human plasma should be considered where appropriate.

Any case of infection associated with the use of the product should be reported to the Australian Red Cross Blood Service, together with details of batches given.

Effects on fertility

No studies examining the effect of Albumex[®] 4 on fertility have been conducted.

Use in pregnancy

Reproductive toxicity studies with Albumex[®] 4 in animals have not been conducted. Such studies are impracticable due to the development of antibodies to human albumin in animal models.

The use of Albumex[®] 4 in human pregnancy has not been established in controlled clinical trials; therefore, it should be given to pregnant women only if clearly needed.

Use in lactation

Like endogenous serum albumin, Albumex[®] 4 may be excreted in milk. No safety information is available.

Paediatric use

There have been no specific clinical studies of Albumex[®] 4 in children.

Use in the elderly

There have been no specific clinical studies of Albumex[®] 4 in the elderly.

Carcinogenicity

Specific studies have not been conducted.

Genotoxicity

Specific studies have not been conducted.

Interactions with other medicines

Hypotension has been reported in patients given albumin who are on angiotensin converting enzyme (ACE) inhibitors. The addition of other drugs to Albumex[®] 4 has not been evaluated. (see **COMPATIBILITY WITH OTHER FLUIDS**).

Effect on laboratory tests

Albumin is an endogenous plasma protein so no specific effects on laboratory tests are anticipated. However, administration of Albumex[®] 4 which may contain some bound bilirubin has been shown to result in elevated serum bilirubin in some patients.

ADVERSE EFFECTS

Adverse reactions to albumin solutions are uncommon and are usually mild and transient.

Adverse reactions with albumin solutions in general include hypotension, chills, fever and allergic reactions including anaphylaxis, urticaria, skin rashes, nausea, vomiting and increased salivation. Mild reactions such as mild hypotension, flushing, urticaria, fever, and nausea normally disappear rapidly when the infusion rate is slowed down or the infusion is stopped (see **Monitoring advice**).

Very rarely, severe allergic reactions such as anaphylactic shock may occur. In these cases, the infusion should be stopped and an appropriate treatment should be initiated.

Adverse events in clinical trials

Adverse reactions by body system from the SAFE study comparing albumin and saline are provided in Table 1.

Table 1: Total adverse reactions reported from the SAFE study

<i>Product</i>	<i>Albumex[®] 4 (n=3497)</i>	<i>Saline (n=3500)</i>
<i>Total adverse drug reactions</i>	22	14
<i>Hepatobiliary disorders</i>		
ascites	-	1
<i>Renal & urinary disorders</i>		
hyperchloraemic acidosis	1	4
hypermnatraemia	1	1
lactic acidosis	-	1
<i>Respiratory, thoracic & mediastinal</i>		
hypoxia	7	1
pleural effusion	-	1
pulmonary embolus	-	1
pulmonary oedema	12	3
<i>Skin & subcutaneous tissue</i>		
oedema	-	1
<i>Vascular</i>		
hypotension	1	-

In an earlier generation of Albumex[®], when used in plasma exchange, 1 % (1/99) of patients had a clinically significant increase in prothrombin time and there was a reduction in levels of potassium, calcium, bicarbonate, total serum protein concentrations and platelet count. These results could reasonably be expected in a plasma exchange procedure.

Post-marketing surveillance

Post-market reporting of adverse reactions is voluntary and from a population of uncertain size, and consequently it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

Overall a low number of reports have been received for the current generation Albumex[®] 4 which primarily involve hypotensive and allergic reactions. The main adverse reactions reported during routine surveillance for the current product are as follows: hypotension, tachycardia, flushing, dizziness, nausea, chills, pyrexia, dyspnoea, anaphylactoid/anaphylactic reaction, urticaria, pruritus and rash (pruritic, macular, generalised). True anaphylactic reactions occur rarely.

DOSAGE AND ADMINISTRATION

Dosage

Hypovolaemia/shock

The management of hypovolaemic shock usually requires the intravenous infusion of at least one litre of Albumex[®] 4 into an average adult patient.

The total volume required cannot be accurately predicted, since it depends on such factors as the initial extracellular fluid volume deficit and the continuing rate of fluid loss.

Plasma exchange

In plasma exchange the infusion rate should be adjusted to match the rate of removal.

Monitoring advice

To avoid circulatory overload the rate and volume of infusion should be monitored frequently.

Myocardial function should also be monitored e.g. central venous pressure, arterial pressure and pulse rate.

It is also recommended that plasma electrolytes, prothrombin time, biochemistry and haematological status be monitored.

Administration

Albumex[®] 4 should always be administered by intravenous (IV) infusion using appropriate IV administration equipment. Albumex[®] 4 is packaged in a glass bottle that must be vented during use.

Albumex[®] 4 does not contain an antimicrobial preservative. It must, therefore, be used immediately after opening the bottle. Any unused solution should be discarded appropriately. Use in one patient on one occasion only.

It is strongly recommended that every time Albumex[®] 4 is administered to a patient, the name and batch number of the product be recorded in order to maintain a link between the patient and the batch of the product.

If the product has been stored in the refrigerator it should be allowed to reach room temperature before administration. Do not use if the solution has been frozen.

The product is normally clear or slightly opalescent but, if it appears to be turbid by transmitted light, it must not be used and the bottle should be returned unopened to the Australian Red Cross Blood Service.

COMPATIBILITY WITH OTHER FLUIDS

The addition of other drugs to Albumex[®] 4 has not been evaluated.

Albumex[®] 4 should not be mixed with protein hydrolysates, amino acid solutions, solutions containing alcohol, or solutions containing drugs that bind to albumin e.g. calcium channel blockers, antibiotics and benzodiazepines.

OVERDOSAGE

Excess human albumin may lead to circulatory overload (see **PRECAUTIONS**).

PRESENTATION AND STORAGE CONDITIONS

Albumex[®] 4 is issued in glass bottles in three sizes:
2 g of human albumin in 50 mL of electrolyte solution;
10 g of human albumin in 250 mL of electrolyte solution;
20 g of human albumin in 500 mL of electrolyte solution.

Storage

Store below 30° C. This product must not be frozen. Protect from light. Do not use after the expiry date.

NAME AND ADDRESS OF THE SPONSOR

CSL Limited ABN 99 051 588 348
189 - 209 Camp Road
Broadmeadows VIC 3047
AUSTRALIA
Distributed by: Australian Red Cross Blood Service

POISON SCHEDULE OF THE MEDICINE

Unscheduled

Date of Therapeutic Goods Administration approval: 23 September 2008

Date of most recent amendment: 12 September 2011

[®] Registered trademark of CSL Limited.

For Medical/Technical Enquiries:

TOLL FREE: 1800 642 865

For Customer Service Enquiries:

TOLL FREE: 1800 063 892
customerservice.plasmaproducts@csl.com.au

www.cslbiotherapies.com.au

Product Information

Albumex[®] 5

Human Albumin 50 g/L

Australia

NAME OF THE MEDICINE

Human albumin, solution for intravenous infusion.

DESCRIPTION

Albumex[®] 5 is prepared from pooled human plasma donated by Australia's voluntary non-remunerated donors. Albumex[®] 5 is a clear, slightly viscous liquid; it is almost colourless, yellow, amber or green. It is prepared using predominantly chromatographic techniques. It is a 5 % w/v protein solution which is iso-osmotic and iso-oncotic with human serum. It has a nominal osmolality of 250 mOsm/kg, is approximately isotonic and the pH is approximately 7. Albumex[®] 5 is heated at 60°C for 10 hours and incubated at low pH to inactivate viruses.

The composition of Albumex[®] 5 is as follows:

Human Albumin	50 g/Litre
Sodium	140 mmol/Litre
Chloride	125 mmol/Litre
Octanoate	8 mmol/Litre

PHARMACOLOGY

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. The metabolic half-life of albumin *in vivo* is about 20 days and the turnover in an adult is approximately 15g per day. There is rapid interchange of albumin between the intra- and extravascular spaces. Albumex[®] 5 has two main functions: maintenance of plasma colloid osmotic pressure and carriage of intermediate products in the transport and exchange of tissue metabolites.

The beneficial effect of albumin human for fluid resuscitation is thought to result principally from its contribution to colloid osmotic pressure (i.e. oncotic pressure).

Albumex[®] 5 is iso-oncotic with human serum. When infused into adequately hydrated patients its effect is to expand the circulating blood volume by an amount approximately equal to the volume of Albumex[®] 5 infused.

Pharmacokinetics

There is no specific pharmacokinetic information on Albumex[®] 5. The general information provided is based on published data for albumin.

Under normal conditions, the total exchangeable albumin pool is 4-5 g/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 average half-life of albumin is about 19 days. The balance between synthesis and breakdown is normally achieved by feedback regulation. Elimination is predominantly intracellular and due to lysosome proteases.

In healthy subjects, less than 10 % of infused albumin leaves the intravascular compartment during the first 2 hours following infusion. There is considerable individual variation in the effect on plasma volume. In some patients the plasma volume can remain increased for some hours. However, in critically ill patients, albumin can leak out of the vascular space in substantial amounts at an unpredictable rate.

CLINICAL TRIALS

The Saline versus Albumin Fluid Evaluation Study

The Saline versus Albumin Fluid Evaluation (SAFE) study was conducted by the Australian and New Zealand Intensive Care Society Clinical Trials Group. This large multicentre, double blind, prospective randomised controlled trial was conducted to determine the effect of fluid resuscitation with either albumin or saline on mortality in a heterogeneous population of patients in the Intensive Care Unit (ICU). The SAFE study randomised 6997 patients to receive either albumin 4 % (Albumex[®] 4 in blinded labelling, n=3497) or saline (n=3500). The two groups had similar baseline characteristics. No predetermined clinical margin of superiority or non-inferiority was made. The study was intended to detect a real mortality difference of at least 3% between the treatment groups, based on an enrolment of 7,000 patients and an estimated baseline mortality rate of 15%.

Randomisation was stratified at each centre when the patients were admitted to ICU to ensure that each institution treated equal numbers of patients for each treatment. Patients with burns or those requiring plasmapheresis and those patients admitted to ICU after cardiac bypass surgery and liver transplant were excluded from the study. The statistical results presented derived from an intention to treat analysis. The study was not explicitly a superiority study and no “per protocol” analysis is available. It is not known to what extent the statistical results of a “per protocol” analysis would agree with, or differ from, the results of the intention to treat analysis.

Death from any cause during the 28 days after randomisation was the primary outcome measure. There were 726/3473 (20.9 %) deaths in the albumin group and 729/3460 (21.1 %) deaths in the saline group (relative risk of death 0.99, 95 % confidence interval 0.91 to 1.09, p=0.87).

There were no statistically significant differences between the two groups in the secondary outcomes measured: mean (\pm SD) number of days spent in ICU (6.5 \pm 6.6 in the albumin group and 6.2 \pm 6.2 in the saline group, p=0.44), days spent in hospital (15.3 \pm 9.6 and 15.6 \pm 9.6 respectively, p=0.30), days of mechanical ventilation (4.5 \pm 6.1 and 4.3 \pm 5.7, respectively, p=0.74) or days of renal replacement therapy (0.5 \pm 2.3 and 0.4 \pm 2.0, respectively, p=0.41). The proportion of patients with new single or multiple organ failure was similar in the two groups (p=0.85). There was no significant difference in survival times during the first 28 days between the two groups (p=0.96).

On each of the first three study days, the patients who had been randomly assigned to receive albumin received less study fluid than did those assigned to saline, resulting in a greater net positive fluid balance in the saline group on each of those days. The ratios of the

volume of albumin to the volume of saline administered during the first four days were as follows: 1:1.3 on day 1, 1:1.6 on day 2, 1:1.3 on day 3, and 1:1.2 on day 4. Overall during the first four days the study showed a ratio of 1.4:1 in the volume of saline used to compare albumin.

This study concluded that in a heterogeneous group of patients in the ICU, use of either 4 % albumin or normal (0.9 %) saline for fluid resuscitation results in similar mortality at 28 days. The trial did not examine the comparative safety of albumin use as an initial resuscitation fluid in pre-hospital, surgery or emergency department settings.

Predefined sub-group analyses were performed for patients with trauma, severe sepsis and acute respiratory distress syndrome as part of the SAFE study. There was a trend towards increased mortality in patients with trauma treated with albumin, which was due to a worse outcome in those patients with trauma and associated brain injury. Conversely, there was a trend towards a better outcome with albumin in patients with severe sepsis. Both these trends should be interpreted with caution. Specifically designed and appropriately powered studies are needed to establish whether these are real treatment effects or due to chance.

A post hoc, follow-up study of patients with traumatic brain injury enrolled in the SAFE Study was published in 2007. This post hoc analysis found that, when comparing albumin with saline for intravascular fluid resuscitation in the ICU, higher mortality rates were observed among patients with severe traumatic brain injury (Glasgow Coma Score, 3 to 8) who received 4 % albumin than among those who received saline. The authors note the study was designed post hoc, and some data were collected retrospectively. The authors add it remains possible that the results represent a chance subgroup finding and that the biologic mechanisms for the observed differences in mortality are unclear such that further detailed analyses of biologic mechanisms associated with intracranial hypertension are required.

INDICATIONS

Hypovolaemia/shock Preservation of an adequate circulating blood volume should be the primary aim of therapy. The initial resuscitating fluid should not be a human blood product, but rather an alternative plasma volume expander should be used as first-line replacement. Albumex[®] 5 may, however, be the initial plasma expander of choice if shock is associated with significant hypoalbuminaemia (albumin concentration less than 25 g/L), or if it is clinically desirable to avoid the infusion of large volumes of crystalloid solutions. Albumex[®] 5 may also be useful following initial resuscitation with crystalloid or synthetic colloid solutions in patients in whom extended support of the intravascular volume is required, such as seriously ill patients with multiple organ failure or the systemic capillary leak syndrome.

Cardiopulmonary bypass Albumex[®] 5 may be used for priming the pump for cardiopulmonary bypass surgery for patients with poor left ventricular function, and other complicating factors such as long bypass time, anaemia or repeat surgery. For post-operative hypovolaemia Albumex[®] 5 may be used if further colloid is required after a moderate amount of synthetic colloid (1-2 L) has been given, or there is ongoing bleeding or anaemia, until cross-matched blood is available.

Plasma exchange Albumex[®] 5 is indicated as a replacement solution in plasma exchange procedures, particularly when the volume exchanged exceeds 20 mL/kg body weight. In patients with thrombotic thrombocytopenic purpura, fresh frozen plasma may be a preferred replacement.

CONTRAINDICATIONS

Albumex[®] 5 must not be used if there is a history of allergy to this product. Albumin is contraindicated in patients with cardiac failure, pulmonary oedema or severe anaemia.

PRECAUTIONS

Allergic reactions: Hypersensitivity reactions occur rarely when human albumin solutions are administered because of the human origin of the product. Should an anaphylactic reaction to Albumex[®] 5 develop, the infusion should be stopped and treatment instituted with adrenaline, hydrocortisone and anti-histamines, as appropriate.

Hypotension: Hypotension has been associated with human albumin solutions. Hypotension following administration of albumin can aggravate myocardial depression when present in patients with shock.

Circulatory overload: Patients with a history of cardiac failure or pulmonary oedema or who have renal insufficiency, severe or stabilised chronic anaemia or are on cardiopulmonary bypass are at special risk of developing circulatory overload if the dosage and rate of infusion are not adjusted to the patients circulatory situation. When being infused with Albumex[®] 5 they should be carefully monitored for this potential complication. At the first clinical signs of circulatory overload (headache, dyspnoea, jugular vein congestion), or increased blood pressure or raised venous pressure associated with pulmonary oedema, the infusion is to be stopped immediately.

The rise in blood pressure which may follow rapid administration of albumin necessitates observation of the injured patient to detect bleeding points which failed to bleed at the lower blood pressure; otherwise, new haemorrhage and shock may occur.

The use of albumin for fluid resuscitation of patients with traumatic brain injury is not recommended.

Albumex[®] 5 contains trace amounts of aluminium ($\leq 200 \mu\text{g/L}$). Accumulation of aluminium in patients with chronic renal insufficiency has led to toxic manifestations such as hypercalcaemia, vitamin D-refractory osteodystrophy, anaemia and severe progressive encephalopathy. Therefore, when large volumes of albumin are contemplated for administration to such patients, serious consideration of these potential risks relative to the anticipated benefits should be given.

Pathogen safety

This product is made from human plasma. Products made from human plasma may contain infectious agents such as viruses and theoretically Creutzfeldt-Jacob Disease (CJD) agents, that can cause disease. The risk that such products will transmit an infectious agent has been

reduced by screening plasma donors for prior exposure to certain infectious agents and by testing for the presence of certain viral markers.

In addition, virus inactivation/removal procedures are included in the manufacturing process. The current process and procedures applied in the manufacture of this product are effective against enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and the non-enveloped virus, hepatitis A (HAV). These procedures contribute significantly to ensure freedom from parvovirus B19. Despite these measures, such products may still potentially transmit disease. There is also the possibility that other known or unknown infectious agents may be present in such products.

Vaccination for patients in receipt of medicinal products from human plasma should be considered where appropriate.

Any case of infection associated with the use of the product should be reported to the Australian Red Cross Blood Service, together with details of batches given.

Effects on fertility

No studies examining the effect of Albumex[®] 5 on fertility have been conducted.

Use in pregnancy

Reproductive toxicity studies with Albumex[®] 5 in animals have not been conducted. Such studies are impracticable due to the development of antibodies to human albumin in animal models.

The use of Albumex[®] 5 in human pregnancy has not been established in controlled clinical trials; therefore, it should be given to pregnant women only if clearly needed.

Use in lactation

Like endogenous serum albumin, Albumex[®] 5 may be excreted in milk. No safety information is available.

Paediatric use

There have been no specific clinical studies of Albumex[®] 5 in children.

Use in the elderly

There have been no specific clinical studies of Albumex[®] 5 in the elderly.

Carcinogenicity

Specific studies have not been conducted.

Genotoxicity

Specific studies have not been conducted.

Interactions with other medicines

Hypotension has been reported in patients given albumin who are on angiotensin - converting enzyme (ACE) inhibitors. The addition of other drugs to Albumex[®] 5 has not been evaluated (see **COMPATIBILITY WITH OTHER FLUIDS**).

Effect on laboratory tests

Albumin is an endogenous plasma protein so no specific effects on laboratory tests are anticipated. However, administration of Albumex[®] 5 which may contain some bound bilirubin has been shown to result in elevated serum bilirubin in some patients.

ADVERSE EFFECTS

Adverse reactions to albumin solutions are uncommon and are usually mild and transient.

Adverse reactions with albumin solutions in general include hypotension, chills, fever and allergic reactions including anaphylaxis, urticaria, skin rashes, nausea, vomiting and increased salivation. Mild reactions such as mild hypotension, flushing, urticaria, fever, and nausea normally disappear rapidly when the infusion rate is slowed down or the infusion is stopped (see ***Monitoring advice***).

Very rarely, severe allergic reactions such as anaphylactic shock may occur. In these cases, the infusion should be stopped and an appropriate treatment should be initiated.

Adverse events in clinical trials

Results from studies with Albumex[®] 4 and 5 (4 % and 5 % albumin solutions respectively) may be applicable.

Adverse reactions by body system from the SAFE study comparing albumin and saline are provided in Table 1.

Table 1: Total adverse reactions reported from the SAFE study

<i>Product</i>	<i>Albumex[®] 4 (n=3497)</i>	<i>Saline (n=3500)</i>
<i>Total adverse drug reactions</i>	<i>22</i>	<i>14</i>
<i>Hepatobiliary disorders</i>		
ascites	-	1
<i>Renal & urinary disorders</i>		
hyperchloraemic acidosis	1	4
hyponatraemia	1	1
lactic acidosis	-	1
<i>Respiratory, thoracic & mediastinal</i>		
hypoxia	7	1
pleural effusion	-	1
pulmonary embolus	-	1
pulmonary oedema	12	3
<i>Skin & subcutaneous tissue</i>		
oedema	-	1
<i>Vascular</i>		
hypotension	1	-

In an earlier generation of Albumex[®], when used in plasma exchange, 1 % (1/99) of patients had a clinically significant increase in prothrombin time and there was a reduction in levels of potassium, calcium, bicarbonate, total serum protein concentrations and platelet count. These results could reasonably be expected in a plasma exchange procedure.

Post-marketing surveillance

Post-market reporting of adverse reactions is voluntary and from a population of uncertain size, and consequently it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

Overall a low number of reports have been received for the current generation Albumex[®] 4 (which may be applicable to Albumex[®] 5) which primarily involve hypotensive and allergic reactions. The main adverse reactions reported during routine surveillance for the current product are as follows: hypotension, tachycardia, flushing, dizziness, nausea, chills, pyrexia, dyspnoea, anaphylactoid/anaphylactic reaction, urticaria, pruritus and rash (pruritic, macular, generalised). True anaphylactic reactions occur rarely.

DOSAGE AND ADMINISTRATION

Dosage

Hypovolaemia/shock

The management of hypovolaemic shock usually requires the intravenous infusion of at least one litre of Albumex[®] 5 into an average adult patient.

The total volume required cannot be accurately predicted, since it depends on such factors as the initial extracellular fluid volume deficit and the continuing rate of fluid loss.

Plasma exchange

In plasma exchange the infusion rate should be adjusted to match the rate of removal.

Monitoring advice

To avoid circulatory overload the rate and volume of infusion should be monitored frequently.

Myocardial function should also be monitored e.g. by measurement of the central venous pressure, arterial pressure and pulse rate.

It is also recommended that plasma electrolytes, prothrombin time, biochemistry and haematological status be monitored.

Administration

Albumex[®] 5 should always be administered by intravenous (IV) infusion using appropriate IV administration equipment. Albumex[®] 5 is packaged in a glass bottle that must be vented during use.

Albumex[®] 5 does not contain an antimicrobial preservative. It must, therefore, be used immediately after opening the bottle. Any unused solution should be discarded appropriately. Use in one patient on one occasion only.

It is strongly recommended that every time Albumex[®] 5 is administered to a patient, the name and batch number of the product be recorded in order to maintain a link between the patient and the batch of the product.

If the product has been stored in the refrigerator it should be allowed to reach room temperature or body temperature before administration. Do not use if the solution has been frozen.

The product is normally clear or slightly opalescent but, if it appears to be turbid by transmitted light, it must not be used and the bottle should be returned unopened to the Australian Red Cross Blood Service.

COMPATIBILITY WITH OTHER FLUIDS

The addition of other drugs to Albumex[®] 5 has not been evaluated.

Albumex[®] 5 should not be mixed with protein hydrolysates, amino acid solutions, solutions containing alcohol, or solutions containing drugs that bind to albumin e.g. calcium channel blockers, antibiotics and benzodiazepines.

OVERDOSAGE

Excess human albumin may lead to circulatory overload (see **PRECAUTIONS**).

PRESENTATION AND STORAGE CONDITIONS

Albumex[®] 5 is issued in glass bottles in three sizes:
2.5 g of human albumin in 50 mL of electrolyte solution;
12.5 g of human albumin in 250 mL of electrolyte solution;
25 g of human albumin in 500 mL of electrolyte solution.

Storage

Store below 30°C. This product must not be frozen. Protect from light. Do not use after the expiry date.

NAME AND ADDRESS OF THE SPONSOR

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Broadmeadows VIC 3047
AUSTRALIA

Distributed by: Australian Red Cross Blood Service

POISON SCHEDULE OF THE MEDICINE

Unscheduled

Date of Therapeutic Goods Administration approval: 23 September 2008

Date of most recent amendment: 12 September 2011

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Product Information

Albumex[®] 20

Human Albumin 20 % (200 g/L)

Australia

NAME OF THE MEDICINE

Human albumin, solution for intravenous infusion.

DESCRIPTION

Albumex[®] 20 is prepared from pooled human plasma donated by Australia's voluntary non-remunerated donors. Albumex[®] 20 is a clear, slightly viscous liquid; it is almost colourless, yellow, amber or green. It is prepared using predominantly chromatographic techniques. It is a 20 % w/v protein solution, which is hyperoncotic with human serum and supplies the oncotic equivalence of approximately four times its volume of human plasma. It is hypo-osmotic compared to human serum. It has a nominal osmolality of 130 mOsm/kg, is approximately isotonic and the pH is approximately 7. Albumex[®] 20 is heated at 60° C for 10 hours and incubated at low pH to inactivate viruses. The composition of Albumex[®] 20 is as follows:

Human Albumin 200 g/L

Sodium 48 - 100 mmol/L

Octanoate 32 mmol/L

PHARMACOLOGY

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. The metabolic half-life of albumin *in vivo* is about 20 days and the turnover in an adult is approximately 15 g per day. There is rapid interchange of albumin between the intra and extravascular spaces.

Albumex[®] 20 is hyperoncotic with human serum and supplies the oncotic equivalence of approximately four times its volume of human plasma. Albumex[®] 20 has two main functions: maintenance of plasma colloid osmotic pressure and carriage of intermediate products in the transport and exchange of tissue metabolites.

The beneficial effect of albumin human for fluid resuscitation is thought to result principally from its contribution to colloid osmotic pressure (i.e. oncotic pressure).

Pharmacokinetics

There is no specific pharmacokinetic information on Albumex® 20. The general information provided is based on published data for albumin.

Under normal conditions, the total exchangeable albumin pool is 4-5 g/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 average half-life of albumin is about 19 days. The balance between synthesis and breakdown is normally achieved by feedback regulation. Elimination is predominantly intracellular and due to lysosome proteases.

In healthy subjects, less than 10 % of infused albumin leaves the intravascular compartment during the first 2 hours following infusion. There is considerable individual variation in the effect on plasma volume. In some patients the plasma volume can remain increased for some hours. However, in critically ill patients, albumin can leak out of the vascular space in substantial amounts at an unpredictable rate.

CLINICAL TRIALS

The Saline versus Albumin Fluid Evaluation Study

The Saline versus Albumin Fluid Evaluation (SAFE) study was conducted by the Australian and New Zealand Intensive Care Society Clinical Trials Group. This large multicentre, double blind, prospective randomised controlled trial was conducted to determine the effect of fluid resuscitation with either albumin or saline on mortality in a heterogeneous population of patients in the Intensive Care Unit (ICU). The SAFE study randomised 6997 patients to receive either albumin 4 % (Albumex® 4 in blinded labelling, n=3497) or saline (n=3500). The two groups had similar baseline characteristics. No predetermined clinical margin of superiority or non-inferiority was made. The study was intended to detect a real mortality difference of at least 3% between the treatment groups, based on an enrolment of 7,000 patients and an estimated baseline mortality rate of 15%.

Randomisation was stratified at each centre when the patients were admitted to ICU to ensure that each institution treated equal numbers of patients for each treatment. Patients with burns or those requiring plasmapheresis and those patients admitted to ICU after cardiac bypass surgery and liver transplant were excluded from the study. The statistical results presented derived from an intention to treat analysis. The study was not explicitly a superiority study and no “per protocol” analysis is available. It is not known to what extent the statistical results of a “per protocol” analysis would agree with, or differ from, the results of the intention to treat analysis.

Death from any cause during the 28 days after randomisation was the primary outcome measure. There were 726/3473 (20.9 %) deaths in the albumin group and 729/3460 (21.1 %) deaths in the saline group (relative risk of death 0.99, 95 % confidence interval 0.91 to 1.09, $p=0.87$).

There were no statistically significant differences between the two groups in the secondary outcomes measured: mean (\pm SD) number of days spent in ICU (6.5 ± 6.6 in the albumin group and 6.2 ± 6.2 in the saline group, $p=0.44$), days spent in hospital (15.3 ± 9.6 and 15.6 ± 9.6 respectively, $p=0.30$), days of mechanical ventilation (4.5 ± 6.1 and 4.3 ± 5.7 , respectively, $p=0.74$) or days of renal replacement therapy (0.5 ± 2.3 and 0.4 ± 2.0 , respectively, $p=0.41$). The proportion of patients with new single or multiple organ failure was similar in the two groups ($p=0.85$). There was no significant difference in survival times during the first 28 days between the two groups ($p=0.96$).

On each of the first three study days, the patients who had been randomly assigned to receive albumin received less study fluid than did those assigned to saline, resulting in a greater net positive fluid balance in the saline group on each of those days. The ratios of the volume of albumin to the volume of saline administered during the first four days were as follows: 1:1.3 on day 1, 1:1.6 on day 2, 1:1.3 on day 3, and 1:1.2 on day 4. Overall during the first four days the study showed a ratio of 1.4:1 in the volume of saline used to compare albumin.

This study concluded that in a heterogeneous group of patients in the ICU, use of either 4 % albumin or normal (0.9 %) saline for fluid resuscitation results in similar mortality at 28 days. The trial did not examine the comparative safety of albumin use as an initial resuscitation fluid in pre-hospital, surgery or emergency department settings.

Predefined sub-group analyses were performed for patients with trauma, severe sepsis and acute respiratory distress syndrome as part of the SAFE study. There was a trend towards increased mortality in patients with trauma treated with albumin, which was due to a worse outcome in those patients with trauma and associated brain injury. Conversely, there was a trend towards a better outcome with albumin in patients with severe sepsis. Both these trends should be interpreted with caution. Specifically designed and appropriately powered studies are needed to establish whether these are real treatment effects or due to chance.

A post hoc, follow-up study of patients with traumatic brain injury enrolled in the SAFE Study was published in 2007. This post hoc analysis found that, when comparing albumin with saline for intravascular fluid resuscitation in the ICU, higher mortality rates were observed among patients with severe traumatic brain injury (Glasgow Coma Score, 3 to 8) who received 4 % albumin than among those who received saline. The authors note the study was designed post hoc, and some data were collected retrospectively. The authors add it remains possible that the results represent a chance subgroup finding and that the biologic mechanisms for the observed differences in mortality are unclear such that further detailed analyses of biologic mechanisms associated with intracranial hypertension are required.

INDICATIONS

Hypoproteinaemia in the acutely ill patient

Albumex[®] 20 is administered when there are existing or anticipated clinical problems or complications from reduced oncotic pressure, and/or as an adjunct to diuretic therapy.

Shock

Albumex[®] 20 may be used for the resuscitation of patients in shock due to acute loss of blood or plasma, but 4 - 5 % human albumin is preferred when available.

Burns

Extensive burns are followed by sequential shifts in the distribution of body water, salt and proteins, resulting in hypovolaemic shock and circulatory failure.

Initially (during the first 24 hours) there is an increased vascular permeability leading to loss of water and proteins into the extravascular compartment, and haemoconcentration. Large volumes of crystalloid solutions should be infused to restore the constricted intravascular fluid space, and smaller amounts of Albumex[®] 20 are required to maintain adequate plasma volume and colloid osmotic pressure.

Adult respiratory distress syndrome

The clinical syndrome is characterised by inadequate oxygenation secondary to pulmonary interstitial oedema, complicating shock and postoperative states resulting in a decreased central venous pressure, decreased plasma albumin concentration, rising blood pressure, reduced cardiac output, lowered pulse rate and a falling renal output.

The acute condition can be controlled by diuretics and Albumex[®] 20 in amounts sufficient to maintain vital signs.

In patients who have undergone abdominal surgery, the intravenous administration of albumin solution (20 %) immediately after the operation has been shown to improve lung compliance and gaseous exchange.

Haemodialysis

Albumex[®] 20 may be used to assist with the rapid removal of excess extravascular fluid and to maintain perfusion pressure.

Plasma exchange

Therapeutic plasma exchange is a procedure in which approximately one plasma volume is exchanged with a colloid replacement solution. The choice of replacement fluid and its concentration are determined by the particular clinical situation and the frequency of the procedure.

Iso-oncotic albumin solution is the preferred replacement material. If the patient's serum albumin level is not maintained, concentrated albumin (20 %) may be indicated. If

exchange occurs less frequently than once a week, less concentrated colloids may be appropriate.

CONTRAINDICATIONS

Albumex® 20 must not be used if there is a history of allergy to this product. Albumin is contraindicated in patients with cardiac failure, pulmonary oedema or severe anaemia.

The infusion of Albumex® 20 is not justified in hypoproteinaemic states associated with chronic cirrhosis, malabsorption, protein losing enteropathies, pancreatic insufficiency or undernutrition.

In chronic nephrosis, infused albumin solution (20 %) is promptly excreted by the kidneys with no relief of the chronic oedema.

PRECAUTIONS

The sodium levels in this product are 48 to 100 mmol/L. This should be noted when the product is used in patients requiring sodium restriction.

The colloid osmotic effect of Albumex® 20 is approximately four times that of plasma and patients should always be monitored for symptoms of circulatory overload (see *Monitoring advice*).

Administration of albumin can aggravate myocardial depression when present in patients with shock. A paradoxical effect of refractory oliguria has been reported in burns patients receiving albumin, possibly because of insufficient accompanying crystalloids.

Allergic reactions

Hypersensitivity reactions occur rarely when human albumin solutions are administered because of the human origin of the product. Should an anaphylactic reaction to Albumex® 20 develop, the infusion should be stopped and treatment instituted with adrenaline, hydrocortisone and antihistamines, as appropriate.

Circulatory overload

Patients with a history of cardiac failure or pulmonary oedema, or who have renal insufficiency, severe or stabilised chronic anaemia or are on cardiopulmonary bypass are at special risk of developing circulatory overload if the dosage and rate of infusion are not adjusted to the patients circulatory situation.

At the first clinical signs of cardiovascular overload (headache, dyspnoea, jugular vein congestion), or increased blood pressure or raised venous pressure associated with pulmonary oedema, the infusion is to be stopped immediately.

In the presence of dehydration, as Albumex[®] 20 is hyperoncotic, it must be given with, or followed by crystalloid solution (see *Administration*).

The rise in blood pressure which may follow rapid administration of albumin necessitates observation of the injured patient to detect bleeding points which failed to bleed at the lower blood pressure; otherwise, new haemorrhage and shock may occur.

The use of albumin for fluid resuscitation of patients with traumatic brain injury is not recommended.

In chronic nephrosis, infused albumin solution (20 %) is promptly excreted by the kidneys with no relief of the chronic oedema.

Albumex[®] 20 contains trace amounts of aluminium ($\leq 200 \mu\text{g/L}$). Accumulation of aluminium in patients with chronic renal insufficiency has led to toxic manifestations such as hypercalcaemia, vitamin D-refractory osteodystrophy, anaemia and severe progressive encephalopathy. Therefore, when large volumes of albumin are contemplated for administration to such patients, serious consideration of these potential risks relative to the anticipated benefits should be given.

Pathogen safety

This product is made from human plasma. Products made from human plasma may contain infectious agents such as viruses and theoretically Creutzfeldt-Jakob Disease (CJD) agents that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain infectious agents and by testing for the presence of certain viral markers.

In addition, virus inactivation/removal procedures are included in the manufacturing process. The current process and procedures applied in the manufacture of this product are effective against enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and the non-enveloped virus, hepatitis A (HAV). These procedures contribute significantly to ensure freedom from parvovirus B19.

Despite these measures, such products may still potentially transmit disease. There is also the possibility that other known or unknown infectious agents may be present in such products.

Vaccination for patients in receipt of medicinal products from human plasma should be considered where appropriate.

Any case of infection associated with the use of the product should be reported to the Australian Red Cross Blood Service, together with details of batches given.

Effects on fertility

No studies examining the effect of Albumex[®] 20 have been conducted.

Use in pregnancy

Reproductive toxicity studies with Albumex[®] 20 in animals have not been conducted. Such studies are impracticable due to the development of antibodies to human albumin in animal models.

The use of Albumex[®] 20 in human pregnancy has not been established in controlled clinical trials; therefore, it should be given to pregnant women only if clearly needed.

Use in lactation

Like endogenous serum albumin, Albumex[®] 20 may be excreted in milk. No safety information is available.

Paediatric use

There have been no specific clinical studies of Albumex[®] 20 in children.

Use in the elderly

There have been no specific clinical studies of Albumex[®] 20 in the elderly.

Carcinogenicity

Specific studies have not been conducted.

Genotoxicity

Specific studies have not been conducted.

Interactions with other medicines

Hypotension has been reported in patients given albumin who are on angiotensin converting enzyme (ACE) inhibitors. The addition of other drugs to Albumex[®] 20 has not been evaluated (see **COMPATIBILITY WITH OTHER FLUIDS**).

Effect on laboratory tests

Albumin is an endogenous plasma protein so no specific effects on laboratory tests are anticipated.

ADVERSE EFFECTS

Adverse reactions to albumin solutions are uncommon and are usually mild and transient.

Adverse reactions reported with albumin solutions in general include hypotension, chills, fever, allergic reactions including anaphylaxis, urticaria, skin rashes, nausea, vomiting and increased salivation. Mild reactions such as mild hypotension, flushing, urticaria, fever, and nausea normally disappear rapidly when the infusion rate is slowed down or the infusion is stopped (see **Monitoring advice**).

Very rarely, severe reactions such as anaphylactic shock may occur. In these cases, the infusion should be stopped and an appropriate treatment should be initiated.

Adverse events in clinical trials

Although formal clinical studies with Albumex[®] 20 have not been conducted to determine the frequency or severity of adverse events, results from studies with Albumex[®] 4 and 5 (4 % and 5 % albumin solutions respectively) may be applicable.

Adverse reactions by body system from the SAFE study comparing albumin and saline are provided in Table 1.

Table 1: Total adverse reactions reported from SAFE study

<i>Product</i>	<i>Albumex[®] 4 (n=3497)</i>	<i>Saline (n=3500)</i>
<i>Total adverse drug reactions</i>	22	14
<i>Hepatobiliary disorders</i>		
ascites	-	1
<i>Renal & urinary disorders</i>		
hyperchloraemic acidosis	1	4
hypernatraemia	1	1
lactic acidosis	-	1
<i>Respiratory, thoracic & mediastinal</i>		
hypoxia	7	1
pleural effusion	-	1
pulmonary embolus	-	1
pulmonary oedema	12	3
<i>Skin & subcutaneous tissue</i>		
oedema	-	1
<i>Vascular</i>		
hypotension	1	-

In an earlier generation of Albumex[®], when used in plasma exchange, 1 % (1/99) of patients had a clinically significant increase in prothrombin time and there was a reduction in levels of potassium, calcium, bicarbonate, total serum protein concentrations and platelet count. These results could reasonably be expected in a plasma exchange procedure.

Post-Marketing Surveillance

Post-market reporting of adverse reactions is voluntary and from a population of uncertain size, and consequently it is not always possible to reliably estimate the frequency of these reactions or establish a causal relationship to product exposure.

Overall a low number of reports have been received for the current generation Albumex[®] 20 which primarily involve chills and fever. The main adverse reactions reported during routine surveillance for the current product are as follows: hypotension, hypertension, tachycardia, decreased oxygen saturation, dyspnoea, flushing, dizziness, chills, pyrexia and muscle spasms. Although true anaphylactic reactions are believed to occur rarely, no reports of anaphylaxis have been received.

DOSAGE AND ADMINISTRATION

Dosage

Hypoproteinaemia in the acutely ill patient

The usual daily dose is 50-75 g human albumin (250 - 375 mL of Albumex[®] 20). The rate of administration should not exceed 2 mL per minute, as more rapid infusion may precipitate circulatory overload and pulmonary oedema.

The infusion of Albumex[®] 20 is not justified in hypoproteinaemic states associated with chronic cirrhosis, malabsorption, protein losing enteropathies, pancreatic insufficiency or undernutrition.

Shock

The dose should be determined by the patient's condition and response to treatment. The usual initial dose of 20 g human albumin (100 mL of Albumex[®] 20) may be administered as a blood volume expander at a rate of 2 to 4 mL per minute.

The rate of infusion may be increased in emergencies and repeated in 15 to 30 minutes if necessary. The total dose should not exceed the level of albumin found in the normal individual i.e. about 2 g per kg body weight in the absence of active bleeding.

If concentrated albumin (> 5 %) is given, it should be accompanied by the intravenous infusion of a crystalloid solution. Failure to supply this additional fluid may lead to dehydration of the tissues.

The precise nature and strength of the crystalloid solution will depend on the requirements of the patient for electrolytes and fluid.

Burns

The usual dose is 20 - 80 g human albumin (100 - 400 mL of Albumex[®] 20) given daily at the rate of about 1 mL per minute.

Beyond 24 hours, Albumex[®] 20 can be used to maintain plasma colloid osmotic pressure. A reasonable goal is the maintenance of a plasma albumin concentration of 25 g/L or a colloid osmotic pressure of 20 mmHg.

The continuing need for albumin is occasioned by losses from denuded areas and decreased albumin synthesis.

Acute respiratory distress syndrome

Commence with a dose of 50 g human albumin (250 mL of Albumex[®] 20) over the first 24 hours together with diuretic therapy. Thereafter the dose is adjusted to maintain vital signs, particularly central venous pressure, urine output and plasma albumin concentration.

Haemodialysis

Patients with significant fluid overload prior to dialysis may benefit from the administration of 20 - 40 g human albumin (100 - 200 mL of Albumex[®] 20) at the end of the dialysis procedure.

Plasma exchange

Replace albumin removed on a gram-for-gram basis, e.g. removal of 2.5 L plasma should be accompanied by replacement with 125 g human albumin (625 mL of Albumex[®] 20), either prediluted or followed by 4 - 5 volumes of an appropriate crystalloid solution (see **Administration - Dilution of Concentrated Albumin 20 %**).

Monitoring advice

It is recommended that blood pressure is monitored during administration of Albumex[®] 20.

To avoid circulatory overload the rate and volume of infusion should be monitored frequently.

Myocardial function should also be monitored e.g. central venous pressure, arterial pressure and pulse rate.

It is also recommended that plasma electrolytes, prothrombin time, biochemistry and haematological status should be monitored.

Administration

Albumex[®] 20 should always be administered by intravenous (IV) infusion using appropriate IV administration equipment. Albumex[®] 20 is packaged in a glass bottle that must be vented during use.

In some cases a dose of albumin is added to a suitable crystalloid solution in the proportion of 1 mL Albumex[®] 20 to 4 mL crystalloid solution and administered by the usual intravenous technique.

Dilution of Concentrated Albumin 20 %: If Albumex[®] 20 is diluted to an iso-oncotic protein concentration (4 – 5 % albumin) prior to administration, this must be done with a crystalloid solution such as 0.9 % saline. Under no circumstances should water be used since the lower tonicity will lead to intravascular haemolysis.

Albumex[®] 20 does not contain an antimicrobial preservative. It must, therefore, be used immediately after opening the bottle. Any unused solution should be discarded appropriately. Use in one patient on one occasion only.

It is strongly recommended that every time Albumex[®] 20 is administered to a patient, the name and batch number of the product be recorded in order to maintain a link between the patient and the batch of the product.

If the product has been stored in the refrigerator it should be allowed to reach room temperature before administration. Do not use if the solution has been frozen.

The product is normally clear or slightly opalescent but, if it appears to be turbid by transmitted light, it must not be used and the bottle should be returned unopened to the Australian Red Cross Blood Service.

COMPATIBILITY WITH OTHER FLUIDS

The addition of other drugs to Albumex[®] 20 has not been evaluated.

Albumex[®] 20 should not be mixed with protein hydrolysates, amino acid solutions, solutions containing alcohol, or solutions containing drugs that bind to albumin e.g. calcium channel blockers, antibiotics and benzodiazepines.

OVERDOSAGE

Excess human albumin may lead to circulatory overload (see **PRECAUTIONS**).

PRESENTATION AND STORAGE CONDITIONS

Albumex[®] 20 is issued in glass bottles in two sizes:
2 g of human albumin in 10 mL of electrolyte solution;
20 g of human albumin in 100 mL of electrolyte solution.

Storage

Store below 30°C. This product must not be frozen. Protect from light. Do not use after the expiry date.

NAME AND ADDRESS OF THE SPONSOR

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Distributed by: Australian Red Cross Blood Service

POISON SCHEDULE OF THE MEDICINE

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