



Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Albumin (human)

Proprietary Product Name: Albunate 5, Albunate
20 and Albunate 25

Sponsor: CSL Limited

September 2014

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About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
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List of abbreviations

Abbreviation	Meaning
AKI	Acute kidney injury
ADR	Adverse drug reaction
ATC code	Anatomic Therapeutic Chemical code
BPWP	Blood Products Working Party
CI	Confidence interval
CCDS	Company Core Data Sheet
COP	Colloid osmotic or oncotic pressure
ECFV	Extracellular fluid volume
EMA	European Medicines Agency
Ph.Eur.	European Pharmacopoeia
EU	European Union
FFP	Fresh frozen plasma
FVIII	Factor VIII
GMP	Good Manufacturing Practice
HAS	Human Albumin Solution
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HUV	Human immunodeficiency virus
HSA	Human serum albumin
HES	Hydroxyethyl starch
ICH	International Conference on Harmonisation
ICU	Intensive care unit
INN	International Non-Proprietary Name

Abbreviation	Meaning
IV	intravenous
MedDRA	Medical dictionary for regulatory affairs
MRP	Mutual Recognition Procedure
N/A	Not applicable
Ph.Eur.	European Pharmacopoeia
PSUR	Periodic Safety Update Report
RCT	Randomised controlled trial
RMP	Risk Management Plan
SPC	SPC Summary of Product Characteristics
SOC	System organ class
TGA	Therapeutic Goods Administration
TSE	Transmissible Spongiform Encephalopathy
USA	United States of America
vCJD	vCJD variant Creutzfeldt-Jacob Disease
vs.	versus

1. Introduction

The trade name Alunate is the sponsor requested trade name for registration of CSL Behring AG human albumin in Australia. The most common trade name internationally for this product is Alburex/AlbuRx. However this is very similar sounding to Albumex, the albumin product already registered in Australia and thus the sponsor has changed the name for proposed registration in Australia to Alunate. The product has also been registered as Albumin SRK 5% and Albumin SRK 20% (Austria). Within the application the following additional names are used when referring to Alunate; Human Albumin CSL Behring, Human Albumin CSL, human albumin solution (HAS).

Alunate 5, 20 and 25 is a product manufactured in Bern, Switzerland.

1.1. Submission type

This is a Category 1 submission. It is a mixed submission of a systematic literature review on all human albumins (published clinical trials and meta-analyses in the proposed indication published since 1990), together with a review of safety data of Alunate and a small post-marketing observational Austrian study with Albumin SRK 5% and Albumin SRK 20%. These Austrian products are the same as the proposed product for registration (Alunate) in this submission.

There are no company sponsored clinical trials on Alunate.

Alunate is human albumin; a blood derived product.

The proposed therapeutic indication is:

“Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and the use of a colloid is appropriate. The choice of albumin rather than artificial colloid will depend on the clinical situation of the individual patient.”

Three strengths are proposed for registration:

- Alunate 5 (human albumin) 50 g/L (5% w/v) solution for intravenous infusion vial (250 mL and 500 mL)
- Alunate 20 (human albumin) 200 g/L (20% w/v) solution for intravenous infusion vial (50 mL and 100 mL)
- Alunate 25 (human albumin) 250 g/L (25% w/v) solution for intravenous infusion vial (250 mL and 500 mL).

2. Clinical rationale

Albumin is responsible for maintaining the colloid osmotic pressure in plasma and thereby sustains the circulating plasma volume. The clinical efficacy of albumin is mainly due these osmotic properties. In dehydrated patients, patients with hypovolemia or with circulatory shock, human albumin 5% solution was shown to support the total plasma volume while in trauma patients or in severely burned patients, the concentrated human albumin 20% and 25% solutions are known to augment the plasma volume by drawing extra vascular water into the circulation.

Albumin also reversibly binds to cations and anions and thus acts as a transport protein for many endogenous and exogenous substances.

Albumin, derived from a variety of blood extraction, separation and purification processes has been in clinical practice for decades. Albunate is one such albumin that has been registered for clinical use in the US since 1976 (with a different trade name). Because of the long development and clinical use history the sponsor of Albunate in the US was not required to provide evidence of efficacy, comparative efficacy or safety. The submission to register Albunate in Australia is due to a request from the BPWP to have a backup for the supply of blood products should there be issues with the current registered albumin product.

There are multiple Guidelines nationally and internationally for the use of crystalloids versus colloid products for this indication, and for different types of colloid products, in addition. The type of recommended product depends on institution preference and patient situation (disease, clinical state, underlying comorbidity). This is evidenced in a review of the literature provided in the literature part of the hybrid submission.

There is no European CPMP for human albumin use.

It is noted that there has been updated LBS guidance released on 27 May 2014. However the sponsor completed the compilation of the dossier in March 2014 for pre submission.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission is based on a three pronged hybrid literature based submission (LBS). The literature review part of this literature based submission focuses on randomised controlled trial and meta analyses around the safety and efficacy of albumin generally (some data which does or is likely to have included Albunate) and based on the proposed indication, which is based on the EU Core Summary of Product Characteristics (SPC) for albumin. This approach was approved by the TGA.

The second part of the hybrid literature based submission consist of company pharmacovigilance data collected from periodic safety activities from 1996 to the present and the third part is a small post-marketing safety study of Albunate (marketed as Albumin SRK in Austria), the product seeking registration.

In summary, the submission contained the following clinical information: Module 1, 2, 3 and 5. The sponsor was given approval to not submit Module 4 based on advice from the nonclinical evaluation stream leader; essentially that statements in the proposed Product Information document relating to nonclinical matters must be consistent with ones contained in the existing approved PI for Albumex.

The literature review consisted of an appropriate search strategy. It located 1,256 publications in the Embase search and 278 from the Cochrane search. The results were tabulated and 84 of the Embase search papers were included in the review, as well as the 278 from the Cochrane and 11 others based on updated editorials and reviews of the original Cochrane data and other publications picked up during preparation of the RMP and this submission; these were selected for Review based on research around the efficacy and safety of any of the albumins. Details of the reasons for selection for each of the 1,256 were provided. This summary has been checked and is appropriate for the discussion around efficacy and safety of albumins in clinical practice. The literature is documented in the clinical dossier.

The primary clinical data to support the use of Albunate is collected from periodic safety activities from 1996 to the present and is summarised, with supporting literature provided. The following were presented;

- Post-marketing Experience

- Efficacy of Albumin in hypovolaemia following shock due to trauma or sepsis
- Efficacy of Albumin in hypovolaemia following surgery
- Efficacy of Albumin in burn patients
- Efficacy of Albumin in the management of patients with liver cirrhosis and ascites
- Meta-analyses
- Safety profile of albumin (data from published literature)

The quality module contained the following:

The quality dossier is based on the current EU Mutual Recognition Procedure dossier and consists of a separate Drug Substance and Drug Product section for each of the three concentrations. It includes data around drug substance control of materials, process validation and evaluation, impurities and container closure system, drug product process validation and or evaluation, control of excipients and control of drug product analytical procedures.

Albunate complies with the Ph. Eur. Monograph (Human Albumin Solution). Although Australian approved terminology has been used for all of the application forms in the product descriptions and labelling documents, as Module 3 is the EU dossier, sodium caprylate and caprylic acid have been used in place of the excipient AANs sodium octanoate and octanoic acid.

Albunate contains a new non-proprietary ingredient sodium tryptophanate, now entered on the TGA Ingredients database. The excipient N-acetyltryptophan is added to stabilise human albumin in accordance with the European Pharmacopoeia (Ph. Eur) monograph 01/2013:0255 Human Albumin Solution and USP 36 Albumin Human monograph. The excipient complies with the Ph. Eur monograph for N-Acetyltryptophan 01/2009:1383. Albunate has been stabilised with sodium tryptophanate since its registration in the US and EU and has over 35 years of clinical use and a safety profile with this excipient.

The active ingredient, human albumin, is manufactured from human source or recovered plasma as described in the TGA-approved CSL Behring Type I PMF.

In summary the clinical module includes:

- Clinical study reports
 - Post marketing experience (AE by SOC)
 - Austrian post marketing survey with Albumin 5% and 20% (Albunate)
 - PSUR 1st October 1997-31 March 2002
 - PSUR April 1 2002- 20 October 2006
 - PSUR 21 October 2006- 20 October 2009
 - PSUR 21 October 2009-20 October 2012
- Rep-efficacy-safety studies
 - Blood volume deficiency
 - rep-analysis-data-more-one-stud (22 studies)
 - stud-rep-uncontrolled (2 studies)
 - stud-rep-controlled (63 studies)
 - tabular listing

The primary clinical data specific to Albunate is the pharmacovigilance and post-marketing data collected from periodic safety activities from 1996 to the present. This consists of:

- An observational study performed in Austria with Albunate (Albumin SRK 5% and Albumin SRK 20%)
- Periodic Safety Update Reports from October 1997 to October 2012
- Adverse Event Line Listings from 1996 to 2013.

This primary data, specific to Albunate, is supported by the publications provided. These uses a variety of different HAS (although some studies are likely to have included patients on Albunate, not specified). Specifically, 5.3 includes meta-analyses and several series of Cochrane reviews – presented in the tabular summaries in 5.2 and also summarised and discussed in 2.5 as supporting studies. 535 is supporting literature for the efficacy and safety of albumin generally.

This literature is thus helpful to understand the well-established place of practice of albumins in clinical practice, gives some data on efficacy in specific population groups and some safety data (where reported). The Austrian study data must be used to examine Albunate specifically, although this primary data is observational only, as is the PSUR.

3.2. Paediatric data

The submission included no paediatric pharmacokinetic / pharmacodynamic / efficacy / safety data.

The application notes that data has been submitted neither to the EU nor the US. There is no paediatric investigation plan (EMA) nor US Paediatric Assessment (US). As there has been registration in those jurisdictions for many decades, it is stated that the provisions for a Paediatric Investigational Plan (EU) or a Paediatric Plan (US) do not apply.

There is no paediatric development plan for Albunate. However Module 1-12 has been submitted by CSL to request listing in a paediatric population in Australia (from newborns through to adults). There is no specific Albunate paediatric data in this application although there is data from use of albumins generally in children since registration; covered in the literature review and post-marketing reviews. This suggests there is efficacy in this population, and further that the spectrum of AEs is similar (although the frequency is unable to be ascertained with observational reported data).

In the proposed PI no specific dosing requirements or pharmacokinetic statements are included for the paediatric population.

3.3. Good clinical practice

No new clinical trials were undertaken for the purposes of registering in this indication. GMP certification has been provided.

4. Pharmacokinetics

4.1. Studies providing pharmacokinetic data

There were no studies providing pharmacokinetic data however pharmacokinetic knowledge of albumin in disease and healthy states and the effect of infusing IV exogenous albumin is well documented. Pharmacokinetically, albumin products are comparable to normal human plasma albumin, with a biological half-life of 18 to 19 days, and the equilibration between an intravascular (40%) and extra vascular body pools (60%) and resulting complex shifts of fluid. The pharmacokinetics of Albunate are expected to be those of other human albumins given intravenously.

4.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

4.2.1. Physicochemical characteristics of the active substance

The following information is derived from the sponsor's summaries.

4.2.2. Pharmacokinetics in healthy subjects

4.2.2.1. Absorption

Sites and mechanisms of absorption

Albumin is given intravenously

4.2.2.2. Bioavailability

Absolute bioavailability

Albunate is infused intravenously and bioavailability studies are not required. Bioequivalence studies were not undertaken.

4.2.3. Pharmacokinetics in the target population

There was no pharmacokinetic data provided.

4.2.4. Pharmacokinetics in other special populations

There was no pharmacokinetic data provided in special populations.

4.3. Evaluator's overall conclusions on pharmacokinetics

There is no pharmacokinetic data presented in this application. Bioequivalence studies between different albumin products have also not been undertaken. Both are feasible but probably of limited clinical relevance in this situation, especially as the clinical rationale for these products is in volume expansion, clinical response is variable and measured/monitored by clinical signs. Further because studies to examine clinical differences between Albunate and other albumins have not been undertaken nor seen as a clinical need, there is arguably little clinical need for detailed pharmacokinetic studies to be undertaken.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

There were no studies providing pharmacodynamic data, although there was summary pharmacodynamic data provided in studies in the literature review.

Human albumin accounts quantitatively for more than half of the total protein in the plasma. The most important physiological functions of albumin are its role in plasma oncotic pressure, its transport function and its role as an extracellular antioxidant in human plasma. Albumin is the major determinant of COP in normal patients; one of the main reasons to use human albumin in states of reduced volume.

Iso-oncotic albumin as with Albunate 5 restores and maintains the circulating blood volume where volume deficiency has been demonstrated. The hyperoncotic Albunate 20 % and 25 % contribute to maintaining the plasma colloid osmotic (oncotic) pressure of plasma and therefore plasma volume by balancing the hydrostatic pressure within the tissue capillaries. Older work has suggested that 1 g of 20 to 25% human serum albumin retains 18 mL of fluid in the

circulation in patients with a normally hydrated interstitium; in dehydrated patients the 5% solution has greater volume effects.

There were a number of publications cited in the LBS provided that showed the efficacy of albumin in increasing COP in critically ill surgical patients, in patients with hypovolemia and septic shock.

However the relationship between volume and clinical outcomes has not been demonstrated; nor has the method of measurement of changing volumes and clinical outcomes been discussed (including crystalloid versus colloid) and within the group of colloids the difference between different types of colloid and between the product under submission has not been discussed.

5.2. Summary of pharmacodynamics

There were no pharmacodynamic studies submitted with Albunate. Although there was literature provided on albumins and change in COP or other PD endpoints, there were a number of factors making this data non-evaluable for this application. The type of volume expander, the type of colloid and the type of albumin are not always clear, studies that are clearly of Albunate and PD endpoints were unable to be located; and the rationale in the application for Albunate specifically and PD outcomes was not well discussed.

5.2.1. Mechanism of action

The predominant mode of action of albumins is to increase COP, transport molecules and drugs and act as a blood anti-oxidant and 'scavenger'.

5.2.1.1. Pharmacodynamic effects

Increasing the COP is useful in patients with shock or dehydration to maintain intravascular volume. Adding HAS to patients with cirrhosis can temporarily maintain COP to reduce overwhelming ascites.

5.2.1.2. Primary pharmacodynamic effects

Not provided.

5.2.1.3. Secondary pharmacodynamic effects

Not provided

5.2.2. Time course of pharmacodynamic effects

Not provided.

5.2.3. Relationship between drug concentration and pharmacodynamic effects

No data was provided on the relationship between albumin concentrations and outcomes; however adequate albumin concentrations are required for oncotic equilibrium. Much of the literature discussed the importance of volume status rather than albumin concentrations and outcome.

5.3. Evaluator's overall conclusions on pharmacodynamics

There were no pharmacodynamic studies submitted with Albunate. Although there was literature provided on albumins and change in COP or other PD endpoints, there were a number of factors making this data non-evaluable for this application. The type of volume expander, the type of colloid and the type of albumin are not always clear, studies that are clearly of Albunate and PD endpoints were unable to be located; and the rationale in the application for Albunate specifically and PD outcomes was not well discussed.

6. Dosage selection for the pivotal studies

There were no pivotal studies. Dosage selection is difficult with HAS as dose and concentration is titrated to an individual clinical state. Further, the relationship with outcomes is more related to volume expansion than a set albumin dose or concentration.

7. Clinical efficacy

7.1. Restoration and maintenance of volume status

Data for evaluation of Albunate was provided by a literature review of predominantly RCTs and meta analyses of albumin usage for the requested indication:

“Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated, and the use of a colloid is appropriate”.

Although these manuscripts were reviewed, they were not evaluated due to:

- multiple types and concentrations of albumin used, and
- Albunate use not specified (presumed use in the US data but numbers/percentages in the trials not specified)
- no specific Albunate data
- multiple indications, multiple settings
- lack of comparative efficacy with other HAS registered in Australia
- lack of comparison to crystalloids

In terms of the volume restoration indication as proposed in this application, there are no clinical studies specifically with Albunate; although it is likely that Albunate was used for at least some the patients in some of the studies. The sponsor however states that data showing efficacy of albumin in hypovolaemia using formulations from other manufacturers can be used as supportive evidence and results can be extrapolated to the Human Albumin CSL formulations.

The clinical efficacy is therefore discussed in the context of Albunate being one of the HAS and examining efficacy for albumins in this indication.

A review of literature provided does suggest the HAS is effective in this setting and this fact was relied upon in the design of the Australian and New Zealand study SAFE study (Saline versus Albumin Fluid Evaluation)¹. SAFE can be used to examine the comparative efficacy of albumins versus crystalloid as it is a local study reflecting local use, was appropriately designed (including enrolment of 6,997 patients) and provides evidence around the indication the sponsor is seeking registration. The albumin in this study was Albumex 4 % which is a HAS already available in Australia but manufactured using a different chromatographic process. SAFE showed that both Albumex 4% and saline were equally effective resuscitation fluids using death as the primary endpoint.

As further discussion point the Cochrane analysis provided in the submission and which included the SAFE study (which notably did add 91% of the weight) showed that for patients with hypovolaemia there was no evidence that albumin reduced mortality when compared with cheaper alternatives such as saline. There is no evidence that albumin reduces mortality in

¹ Finfer, S., et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *New England journal of medicine*, 2004; 350:2247-2256

critically ill patients with burns and hypoalbuminaemia and there is a suggestion that albumin may increase the risk of death.² In the more recent Cochrane Review of November 2011 (Roberts I et al. 2011)³ results of the SAFE trial contributed 75.2 % of the weight. This Review concluded that there is still no conclusive evidence that HAS reduces mortality in patients with hypovolaemia, burns and hypoalbuminaemia. Given the limitations of the data in the meta-analyses, the SAFE study still remains the backbone of the evidence that HAS does not decrease mortality compared to crystalloid.

However the reality of clinical practice in Australia is that there are pockets of clinical care that use HAS and subsets of the population that appear to benefit, for example paracentesis in patients with fluid overload and low serum albumin such as gastroenterology. For this reason, although reviewed the literature will not be discussed manuscript by manuscript as to the efficacy of HAS, but rather whether there is sufficient evidence to support a listing for a new albumin on efficacy and safety grounds.

7.1.1. Pivotal efficacy studies

There were no pivotal efficacy studies undertaken.

7.1.2. Analyses performed across trials (pooled analyses and meta-analyses)

The literature provided in Module 5 showed meta-analyses on a variety of clinical practice points. These include whether albumin generally was actually more effective than saline in clinical care. The meta-analyses suggested saline was more effective for the indication requested in this application.

7.1.3. Evaluator's conclusions on clinical efficacy for volume restoration and maintenance

Clinical data published and presented here since a publication date of 1990 has shown that HAS generally has the following effects:

- it raises a lowered plasma COP
- in a normally hydrated or mildly dehydrated patient, 1 g of human serum albumin retains 16 to 18 mL of fluid within the circulation
- in a hypovolaemic patient, the intravascular volume effects of HAS correspond to the volume infused rather than the albumin dose or concentration
- Crystalloid is as effective as HAS as volume restoration in overall mortality in ICU patients

There is published RCT and Cochrane Library evidence that HAS is effective in replacing fluid volume in patients with hypovolaemia following shock due to trauma or sepsis, hypovolaemia following surgery and in burn patients, and for the treatment of ascites in liver cirrhosis.

The major study on which the claim of efficacy for treatment of hypovolaemia following trauma, shock, or acute respiratory disorder syndrome is based is the SAFE study which was a robust, double blind, randomised, prospective, multi-centre study carried out by a clinical trials group across Australia and New Zealand. It included 6,997 patients based on its primary end point, all-cause mortality at 28 days. It was designed to reflect clinical practice and the objective measures of haemodynamic efficacy but showed HAS to be equivalent to saline. The albumin used was Albumex 4%.

² Alderson, P., et al., Human albumin solution for resuscitation and volume expansion in critically ill patients. The Cochrane database of systematic reviews, 2004(4): p. CD001208.

³ Roberts, I, et al. Human albumin solution for resuscitation and volume expansion in critically ill patients Cochrane Database of Systematic Reviews 2011 Cochrane

The literature provided in this submission is thus supportive data only for evaluating efficacy and safety of HAS as a class, not for a new albumin. The evidence in the literature review discussed several aspects: are colloids effective at improving COP; does increasing COP with colloids translate into a clinically meaningful endpoint (morbidity or mortality); are there differences in efficacy between the colloids; are there differences between the albumins; is there evidence to support a concentration of 5% versus 20 or 25% or is volume the key variable for efficacy. If so does it matter how volume is restored?

It is reasonable to conclude that the meta-analyses and RCTs presented in this submission suggest that albumins are effective at expanding intravascular volume; however the effect on clinically relevant endpoints (such as death and morbidity) is unlikely to be any more than that achieved with crystalloid. It could also be argued that the in comparison of albumins with different colloids, although may show safety differences in specific groups, are all reasonably similarly effective at restoring blood volume. The issue for this application is the entry into the market of a new to Australia (but old to the rest of the world) HAS, and the safety and efficacy of this product.

This submission does not have any clinical trial evidence presented for Alunate.

However because the manufacturing of the already registered Albumex 4% is relatively similar, and because it is possible that it is the volume effect rather than the albumin type is more important, and because it has been available across the globe for over 40 years and clinicians use it clinically, it would be reasonable to assume this albumin product has efficacy at volume expansion. However it cannot be assumed that this product is even as effective as Albumex without comparative clinical and pharmacokinetic/pharmacodynamic data.

These conclusions hold true for the effectiveness of HAS for the maintenance and/or the restoration of haemodynamics in surgical patients, burns (where one meta-analysis suggested the outcome was worse if albumin was used) and decompensated cirrhosis with associated complications such as spontaneous bacterial peritonitis.

In terms of the efficacy for the meta-analyses and systematic reviews, the conclusions are similar. There have been many have been published since 1998 that look at the outcome of volume resuscitation with different fluids; undertaken with the purpose of trying to address the perennial crystalloids versus colloid debate as well as to look at the use of the more expensive colloid resuscitation fluids. These reviews are difficult to summarise due to many heterogeneous factors including heterogeneity of clinical patient groups, the age and quality of the publications used, varied dosages of the fluids, differing types and concentrations of albumin used as well as different treatment protocols. Their direct relevance to the question of this application; is there enough efficacy data to support registration of Alunate is also unanswered by these meta-analyses; unless it is assumed that Alunate and the other available HAS are all similar enough to be interchangeable. However there is no evidence presented to support that.

8. Clinical safety

8.1. Studies providing evaluable safety data

There were no studies providing comparable and evaluable safety data and there was no clinical trial data for the drug in this application. For this section, the observational Austrian study "Observation Study with Albumin SRK 5% and Albumin SRK 20%" was evaluated.

Pharmacovigilance data was also reviewed. 'Results' sections in the supporting literature documents were also viewed for safety information; this data was poorly reported in all but a few recent studies and meta-analyses. It should be noted that safety data in the literature was for HAS generally, not for Alunate.

It is noted that there have not been any regulatory actions taken on Human Albumin CSL Behring 5%, 20%, and 25% for safety reasons for 17 years; since the beginning of the reporting period of the first Periodic Safety Update Report (1997). Further, one of the meta-analyses on safety of albumin versus other colloids showed albumin to be safer.⁴ Overall it also showed that on the basis of large scale pharmacovigilance study results, albumin infusion resulted in a low rate of both total adverse events (3.1 to 8.6 per 105 infusions) and serious adverse events (1.29 per 106 infusions) overall.

Evidence of significant safety concerns associated with albumin administration, as compared to colloids overall is small and the known risks of hypotension and immunological reactions with HAS occur infrequently.⁵ Specifically, the most relevant systematic review of the relative safety of colloids showed that starch infusions caused more anaphylactoid reactions (4.51 relative ratio), pruritus (1.78 relative ratio), and coagulopathy (relative ratio not reported) compared with HAS administration. In addition, multivariate analysis of larger, blinded randomised controlled trials showed a reduction in mortality associated with HAS administration (OR 0.78; 95 % CI: 0.76-0.81).⁴

8.1.1. Pivotal efficacy studies

There were no pivotal efficacy studies.

8.2. Pivotal studies that assessed safety as a primary outcome

There were no pivotal studies that assessed safety as a primary outcome.

8.2.1. Other studies evaluable for safety only

8.2.1.1. Observational study

The observational Austrian study "Observation Study with Albumin SRK 5% and Albumin SRK 20%."

8.3. Patient exposure

Over 40 years in many countries around the globe.

8.4. Adverse events

Risks that have been identified during post-marketing use of HAS were covered in the Risk Management Plan. These were reviewed but are not further detailed as are well described and common to the pharmaco therapeutic group of HAS plasma substitutes. There are not any new AEs that have been identified.

A meta-analysis of colloids has concluded that on the basis of large-scale pharmacovigilance study results, HAS infusion resulted in a low rate of both total adverse events (3.1 to 8.6 per 105 infusions) and serious adverse events (1.29 per 106 infusions).⁴

8.4.1. Treatment related adverse events (adverse drug reactions)

The majority of clinical studies investigating the effect of HAS treatment on outcomes such as mortality and morbidity, and those providing safety data are summarised in Module 5 (literature review, where provided) and Section 2.5.4 of the application. Where relevant the

⁴ Barron, M.E., M.M. Wilkes, and R.J. Navickis, A systematic review of the comparative safety of colloids. *Archives of surgery* 2004; 139: 552-563

⁵ Green, R.S. and R.I. Hall, Starches Are Not Preferable to Albumin During Cardiac Surgery: A Contrary Opinion. *J Cardiothorac Vasc Anesth.* 2008; 22: 485-491

data has been summarised in the sections below. This data is mainly comparing efficacy and safety across the different colloid products and therefore supporting data for safety observations only. There was no new treatment related adverse events noted.

8.4.2. Deaths and other serious adverse events

Mortality data in agents that expand volume has become of interest since the 1998 Roberts meta-analysis suggesting the albumin increased the death rate in ICU patients. There was a lot of controversy over the method of this meta-analysis - multiple subgroup analyses were done subsequently, and the SAFE study was designed as was a RCT to address this issue.¹ This showed that the mortality was similar between crystalloid and colloid. Subsequently a subgroup analysis suggested HAS might be harmful in acute brain injury patients.

Serious adverse events and other adverse events of interest have not been collected either systematically or consistently in the clinical studies published for the different indications of HAS. On reviewing the meta-analyses and RCTs there appears no new safety issue with HAS.

Further there are no new clinical studies with this application apart from the observational post-marketing study.

8.4.3. Discontinuation due to adverse events

The following table provides a summary, taken from the application on the specific laboratory measurements in the efficacy studies.

Table 1: RCTs with specific laboratory measurements related to safety

Author/year	Study drug(s)	Outcomes	Study title	Main safety findings
Schramko et al., 2009	HA 4 % vs HES 6 %	Haemostasis	Rapidly degradable hydroxyethyl starch solutions impair blood coagulation after cardiac surgery: A prospective randomised trial.	HES solutions impaired coagulation while HA had no effect.
Niemi et al., 2006	HA 4 % vs gelatine 4 % vs HES 6 %	Haemostasis	Gelatin and hydroxyethyl starch, but not albumin, impair haemostasis after cardiac surgery.	HES and gelatine effected coagulation and HA had no detrimental effect.
Niemi et al., 2005	HA 4 % vs HES 6 %	Haemostasis	Albumin induced hypercoagulability does not reduce blood loss in patients undergoing total hip arthroplasty.	Haematocrit value, platelet count, bleeding time, prothrombin time value, APTT, FV activity and fibrinogen concentration were comparable between the groups.
Bellomo et al., 2006	SAFE sub-group	Electrolytes/ acid-base status	The effects of saline or albumin resuscitation on acid-base status and serum electrolytes.	No major differences in patients' acid-base variables between 2 groups.
Bellomo et al., 2009	SAFE sub-study	Haemostasis	Effects of saline or albumin resuscitation on standard coagulation tests.	APTT: prolonged by 2.7 sec (HA); shortened by 0.9 sec (saline).
Celik et al., 2003	HA 5 % vs HES 3 % vs polygeline 3.5 %	Histamine release	Early and late histamine release induced by albumin, hetastarch and polygeline: some unexpected findings.	Histamine release occurred frequently in all three groups.
Van der Linden and Ickx, 2006	Comparison of different colloidal solutions	Biological markers of coagulation	The effects of colloid solutions on haemostasis.	HA has the least effects, compared to HES products, dextrans, gelatine.
Hecht-Dolnik et al., 2009	HA vs HES (products not further specified)	Transfusion requirements in CABG pts	Hetastarch increases the risk of bleeding complications in patients after off-pump coronary bypass surgery: a randomised clinical trial.	HES increased transfusion requirements compared to HA.
Brutocao et al., 1996	HES 6 % vs HA 5 %	Clinical bleeding, laboratory coagulation parameters	Comparison of Hetastarch with Albumin for postoperative volume expansion in children after cardiopulmonary bypass.	No differences in coagulation parameters up to 20 mL/kg of colloid; > 20 mL/kg HES 6 %: increase in prothrombin time.

8.5. Post-marketing experience

These are covered in

1. The Austrian post-marketing survey "The observational Austrian study (module 2.7.6) "Observation Study with Albumin SRK 5% and Albumin SRK 20%" and
2. The PSUR

The Austrian study was a very small study (211 subjects observed over 1999 to 2000) who had an Albumin SRK 5% ((250 mL and 500 mL) or 20% (50 mL and 100 mL) infusion, this product is the Alunate product in this application. Inclusion criteria included traumatised patients

suffering volume loss, shock, burns, patients for whom the administration of HAS is indicated in connection with an accident or an operation (Austrian Codex Technical Information 1998/1999). Patients were excluded if the product would be contraindicated or who would be considered included in any of the warnings listed in the current technical information (Austrian Codex Technical Information 1998/1999). Overall five patients died due to the severity of their injuries (not otherwise specified); non-serious ADRs were reported by 20 patients (9.5%); in most cases these were classified as mild ("light") to moderate ("medium") and all patients recovered from these ADRs.

The study evaluated safety and clinical effectiveness, based on a 4 point scale: "very good", "good", "poor" and "unclear". For patients whose efficacy was not evaluated (due to multiple events) the effectiveness was recorded as "not evaluated". The clinical evaluation of Albunate was given as "very good" or "good" for 81.6% of patients (n = 172) and for 1.9% as "not good" ("poor", n = 4). The remaining patients (16.6%, n = 35) could not be evaluated because of multiple events.

Eleven patients (5.2%) had a drop in BP which was classified as mild for 8 and moderate for 3 patients. Nine patients (4.3%) had erythema (mild in 7 and moderate in 2 patients). No other ADRs were reported. No patient experienced an anaphylactic shock, nor was Quincke's oedema observed for any patient.

The data provided was pretty low quality although it is noted that individual patient data is available on request. For example, it is unknown who the efficacy data is evaluated by - presumably by the doctor and hence the efficacy bias is likely to be large. Also there is no reference nor comparison group. Further the efficacy scale is not robust. The safety data displays ADEs widely known to occur with albumin. It is reassuring that no new events were detected (although there were small numbers).

This study is helpful in terms of efficacy and safety data with the HAS specified in this application.

The PSUR has identified no new reports since 1997.

8.6. Safety issues with the potential for major regulatory impact

8.6.1. Liver toxicity

Nil reports.

8.6.2. Haematological toxicity

Incompatibility reactions have been previously reported when HAS are mixed with other medicines/coagulation products or diluted with water.

HAS does not appear to affect the blood coagulation profile, in contrast to some starches or gelatin. However, it has been shown to be associated with prolongation of APTT, as have the infusion of larger fluid volumes of other agents.⁶ However, in a meta-analysis of colloids, artificial colloid administration was consistently associated with coagulopathy and clinical bleeding, most frequently in cardiac surgery patients receiving HES.⁴

8.6.3. Serious skin reactions

Nil reports. Pruritus occurrence was significantly increased by HES exposure (OR 1.78; 95 % CI: 1.23 to 2.58).

⁶ Bellomo, R., et al., Effects of saline or albumin resuscitation on standard coagulation tests. Critical care and resuscitation : *Journal of the Australasian Academy of Critical Care Medicine*, 2009. 11: 250-256.

8.6.4. Cardiovascular safety

Hypotensive reactions have been reported in many clinical trials. In some cases where there is a 'batch' effect, it has been related to elevated activity of prekallikrein activator (PKA) which can occur in storage.

Following a systematic review of the comparative safety of colloids,⁴ it was reported that with HAS as the reference colloid, the incidence rate ratio for anaphylactoid reactions was:

- 4.51 (95 % CI: 2.06 to 9.89) after HES administration
- 2.32 (95 % CI: 1.21 to 4.45) after dextran
- 12.4 (95 % CI: 6.40 to 24.0) after gelatin

8.6.5. Unwanted immunological events

Hypersensitivity and anti-erythrocyte antibodies occur infrequently with HAS.

8.7. Other safety issues

8.7.1. Safety in special populations

8.7.1.1. Paediatrics

Human albumin solution (HAS) has been used for many years in special populations including geriatrics and paediatrics. Although there have been no studies in children with Albutate, there are clinical trials in children with other albumins and also other colloids (for example HES). It appears that children receiving colloids improve intravascular volume. HAS is widely used and there were a few submitted publications in the literature review showing it had been used in children and appeared safe, or at least as safe as other colloids, for example.⁷ Sadly data on the effect on overall outcome (morbidity or mortality) was not collected.

From 18 September 1996 to 1 September 2013, a total of five reports involving the use of Albutate in children (< 12 years) were retrieved from the CSL safety database. Primary preferred terms (PTs) include blood pressure systolic decreased, hypersensitivity, medication error, anti-erythrocyte antibody and anaphylactic shock. All patients recovered.

Additionally, two reports involving the use of Albutate in adolescents (≥ 12 to < 18 years of age) were reported. Primary preferred terms (PTs) include type I hypersensitivity and flushing. The patients received human albumin 20% and AlbuRx 25%, respectively. Both patients recovered.

There were no variations in benefit and no indication of a new safety concern from these 7 reports.

8.7.1.2. Elderly use

There is no specific Albutate data in the elderly but as albumin is infused as a solution and the elderly are less able to tolerate fluid overload, care should be taken if albumin products are being used in conditions where hypervolaemia could represent a special risk for the patient; these pathophysiological situations are well known for practitioners using volume expansion, are already documented in the PI and would not be specific to Albutate.

Cumulatively, from 18 September 1996 to 1 September 2013, there were 60 case reports for Albutate in the elderly patient population (≥ 65 years old). Age span ranged from 65 to 87 years of age. There were no reports suggesting a different safety profile in the elderly compared to the known effects. There has been no indication of any new safety concerns from the post-marketed use of Albutate in the elderly.

⁷ Stoddart P A et al. A comparison of 4.5% human albumin solution and Haemaccel in neonates undergoing major surgery. *Paediatric anaesthesia* 1996; 6:103-106.

8.7.1.3. Pregnant or breast feeding women

HAS is a normal constituent of human blood. Apart from risk of infection or volume alterations there is theoretically unlikely to be teratogenetic concerns from infusion of albumin. No animal reproduction studies have been conducted with Albutate. Clinical experience with HAS generally has not reported harmful effects on the course of pregnancy, the fetus or the neonate. The use of Albutate in human pregnancy has not been examined in clinical trials (controlled/uncontrolled).

Two non-serious reports (same patient) with preferred term (PT) of exposure during pregnancy have been received for Albutate, reported from the literature.⁸ A woman requiring surgery while pregnant received albumin. A post-op ultrasound scan confirmed a viable pregnancy although there was no follow-up data after 5 days.

8.7.1.4. Hepatic impairment

HAS has been studied extensively in patients with decompensated liver cirrhosis and is widely used in this indication globally. It has been shown to reduce the prevalence of circulatory dysfunction after paracentesis and to improve outcomes in patients with spontaneous bacterial peritonitis reviewed in.⁹

Cumulatively, from 18 September 1996 to 1 September 2013, a total of 25 reports involving patients with hepatic impairment were retrieved from CSL safety database. A total of 95 events were reported in the 25 cases. Review of these events indicated an AE pattern similar to that of the overall patient population.

8.7.1.5. Renal Impairment

Cumulatively, from 18 September 1996 to 01 September 2013, a total of 20 reports involving patients with a history of renal impairment were retrieved from CSL safety database. A total of 64 events were reported in these 20 cases. Review of these events indicated a pattern similar to that of the overall patient population.

There have been literature and prospective observational studies regarding HAS use in renal patients; some showing bias in terms of HAS being used for the sickest patients. A recent systematic review examined comparative safety of colloids based on clinical studies reported from 2002 to 2010 included sixty-nine publications (42 RCTs with 10,382 patients, 8 cohort studies, 7 nonrandomised controlled studies, 7 meta-analyses, 4 systematic reviews, and 1 pharmaco-surveillance study).¹⁰ Except for an observational study where HAS was reserved for sicker patients, there was no other reported deleterious renal effects attributable to hyperoncotic albumin. One study actually suggested albumin-mediated renal protection.

8.8. Safety related to drug-drug interactions and other interactions

Albutate is an albumin and as albumin has a significant role in transport of drugs and other agents, there are potentially drug-drug interactions from competitive albumin binding. However to date these have not been reported as clinically significant.

As albumin is used by IV administration, drug-drug interactions in the gut or food-drug interactions are unlikely to occur.

⁸ Lazaridis, A., et al., A Rare Case of Small Bowel Obstruction Secondary to Ovarian Torsion In An IVF Pregnancy. *BMJ (Cases)*, 2013(Rep Published online [15 February 2013]).

⁹ Gines, P., et al., Review article: albumin for circulatory support in patients with cirrhosis. *Alimentary pharmacology & therapeutics* 2002; 16:24-31.

¹⁰ Groeneveld, A.B et al Update on the comparative safety of colloids: a systematic review of clinical studies. *Annals of surgery* 2011;253:470-483.

There were no relevant drug-drug interactions studies performed and the sponsor states there are no studies planned.

8.9. Evaluator's overall conclusions on clinical safety

Overall the safety profile of HAS, a group of products that has been in clinical use for many decades is well documented. Mortality outcomes have been investigated in several studies, with the most relevant in the SAFE study (due to the recency study, it being undertaken in an Australasian population and using it in the indication requested in the application) showing similar mortality to saline. Several meta-analyses including one of colloid products have suggested similarly.

In terms of specific concerns around potential safety with Albunate; HAS do not appear to affect the blood coagulation profile (although it has been shown to be associated with prolongation of APTT); HAS does not appear to affect the electrolyte/acid base balance; anaphylactoid reactions do occur but this is likely to be more common in HES infusions; the review of relevant literature has not clearly shown a signal on renal outcomes with HAS, although it is becoming clear that the plasma expansion effects need to be separated from the albumin effects. Specifically the meta-analyses suggest volume overload with HAS could be dangerous, particularly in the elderly. The concentration, volume and the infusion rate should be adjusted to the patient's status and individual requirements using measures of circulating volume, not plasma albumin levels. This fact is important and could be made clearer in the proposed PI and CMI.

The relevance of the product under review, Albunate, to the literature on HAS is that Albunate is an HAS. The SAFE study used Albumex 4%. There is no other safety data on Albunate apart from the post-marketing Australian observation study which showed an AE profile similar to other HAS. The PSUR for is unremarkable and no new AEs have been reported.

Safety concerns:

1. Information around fluid and oncotic overload and importance of appropriate assessment prior to using Albunate clearly in the PI, CMI and sponsor advertising.
2. Post-marketing database to be collected on efficacy, safety especially in special groups for a period of one year.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of HAS in the proposed usage are:

- [information redacted]
- Albunate has nearly 40 years of use in US, Canada and Europe with no new safety concerns
- Clinical place of HAS and the clinical risk-benefit analysis/place of use is becoming more defined in practice compared to at the time of initial registration in the US.

9.2. First round assessment of risks

The risks of Albunate in the proposed usage are:

- Clear need for both 20% and 25% not ascertained
- Lack of trial efficacy and safety data to be aware of true efficacy

- Comparison with current HAS in Australia not made.

9.3. First round assessment of benefit-risk balance

Overall, the data in the application did not contain any data to enable a comparison between Alunate and Albumex or any of the other formulations of HAS used in the literature. If both are used in Europe and the US and the formulations all comply with the European and US Pharmacopoeia for Human Albumin then that could be considered. However it would be a stronger case if pharmacology, bioequivalence and clinical data could be provided considering there is no stand-alone data and clinical evidence in those areas for Alunate.

Notwithstanding, it is clear that there is global clinical practice usage data to suggest that as a HAS, Alunate is effective and safe for intravenous infusions for the indication of restoring and maintaining volume. In terms of overall survival, there was no data available to examine this. The clinical evaluator recommended that the 5% concentration be registered in keeping in line with the SAFE study and one of the hyperoncotic concentrations; for consistency it is suggested that this should be with Albumex 20% concentration.

10. First round recommendation regarding authorisation

Advise that the TGA obtain expert clinical advice.

10.1. First round comments on clinical aspects of the safety specification in the draft RMP

The Safety Specification in the draft Risk Management Plan is satisfactory.

Because of the widespread clinical use of Alunate, and documented literature around HAS there are not any additional risk management measures that can be foreseen from a clinical perspective. However the specific product Alunate has not been used in Australia and there still remains a lack of clinical trial data with Alunate.

It is noted that epidemiological studies to elucidate safety or efficacy issues, study drug utilisation or measure effectiveness of risk minimisation measures have not been conducted for Alunate. Therefore close monitoring and pharmacovigilance of this product in the Australian setting is required.

It is also noted that Alunate is a human blood product and therefore ongoing infection vigilance is required. There have not been reports of virus transmission (including HAV, HBV, HCV, HIV or Parvovirus B19) with albumin manufactured to European Pharmacopoeia specifications by established processes, and no cases of transmission of vCJD or other, as yet unknown infectious agents identified with HAS products. There are no confirmed reports of virus transmission with Alunate. Any possible transmission of Transmissible Spongiform Encephalopathies (TSE) is minimised through donor deferral and by avoiding the use of bovine derived materials by CSL Behring during manufacture according to the recommended CPMP guideline "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products (CPMP/BWP/877/96).

As Alunate is a new HAS and without specific clinical trial data to support its evaluation of clinical efficacy and safety, if registered it is recommended that CSL maintain a pharmacovigilance database for Alunate used in the first 12 months of registration. However it is acknowledged that the TGA does not have a process for conditional registration nor pharmacovigilance over and above the current reporting systems. Advice from a clinical expert would be helpful on the possibility of setting up such a database within a current clinical system (for example, the Australasian ICU trial group or similar).

10.2. Additional expert input

It is suggested that additional expert advice is obtained from:

An expert in the use of albumin products in the current Australian clinical context; critical care is likely to be the largest user but also used clinically in hepatology and other clinical specialties

Information to be obtained is the clinical place of albumin therapies in practice, issues with supply and the relative need for another albumin product. Information also, regarding the need and the use of the different strengths of product for example 5, 20 and 25%. Information to be obtained on the feasibility of collecting information on the registration of a new product without the standard clinical trial package but having been used in clinical practice in other jurisdictions with no new safety concerns for 17 years.

11. Clinical questions

1. What was the evidential basis for registration in European countries in 1997? Can the EMA/EMA evaluation reports from 1997 be provided?
2. Why are both the 20% and 25% concentrations are being proposed for registration in Australia? That is, what is the clinical need for both 20% and 25%; in addition to 5%?
3. What are the current volumes of use of Albumex 4% and 20% in Australia?
4. What is the current place of albumin in clinical practice in Australia?
5. [information redacted]
6. Please justify differences between the PI for Albumex and the proposed PI for Alunate?
7. Why are three separate PIs proposed for the three different concentrations? Could different concentrations be included in the one PI?

12. Second round evaluation of clinical data submitted in response to questions

A second round evaluation was not prepared. The Delegate reviewed the information provided by the sponsor in response to the questions raised above and the response is included in the Delegate's summary presented in the AusPAR.

13. References

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4. Green, R.S. and R.I. Hall, Starches Are Not Preferable to Albumin During Cardiac Surgery: A Contrary Opinion. *J Cardiothorac Vasc Anesth* 2008; 22: 485-491.
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Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia

Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605

<https://www.tga.gov.au>