



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Albumin (human)

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

Sponsor: CSL Limited

May 2017

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- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
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Common abbreviations

Abbreviation	Meaning
ADR	Adverse drug reaction
APTT	activated partial thromboplastin time
ARCBS	Australian Red Cross Blood Service
ASA	Australian Specific Annex (to the RMP)
BPWP	Blood Products Working Party
CI	Confidence interval
CMI	Consumer Medicine Information
COP	Colloid osmotic or oncotic pressure
CSL	CSL Limited
DHCPL	dear health care provider letter
EMA	European Medicines Agency
EMEA	European Medicines Evaluations Agency
EU	European Union
GMP	Good Manufacturing Practice
HAS	Human Albumin Solution
HSA	Human serum albumin
HES	Hydroxyethyl starch
ICH	International Conference on Harmonisation
ICU	Intensive care unit
IV	intravenous
LBS	literature based submission
MedDRA	Medical dictionary for regulatory affairs
NBA	National Blood Authority

Abbreviation	Meaning
Ph.Eur.	European Pharmacopoeia
PMF	Plasma Master File
PSUR	Periodic Safety Update Report
RCT	Randomised controlled trial
RMP	Risk Management Plan
RR	Relative risk
SPC	Summary of Product Characteristics
SOC	System organ class
TGA	Therapeutic Goods Administration
USA	United States of America

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New biological medicine
<i>Decision:</i>	Approved
<i>Date of decision:</i>	15 July 2015
<i>Date of entry onto ARTG</i>	30 July 2015
<i>Active ingredient:</i>	Albumin (human)
<i>Product names:</i>	Albunate 5: 250 mL; Albunate 5: 500 mL; Albunate 20: 50 mL; Albunate 20: 100 mL; Albunate 25: 50 mL and Albunate 25: 100 mL
<i>Sponsor's name and address:</i>	CSL Limited ¹ 189-209 Camp Road Broadmeadows VIC 3047
<i>Dose form:</i>	Solution
<i>Strengths:</i>	50 g/L, 200 g/L and 250 g/L
<i>Container:</i>	Vial
<i>Pack sizes:</i>	1
<i>Approved therapeutic use:</i>	<i>Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated and use of a colloid is appropriate</i> <i>The choice of albumin rather than artificial colloid will depend on the clinical situation of individual patient</i>
<i>Route of administration:</i>	Intravenous infusion
<i>Dosage:</i>	The concentration of the albumin preparation, dosage and the infusion rate should be adjusted to the patient's individual requirements. For further details see the Product Information.
<i>ARTG numbers:</i>	223744, 223741, 223739, 223743, 223740, 223742

Product background

This AusPAR describes the application by CSL Limited (the sponsor) to register Albunate 5, Albunate 20 and Albunate 25 for the following indication:

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

¹ Current sponsor is CSL Behring Australia Pty Ltd

The choice of albumin rather than artificial colloid will depend on the clinical situation of the individual patient.

Albumin (human serum albumin (HAS)) is a biological medicine. However, the sponsor is not proposing this product is a biosimilar to Albumex (the only albumin product currently registered and marketed in Australia). Instead, the sponsor is proposing registration as a stand-alone product.

The sponsor is seeking to register a Swiss manufactured albumin product. Currently there is only one albumin product registered and marketed in Australia: Albumex, which is manufactured at the sponsor's Broadmeadows site in Melbourne (from Australian starting plasma collected by the Australian Red Cross Blood Service (ARCBS)). This is a different situation from that in other similar high-income countries, where various different albumins are registered and marketed.

The Swiss manufactured albumin (Albunate) and the Australian manufactured albumin (Albumex) are produced using different methods. However, both products are manufactured from large pools of human plasma in compliance with the European Pharmacopoeia (Ph.Eur.) monograph for "Human Albumin Solution".

There have been shortages of albumin in Australia. The sponsor has advised that this Swiss manufactured albumin is proposed to support continuous supply of albumin in Australia.

Regulatory status

Overseas regulatory history

Albunate is a plasma derived product in clinical use for nearly 40 years. It has been registered and used in multiple jurisdictions but with different trade names. In the US the trade name and concentrations registered are: AlbuRx, 5% and 25%; these have been registered since 1976.

In Switzerland the trade name is Albumin CSL, registered at 5%, 20% and 25% concentrations since 1978.

It has been registered in 25 other European markets and European Economic member states since 1997 with the trade name of Alburex, and others, 5%, 20% and 25%, and a number of other Asian/Middle Eastern States.

Overall the 20% strength is more commonly registered in Europe while the 25% strength is registered in the US and Canada. The 20% and 25% strengths (hyper-oncotic albumin) are used in similar settings.

No application has been rejected or withdrawn in the other markets.

Product Information

The product information (PI) documents approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

Drug substance (active ingredient)

Structure

Human serum albumin (HSA) is a single peptide chain of 585 amino acid residues and contains essentially no carbohydrate. It has a very low content of tryptophan and methionine and a moderately low content of isoleucine and glycine. HSA is relatively resistant to denaturation. The molecular weight of HSA is approximately 66,500 Daltons; the Stokes-Einstein radius is 3.53 nm, and the isoelectric point is around pH 5. The viscosity of HSA is low because its molecule is shaped as a symmetrical ellipsoid.

Manufacture

The proposed human albumin 5%, 20% and 25% solutions are manufactured according to the Kistler and Nitschmann procedure.

After skin thawing, the frozen plasma containers are cut, the plastic containers removed and the frozen plasma blocks continuously pooled into a double jacketed 300 litre thawing tank. The plasma is then thawed under constant stirring to a temperature of - 2 to + 3°C. The cryoprecipitate (cold insoluble globulins) is removed by continuous centrifugation at a temperature of 0 to 6°C and subsequently used for the manufacture of factor VIII, if the plasma quality is suitable for the isolation of coagulation factors, or discarded. The cryo-poor plasma is collected either in a 45.00 L stainless steel tank or directly transferred into the fractionation tank. After the homogenisation in the fractionation tank, the plasma pool samples are drawn.

The pH of the plasma is lowered to pH 5.7 to 6.0 with acetate acetic acid buffer (pH 4). Ethanol 96% is added continuously to a concentration of 19% (V/V) while stirring and cooling to a temperature of - 5.5°C ± 1.0°C. The pH is then adjusted to 5.70 to 5.90. The suspended precipitate A is removed by filtration after addition of perlite (volcanos earth filter aid) on polypropylene sheets. Precipitate A is used in the manufacture of immunoglobulin products.

The filtrate of Precipitate A is collected in another stainless steel tank for further processing to albumin. The temperature is reduced to - 7 ± 0.5°C, and simultaneously 96% ethanol is added to a final concentration of 40% (V/V). The pH of this solution is adjusted, if necessary, to 5.95 to 6.00. Fraction IV precipitates and is then, by the use of filter aids (perlite and diatomaceous earth), filtered through a filter matrix support in order to remove the precipitate.

The pH value of filtrate IV is adjusted by 1.1 M acetic acid to 4.8 ± 0.1 at a constant ethanol concentration of 40% and under cooling to a temperature of - 7 ± 1°C. Precipitate C precipitates and is then separated from the ethanol solution by filtration with diatomaceous earth. Precipitate C contains almost exclusively albumin and filter aids. For further processing Precipitate C from one or more fractionation lots is first resuspended in water for injection (1 kg paste + 1.7 kg water for injection) and then filtered at pH 4.7 ± 0.1 through asbestos free depth filters. The pH of Filtrate d is adjusted to 7.2 ± 0.1 by means of 1 M NaOH.

The neutralised solution is concentrated to about 130 to 140 g/kg albumin by ultrafiltration, then diafiltered first with at least five times the actual volume of 0.1 to 0.3 M sodium chloride, then with 0 to 3 times the amount of water for injection. By this process aluminium, other low molecular salts and ethanol are removed. A sample of the solution is drawn to examine the protein content and the sodium concentration.

The final adjustment of the properties of the final product is achieved by calculated analysis. The sodium content is adjusted by sodium chloride to a concentration of 140 mmol/L. Then 0.08 mmol sodium caprylate and 0.08 mmol sodium N-acetyltryptophanate per gram of protein, corresponding to 20 mmol/L for 25% albumin, 16 mmol/L for 20% albumin and 4 mmol/L for 5% albumin, are added to the albumin solution as stabilisers. Water for injection is added to a protein concentration of 233.6 g/kg (for 25% albumin) 188 g/kg (for 20% albumin) and 49 g/kg (for 5% albumin). If necessary the pH is adjusted by hydrochloric acid or sodium hydroxide solution, respectively.

In the manufacture of Albumex additional steps including anion and cation exchange and gel exclusion chromatography are used. In terms of manufacturing process, this distinguishes the two products Albumex and Albunate from one another. Data has not been provided to demonstrate comparability or similarity between these 2 products.

All viral/prion safety issues have been addressed in a secondary specialist evaluation.

Drug product

The drug products contain appropriate amounts of albumin as the captive ingredient according to Ph. Eur. as well as the following excipients: sodium N-acetyltryptophanate: stabiliser; sodium caprylate: stabiliser; sodium chloride: tonicity agent; water for injections: solvent. Protein content is adjusted as required to manufacture 5%, 20% and 25% Human Albumin Solution (HAS). The drug product meets the European Pharmacopoeia (Ph.Eur.) standard.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data: the product is photo-stable.

The proposed shelf life is 36 months when stored at 25°C. This is supported by the data.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

In their response to questions the sponsor confirmed that Albunate and Albumex are manufactured by very different processes. Although the processes for both Albunate and Albumex produce a final product which meets the Ph. Eur. monograph for 'Human Albumin Solution' (01/2013:0255) the evaluator commented that the use of consecutive cold ethanol precipitation method alone (Albunate) as opposed to a combined method of Cohn cold ethanol precipitation followed by multiple chromatographic steps (the currently registered Albumex) will possibly lead to products that while similar in albumin content are not similar in other impurities such as clotting factors. Quality data has not been provided to address the level of similarity between the proposed product and the currently registered Albumex product.

For this reason and because of the admitted differences in the manufacturing processes for the two albumin products the evaluator felt that the PI for Albunate should make it clear that Albunate was not identical to Albumex in its mode of manufacture. The sponsor has done this.

The above issues have been resolved following discussions between the quality evaluation area and the Delegate.

Conditions of registration

Batch Release Testing by the TGA Laboratories Branch. It is a condition of registration that, as a minimum, the first five independent batches of;

Albunate 5 (50 g/L (5% w/v) 250 mL)

Albunate 5 (50 g/L (5% w/v) 500 mL)

Albunate 20 (200 g/L (20% w/v) 50 mL)

Albunate 20 (200 g/L (20% w/v) 100 mL)

Albunate 25 (250 g/L (25% w/v) 50 mL)

Albunate 25 (250 g/L (25% w/v) 100 mL)

imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

III. Nonclinical findings

It was agreed, pre-submission, that a nonclinical evaluation was not required, as long as the nonclinical aspects of the proposed Australian PI for the Swiss manufactured Albunate were the same as those for the already-registered Australian-manufactured Albumex.

Albumin is unlikely to have toxicological effects on humans because it is of human origin.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

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, HAS 5% was shown to support the total plasma volume while in trauma patients or in severely burned patients, the concentrated HAS 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 Blood Products Working Party

(BPWP) to have a backup for the supply of blood products should there be issues with the current registered albumin product.

Guidance

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 literature based submission (LBS) guidance released on 27 May 2014. However the sponsor completed the compilation of the dossier in March 2014 for pre submission.

Contents of the clinical dossier

The submission is based on a three pronged hybrid LBS. The literature review part of this 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 Albutate) and based on the proposed indication, which is based on the European Union (EU) Core Summary of Product Characteristics (SmPC) 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 Albutate (marketed as Albumin SRK in Austria), the product seeking registration.

The sponsor was given approval to not submit nonclinical data based on advice from the nonclinical evaluation stream leader; essentially that statements in the proposed PI 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 Risk Management Plan (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 primary clinical data to support the use of Albutate is collected from periodic safety activities from 1996 to the present and was 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 Australian approved names AANs sodium octanoate and octanoic acid.

Albunate contains a new non-proprietary ingredient sodium tryptophanate. The excipient N-acetyltryptophan is added to stabilise human albumin in accordance with the Ph. Eur monograph² and United States Pharmacopeia (USP) monograph.³ The excipient complies with the Ph. Eur monograph for N-Acetyltryptophan.⁴ 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) Plasma Master File (PMF).

In summary the clinical module includes:

Clinical study reports

- Post marketing experience (AE by system organ class (SOC))
 - Austrian post marketing survey with Albumin 5% and 20% (Albunate)
 - Periodic Safety Update Report (PSUR) 1 October 1997 to 31 March 2002
 - PSUR 1 April 2002 to 20 October 2006
 - PSUR 21 October 2006 to 20 October 2009
 - PSUR 21 October 2009 to 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)

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

² 01/2013:0255 Human Albumin Solution

³ United States Pharmacopeia (USP) 36 Albumin Human monograph

⁴ Ph. Eur. monograph for N-Acetyltryptophan 01/2009:1383

- Adverse Event Line Listings from 1996 to 2013.

This primary data, specific to Alburnate, is supported by the publications provided in the clinical module. These use a variety of different HAS products (although some studies are likely to have included patients on Alburnate, not specified). Specifically, the module includes meta-analyses and several series of Cochrane reviews – presented in the tabular summaries in the clinical module and also summarised and discussed in the clinical summary as supporting studies. Also included in the clinical module 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 Alburnate specifically, although this primary data is observational only, as is the PSUR.

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 Alburnate. However CSL has requested listing in a paediatric population in Australia (from newborns through to adults). There is no specific Alburnate 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.

Good clinical practice

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

Pharmacokinetics

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 intravenous (IV) exogenous albumin are 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 Alburnate are expected to be those of other human albumins given intravenously.

Evaluator's 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 Albutate 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.

Pharmacodynamics

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 colloid osmotic or oncotic pressure (COP) in normal patients; one of the main reasons to use human albumin in states of reduced volume.

Iso-oncotic albumin as with Albutate 5 restores and maintains the circulating blood volume where volume deficiency has been demonstrated. The hyperoncotic Albutate 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.

Evaluator's conclusions on pharmacodynamics

There were no pharmacodynamic studies submitted with Albutate. Although there was literature provided on albumins and change in COP or other pharmacodynamic 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 Albutate and pharmacodynamic endpoints were unable to be located; and the rationale in the application for Albutate specifically and pharmacodynamic outcomes was not well discussed.

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.

Efficacy

Restoration and maintenance of volume status

Data for evaluation of Albutate was provided by a literature review of predominantly randomised controlled trials (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
- Albutate use not specified (presumed use in the US data but numbers/percentages in the trials not specified)
- no specific Albutate 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 Albutate; although it is likely that Albutate 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 Albutate 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)⁵. 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 critically ill patients with burns and hypoalbuminaemia and there is a

⁵ 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

suggestion that albumin may increase the risk of death.⁶ In the more recent Cochrane review of November 2011 (Roberts I et al. 2011)⁷ 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.

Studies providing efficacy data

There were no pivotal efficacy studies undertaken.

Evaluator's conclusions on efficacy

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 intensive care unit (ICU) patients.

There is published randomised controlled trial (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%.

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

⁶ Alderson, P., et al., Human albumin solution for resuscitation and volume expansion in critically ill patients. The Cochrane database of systematic reviews, 2004(4): CD001208.

⁷ Roberts, I, et al. Human albumin solution for resuscitation and volume expansion in critically ill patients Cochrane Database of Systematic Reviews 2011 Cochrane

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 about 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 Albunate.

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 Albunate is also unanswered by these meta-analyses; unless it is assumed that Albunate and the other available HAS are all similar enough to be interchangeable. However there is no evidence presented to support that.

Safety

Studies providing 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 Albunate.

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 PSUR (1997). Further, one of the meta-analyses on safety of

albumin versus other colloids showed albumin was safer.⁸ 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.⁹ 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 % confidence interval (CI): 0.76 to 0.81).⁸

Patient exposure

Over 40 years in many countries around the globe.

Safety issues with the potential for major regulatory impact

Haematological toxicity

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

Human Albumin Solution (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 activated partial thromboplastin time (APTT)¹⁰, as have the infusion of larger fluid volumes of other agents.¹¹ 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 Hydroxyethyl starch (HES).⁸

Serious skin reactions

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

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,⁸ it was reported that with HAS as the reference colloid, the incidence rate ratio for anaphylactoid reactions was:

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

⁸ 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

⁹ 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

¹⁰ The activated partial thromboplastin time (APTT) is a test that characterises blood coagulation (clotting).

¹¹ 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

Unwanted immunological events

Hypersensitivity and anti-erythrocyte antibodies occur infrequently with HAS.

Safety in special populations***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 Alunate, 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.¹² 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 Alunate 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 Alunate 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.

Elderly use

There is no specific Alunate 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 Alunate.

Cumulatively, from 18 September 1996 to 1 September 2013, there were 60 case reports for Alunate 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 Alunate in the elderly.

Pregnant or breast feeding women

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

¹² 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.

Two non-serious reports (same patient) with preferred term (PT) of exposure during pregnancy have been received for Alunate, reported from the literature.¹³ 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.

Hepatic impairment

Human Albumin Solution 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.¹⁴

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.

Renal impairment

Cumulatively, from 18 September 1996 to 1 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 non-randomised controlled studies, 7 meta-analyses, 4 systematic reviews, and 1 pharmaco-surveillance study).¹⁵ 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.

Post-marketing data

These are covered in

1. The Austrian post-marketing survey “The observational Austrian study “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 adverse drug reactions (ADRs) were reported by 20 patients

¹³ 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])

¹⁴ Gines, P., et al. Review article: albumin for circulatory support in patients with cirrhosis. *Alimentary pharmacology & therapeutics* 2002; 16: 24-31

¹⁵ 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

(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.

Evaluator’s conclusions on 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 of the 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 Hydroxyethyl starch (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 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.

First round benefit-risk assessment

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.

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.

First round assessment of benefit-risk balance

Overall, the application did not contain any data to enable a comparison between Albunate 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 Albunate.

Notwithstanding, it is clear that there is global clinical practice usage data to suggest that as a HAS, Albunate 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 the 5% concentration be registered in keeping in line with the SAFE study and one of the hyperoncotic concentrations; for consistency with Albumex the clinical evaluator suggested the 20% concentration.

First round recommendation regarding authorisation

Advise that the TGA obtain expert clinical advice.

Clinical questions

1. What was the evidential basis for registration in European countries in 1997? Can the European Medicines Agency (EMA)/ European Medicines Evaluations Agency (EMA) evaluation reports from 1997 be provided?
2. Why are both the 20% and 25% concentrations 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 Albunate?
7. Why are three separate PIs proposed for the three different concentrations? Could different concentrations be included in the one PI?

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 (please see the Delegate's review in the overall conclusion and risk benefit analysis section below).

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP (Version: 2.0, dated December 2013) with an Australian Specific Annex (ASA) Version: 1.1, dated July 2014 which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown in Table 1.

Table 1: Summary of ongoing safety concerns

Summary of safety concerns	
Important identified risks	Anaphylactic reactions
Important potential risks	Transmission of infectious agents
Important missing information	Non identified

Pharmacovigilance plan

The sponsor proposed routine pharmacovigilance activities to monitor all the specified ongoing safety concerns. The ASA states:

'The pharmacovigilance organisation in Australia is not a separate function but operates within CSL's global pharmacovigilance system, with sites in the EU, USA and Australia. The pharmacovigilance system complies with the regulatory requirements of all the above regions. A qualified person for pharmacovigilance is nominated for Australia and this person resides in Australia.'

Risk minimisation activities

The sponsor has concluded that routine risk minimisation activities are sufficient for all the specified ongoing safety concerns.

Reconciliation of issues outlined in the RMP report

Table 2 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the RMP evaluator and the evaluation of the sponsor's responses.

Table 2: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>Safety considerations may be raised by the clinical evaluator through the consolidated TGA request for information. It is important to ensure that the information provided in response to these include a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.</p>	<p>The sponsor reports: "The clinical evaluator recommended additional wording under 'Dosage' for inclusion of information relating to fluid and oncotic overload. A statement 'Infusion rate and volume need to be adapted according to clinical conditions, most notably in the elderly or in the paediatric population.' has been included in the revised PI documents" and the important potential risk: 'Hypervolaemia and haemodilution in high risk patients' has now been included as a safety concern.</p> <p>[information redacted]If Albutate is supplied in Australia, assurance is provided that safety surveillance will be performed in accordance with CSL Behring's on-going routine pharmacovigilance practices".</p>	<p>This is acceptable.</p> <p>The Delegate has advised that this response is acceptable.</p>
<p>Notwithstanding the evaluation of the clinical aspects of the safety specification: 'Potential for off-label use' of the EU-RMP states that the potential for off-label use is a class-effect for all HA products and it cannot be excluded that HA products are used outside the approved indications. Consequently it is suggested that the sponsor</p>	<p>The sponsor states: "The definition of important identified risk and important potential risk (Good Pharmacovigilance practices (GVP) Annex I) is 'what constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk and the impact on public health'. Currently, there is no available data</p>	<p>This is acceptable.</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>consider including 'Off-label use' as an important potential risk. It is noted that routine pharmacovigilance and routine risk minimisation activities are already proposed for this ongoing safety concern and only the ASA need be revised accordingly.</p>	<p>and/or evidence showing that off-label use of HAS causes serious individual risk or public health concerns. Therefore, 'off-label use' has not been listed in the ASA Summary table of Safety Concerns as an important potential risk. Spontaneous and other reports of off-label use will be reviewed in accordance with CSL Behring's ongoing routine pharmacovigilance practices."</p>	
<p>For completeness it is suggested that the sponsor consider including 'Use in Pregnancy and lactation' and 'Use in paediatric patients' as missing information. Consideration must be given as to what pharmacovigilance and risk minimisation activities will be proposed for these new ongoing safety concerns and only the ASA need be revised accordingly.</p>	<p>The sponsor has provided justification for not including 'Use in Pregnancy and lactation' and 'Use in paediatric patients' as missing information.</p>	<p>This is acceptable.</p>
<p>The RMP Questions and Answers (Version 1.3, October 2012) as found on the TGA website state: "The ASA should identify any differences between the EU-RMP and the local implementation of risk management activities, for example: any differences between the risk minimisation activities undertaken as reflected in the content of the EU Summary of Product Characteristics (SmPC) and the proposed Australian PI, and the</p>	<p>The sponsor states: "The routine pharmacovigilance and risk minimisation measures undertaken as reflected in the current content of the EU SmPC and the proposed Australian PI are consistent. Human Albumin CSL Behring has no additional risk minimisation measures. A detailed comparison of the actual content and wording of the EU SmPC and the proposed Australian PI (and CMI) has been added as an Annex to the ASA (see section 1.13.1, Australian Specific Annex,</p>	<p>This is acceptable.</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
<p>reasons for the difference.” Consequently the ASA should be revised to include a risk minimisation activities table detailing all planned risk minimisation measures in the Australian context and the EU-RMP context. This table should include a comparison of the actual content and wording of the EU SmPC and the proposed Australian PI and CMI for all of the specified ongoing safety concerns and missing information to identify and provide reasons for any observed differences, particularly where it appears the EU SmPC is more restrictive.</p>	<p>Annex 1).”</p>	
<p>A table summarising the pharmacovigilance and risk minimisation activities for all of the specified ongoing safety concerns and missing information proposed for Australia should be included in the revised ASA.</p>	<p>The sponsor states: “Tables summarising planned pharmacovigilance actions (see section 1.13.1 Australian Specific Annex, 3.2) and risk minimisation activities (see section 1.13.1 Australian Specific Annex, Annex 1) for all safety concerns proposed for Australia have been included in the revised ASA”.</p>	<p>This is generally acceptable, although Table 3.2: ‘Safety concerns and overview of planned pharmacovigilance actions’ is included in Section 3: ‘Risk Minimisation Plan’ of the ASA. This table should logically be relocated to Section 2: ‘Pharmacovigilance Practice’ of the ASA or included as a separate annex to the</p>

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
		ASA. This amendment to the ASA can be dealt with administratively when this document is next updated.
<p>In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft PI document be revised to include a precautionary statement to the effect that the Alunate product range is not interchangeable with Albumex product range, which may be cross-referenced to the dosage and administration section.</p>	<p>[information redacted] The distribution and supply of blood products are managed by the NBA. In the case of Alunate being supplied, an appropriate communication plan would be prepared and provided to all stakeholders (including the NBA, the ARCBS and clinicians). Therefore CSL Behring does not propose to include statements about interchangeability in the Alunate PI".</p>	<p>This is generally acceptable, although the sponsor should explicitly include such an assurance in a revised ASA, including the provision to the TGA of the details of such a communication plan before Alunate is supplied, preferably before this application is approved.</p>
<p>In addition the draft EU 'Guideline¹⁶ states: "In section 4.4 a new warning statement is introduced for patients with brain injury and burns taking into consideration the results of the SAFE-TBI study and the most recent Cochrane analysis." The Delegate is asked to consider whether such a precautionary statement should be included in the Australian</p>	<p>The sponsor states: "CSL Behring acknowledges the concerns related to traumatic brain injury (TBI) and burns. The 'Guideline on core SmPC for human albumin solution' rev 3.0 is still in draft form while input from stakeholders is reviewed. CSL Behring, as an interested stakeholder, performed a careful analysis of the available data to assess the safety profile of</p>	<p>This is acceptable.</p>

¹⁶ EMA/CHMP/BPWP/494462/2011 rev.3 draft EU 'Guideline on core SmPC for human albumin solution.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
PI to enhance safe use of these products.	albumin and provided comment on the draft SmPC. CSL Behring's conclusions were the available data showed no compelling evidence that albumin is harmful in TBI and burned patients and therefore does not propose to change the Alunate PI until the Core SmPC is finalised. Accordingly, the EU SmPC which has recently been updated does not contain such a statement."	
In regard to the proposed routine risk minimisation activities, it is recommended to the Delegate that the draft CMI document be revised to adequately reflect any changes made to the Australian PI as a result of the above recommendations.	The sponsor states: "The CMI will be updated as appropriate when the changes made to the PI have been finalised."	This is acceptable.

Summary of recommendations

Suggested wording for conditions of registration

RMP:

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

At this time no wording can be provided, as it is recommended that an acceptably revised ASA be submitted before this application is approved.

VI. Overall conclusion and risk/benefit assessment

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

Introduction

Use of albumin in clinical practice in Australia

Randomised studies have not convincingly shown a benefit of colloids (such as albumin) over crystalloids in critically ill patients on the outcome of mortality (see results of Cochrane review below). Anecdotal evidence suggests that there is wide variation in the use of albumin across hospitals in Australia, with no particular pattern to the variation.

The TGA therefore sought the views of two external clinical experts on the use of albumin in Australia. The following responses were provided:

External clinical expert 1

1. Volume replacement – plus some beliefs of benefits in sepsis and subarachnoid haemorrhage (SAH)
 - a. Caironi P, et al ALBIOS Study Investigators. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med*. 2014;370:1412-1421.
 - b. Suarez JI, et al. Human albumin administration in subarachnoid haemorrhage: results of an international survey. *Neurocrit Care*. 2014;20:277-286.
 - c. Suarez JI, and Martin RH. Treatment of subarachnoid haemorrhage with human albumin: ALISAH study. Rationale and design. *Neurocrit Care*. 2010;13:263–277.
 - d. ALISAH II, a Phase III, randomised, placebo-controlled trial to test the efficacy of albumin, is underway.
2. Without much data 20% albumin is often used as a slow infusion to boost low albumin levels, to promote diuresis with the help furosemide or as a colloid backup during dialysis to allow better volume expansion whilst removing fluid.

External clinical expert 2

There are four main areas of usage:

1. Albumex 4% is routinely used for plasmaphoresis, to treat various immunological and haematological disorders (for example TTP and paraproteinaemias).
2. Albumex 4% or 20% is used by perfusionists to prime the heart-lung machine for most cardiac surgery.
3. Resuscitation in trauma and major surgery. Albumex 4% is sometimes used as a resuscitation fluid to correct hypovolaemia; in most cases used by anaesthetists during surgery, including trauma and emergency surgery. It is less commonly used by intensive care and emergency physicians (because of the SAFE study showing no benefit over simple crystalloid solutions). Albumex 20% is far less commonly used in these settings. Albumin solutions are rarely used by junior doctors or any others working in general medical and surgical hospital wards.
4. Albumex 20% is used to restore plasma oncotic pressure in patients with ascites (following an ascitic tap).

The two clinical experts were also asked about the implications of an albumin shortage in Australia:

External clinical expert 1

This happened for a short period a couple of years ago and there were very dissatisfied local clinicians. Nevertheless many places/countries hardly allow albumin administration due to its expense.

External clinical expert 2

There is an absolute need for albumin solutions in situations 1, outlined above (under advice from external clinical expert 2). There is a strong indication for their use in situations 2 and 4. For situation 3, albumin solutions have a probable benefit in uncommon but life threatening scenarios, typically in shock states in which there is some concern about overuse of other colloids (Gelofusin, Voluven). In many of these scenarios other IV fluids can be used, but it may not be ideal. There is a possible (but theoretical) risk of avoidable patient harm.

Quality

The quality evaluator recommended approval, but with batch release conditions of registration.

Nonclinical

It was agreed, pre-submission, that a nonclinical evaluation was not required, as long as the nonclinical aspects of the proposed Australian PI for the Swiss manufactured Alunate were the same as those for the already registered Australian manufactured Albumex.

Albumin is unlikely to have toxicological effects on humans because it is of human origin.

Clinical

This was a literature based submission (an approach approved by the TGA pre-submission) that comprised:

- randomised controlled trials (RCTs) and meta analyses around the efficacy of albumin generally
- pharmacovigilance data collected from periodic safety activities from 1996 to the present, specifically for Alunate
- a small post-marketing safety study of Alunate (marketed as Albumin SRK), from Austria.

Alunate was registered in Europe (through national licenses) and the US as a “well established use” product. There were no sponsor initiated trials.

The clinical evaluator noted that there was no direct comparison between Alunate and Albumex, but also noted that “there was 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.”

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 with Albumex suggest the 20% concentration.” The sponsor has replied that both the 20% and 25% strengths should be registered so that in the event of a shortage there is “flexibility to respond as quickly as possible with either registered product, depending on stock availability”.

Efficacy

Human albumin, as a therapeutic agent, was developed 60 years ago. In the 1980’s and 1990’s, several authoritative bodies considered recommendations for appropriate use. Broadly speaking, the consensus was that administration of albumin was probably

justified in cases of acute circulatory problems caused by hypovolemia. Since then, further evidence has accumulated and there have been questions about whether albumin (and colloids in general) was any more efficacious than crystalloids. The accumulated evidence on the outcome of mortality was meta-analysed in a Cochrane systematic review; some excerpts are given below.¹⁷

Albumin or plasma protein fraction

Twenty-four trials reported data on mortality, including a total of 9,920 patients. The pooled relative risk (RR) was 1.01 (95% CI 0.93 to 1.10). When trials by Boldt were removed, the results were unchanged (RR 1.01; 95%CI 0.93 to 1.10). When we excluded the trial with poor quality allocation concealment, pooled RR was 1.00 (95% CI 0.92 to 1.09).

Comment: Some of the trials would have included the Swiss manufactured Alburnate, but it is not possible to identify which ones. 80% of the weight towards the pooled estimates in the meta-analysis came from the SAFE study, conducted in Australia and New Zealand. That study used the Australian manufactured Albumex (4.0%).

Hydroxyethyl starch

Twenty-five trials compared hydroxyethyl starch with crystalloids, including a total of 9,147 randomised patients. The pooled RR for mortality was 1.10 (95% CI 1.02 to 1.19). When trials by Boldt were removed, the results were unchanged.

Modified gelatin

Eleven trials compared modified gelatin with crystalloid, including a total of 506 randomised patients. The pooled RR for mortality was 0.91 (95% CI 0.49 to 1.72). When trials by Boldt were removed, the results were unchanged.

Dextran

Nine trials compared dextran with a crystalloid, including a total of 834 randomised patients. The pooled RR for mortality was 1.24 (95% CI 0.94 to 1.65).

Implications for practice

There is no evidence from randomised controlled trials that resuscitation using colloids compared with crystalloids reduces the risk of death in patients with trauma, burns or following surgery. The use of hydroxyethyl starch might even increase mortality. Since colloid use is not associated with improved survival and colloids are considerably more expensive than crystalloids, it is hard to see how their continued use in clinical practice can be justified.

Safety

Antibody reactions against albumin associated, still unidentified antigens, may occur. This is manifested by fever, urticaria and nausea. These symptoms typically disappear if the infusion rate is decreased or if the infusion is stopped.

Severe anaphylaxis and shock can occur; it is exceedingly rare.

Circulatory overload may develop as a non-specific volume effect if albumin is administered in too large quantities or too rapidly relative to the needs of the individual patient.

¹⁷ Perel P, et al. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database of Systematic Reviews* 2013, Issue 2. Art. No.: CD000567. DOI: 10.1002/14651858.CD000567.pub6. Last updated 17 Oct 2012

Virus validation studies have demonstrated that viruses are eliminated by at least two different mechanisms during manufacture. There are no documented cases of transmissions of viruses or other infectious agents by albumin solutions.

In 1996, four ADRs (transient hypotension during major surgery) were reported after the treatment with one batch of Human albumin "SRK", former name of Human albumin "ZLB" (that is, Swiss manufactured Albutate that is the subject of this submission). The batch withdrawn by the manufacturer from the US market after batch analysis showed an increased activity of the prekallikrein activator (PKA). It was shown that the increase occurred after batch release during the storage; and, although never proven, the increase was considered a possible reason for the ADRs. Therefore the manufacturer identified critical steps in the production and introduced specific measures to prevent an elevation of PKA activity during shelf life. In Austria the manufacturer was instructed by the authorities to perform studies on PKA activity during the storage. The results submitted did not show an increase of PKA during shelf life.

A non-randomised, post-marketing study (prospective, no control group) was conducted in Austria (n = 211). The participants were critically ill surgical patients. Either Albutate 5% or 20% was administered for volume replacement or correction of an oncotic deficit. Five patients died because serious preceding traumatic injuries, 11 patients showed slight to moderate hypotension, 9 patients showed light or moderate erythema. No case of severe anaphylactic reaction and no other undesirable effects were observed. Inferences from the study were limited because there was no control group; and also because of the small sample size.

Risk management plan

Summary of safety concerns

Table 4: Summary of ongoing safety concerns including the mitigation strategy

Risk category	Risk	Mitigation strategy
Important identified risks	Anaphylactic reactions	<p>Routine: addition of information to PI</p> <p>Contraindications: Hypersensitivity to albumin preparations or to any of the excipients.</p> <p>Precautions: Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. In case of shock, standard medical treatment for shock should be implemented.</p> <p>Adverse effects: Mild reactions with human albumin solutions such as flush, urticaria, fever and nausea occur rarely. These reactions normally disappear rapidly when the infusion rate is slowed down or the infusion is stopped. Very rarely, severe reactions such as shock may occur. In these cases, the infusion should be stopped immediately and an appropriate treatment should be initiated.</p>
Important potential	Transmission of infectious	Routine: addition of information to PI

Risk category	Risk	Mitigation strategy
risks	agents	<p>Precautions: Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. There are no reports of virus transmissions with albumin manufactured to European Pharmacopoeia specifications by established processes.</p> <p>It is strongly recommended that every time that Alunate is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.</p>
Missing information	None identified	

The two external clinical experts were asked whether any measures beyond routine pharmacovigilance were required. They both stated routine pharmacovigilance was adequate.

Risk-benefit analysis

Delegate's considerations

Efficacy and safety

This Swiss manufactured albumin (Alunate) has been marketed in several countries (with regulatory systems similar to Australia) for about four decades. The proposed registration is to ensure a continuous supply of albumin in Australia. [Information redacted].

There are no sponsor initiated trials for Alunate. The product has been approved in all markets based on literature submissions; or initially as an "established use" product.

Albumin is a biologically derived product. However, the sponsor is not making any claim that Alunate is a biosimilar of Albumex. Instead, the sponsor is seeking registration of Alunate as a stand-alone product.

Literature based evidence for the efficacy of albumin is patchy, with some experts arguing that, for hypovolaemia, crystalloids might be just as effective. The TGA sought the views of two external clinical experts who advised that albumin currently has an established place in Australian clinical practice; as it does globally.

In terms of safety, mild reactions such as flush, urticaria, fever and nausea occur rarely. These reactions normally disappear rapidly when the infusion rate is slowed down or the infusion is stopped. Even more rarely, severe reactions such as anaphylaxis may occur. No cases of virus transmission with human albumin manufactured to European Pharmacopoeia standards have been reported.

In the responses to questions raised by the TGA the sponsor confirmed that Albunate will be registered but not supplied unless there is a shortage of albumin.

Registration of both 20% and 25% concentrations

Both the external clinical experts advised that only one of the 20% or 25% concentrations is needed. The sponsor agreed that there was no clinical need to have both strengths registered. However, the sponsor, still wanted to register both the 20% and 25% strengths in the event of a shortage, so that there is “flexibility to respond as quickly as possible with either registered product, depending on stock availability”.

Mixing of Albumex and Albunate in the one infusion or one-episode-of-care

The sponsor provided the following response:

“[information redacted] There could be an overlapping period when both products are on the market at the same time. However both Human Albumin solutions should not be mixed in the same infusion. As indicated in the labelling, Albunate should not be mixed with other products: “Human albumin must not be mixed with other medicinal products, whole blood and packed red cells.”

The simultaneous presence of several different Human Albumin solutions on the same market is very common. For many years CSL Behring has marketed different Human Albumin solutions at the same time in the same countries for example US, Europe and China. Besides, several other Human Albumin solutions from different companies are also marketed worldwide. No safety concern has been raised concerning the presence of different Human Albumin solution products on the market simultaneously.

Both Albunate and Albumex comply with the European Pharmacopoeia (Ph. Eur.) requirements for ‘Human Albumin Solution’. As per the Ph. Eur., Human Albumin solution may contain excipients such as sodium caprylate (sodium octanoate) or N-acetyltryptophan or a combination of the two. Albunate and Albumex differ in the stabilisers added to formulate a parenteral solution. Albumex contains 32 mmol/L sodium octanoate whereas Albunate contains 16 mmol/L sodium octanoate and 16 mmol/L sodium N-acetyltryptophanate. Should both formulations be administered to a patient in a single day, the relative proportion of N-acetyltryptophanate would be between 0% (Albumex only) and 50% (Albunate only). The relative merits of these stabilisers have been examined. No safety concern arises from the relative proportion of N-acetyltryptophanate, should mixing occur.

[Information redacted] CSL Behring provides the assurance that an appropriate logistical and communication plan developed and executed in conjunction with the NBA and Australian Red Cross Blood Service (ARCBS) will be in place.

Conditions of registration

The RMP evaluator stated that: “At this time no wording can be provided (for the condition of registration about the RMP).” Finalisation of the wording is pending.

The quality evaluator has specified the following Conditions of Registration:

Batch Release Testing by the TGA’s Office of Laboratories and Scientific Services (OLSS)

It is a condition of registration that, as a minimum, the first five independent batches of

Albunate 5 (50 g/L (5% w/v) 250 mL)

Albunate 5 (50 g/L (5% w/v) 500 mL)

Albunate 20 (200 g/L (20% w/v) 50 mL)

Albunate 20 (200 g/L (20% w/v) 100 mL)

Albunate 25 (250 g/L (25% w/v) 50 mL)

Albunate 25 (250 g/L (25% w/v) 100 mL)

imported into Australia are not released for sale until samples and/or the manufacturer’s release data have been assessed and endorsed for release by the TGA.

The sponsor should supply:

Certificates of Analysis of all active ingredient (drug substance) and final product.

Information on the number of units to be released in Australia with accompanying expiry dates for the product and diluents (if included).

Evidence of the maintenance of registered storage conditions during transport to Australia.

Question for sponsor

- [Information redacted] the possibility of one patient receiving a mix of Albumex and Albunate in the one infusion
 - what safety risk this may pose
 - how any risk should be mitigated.

Summary of issue/s

- Albunate has been registered and marketed in several countries for four decades.
- This is a literature based submission. Albumin has been registered as a “well established use” product. There are no company sponsored, clinical endpoint studies.
- [information redacted]
- Literature based evidence for the efficacy of albumin versus crystalloids is patchy, with some experts arguing that, for hypovolaemia, crystalloids might be just as effective.
- Albumin currently has an established place in Australian clinical practice; as it does globally.
- In terms of safety, mild reactions such as flush, urticaria, fever and nausea occur rarely. These reactions normally disappear rapidly when the infusion rate is slowed down or the infusion is stopped. Even more rarely, severe reactions such as anaphylaxis may occur. No cases of virus transmission with human albumin manufactured to European Pharmacopeia standards have been reported.

Proposed action

The Delegate had no reason to say, at this time, that Albunate should not be approved for registration.

Request for ACPM advice

The ACPM is asked to advise on whether efficacy and safety have been satisfactorily established.

Response from sponsor***Request for ACPM's advice***

CSL welcomes the Delegate's comment in the Pre ACPM preliminary assessment: "*I have no reason to say, at this time, that Albunate should not be approved for registration*".

Background (including overseas regulatory history)

The background to the product is accurate. [Information redacted] There is currently no alternative albumin product available on the Australian market.

CSL acknowledges the views of the two external clinical experts detailed 'Use of albumin in clinical practice in Australia'.

The overview/regulatory history as provided is accurate and correctly reflects that Albunate (with different trade names) has been in clinical use for nearly 40 years and is approved in Switzerland, the USA, the EU, Canada and a number of other Asian and Middle Eastern countries.

Biological chemistry evaluation

CSL has no comment on the biological chemistry evaluation summarised by the Delegate. CSL notes that all issues regarding the manufacturing processes of Albunate versus Albumex have been resolved following discussions between the quality evaluation unit and the clinical Delegate.

Nonclinical evaluation

As stated, it was agreed at a pre-submission meeting that a nonclinical evaluation was not required.

Clinical evaluation

The summary of clinical evaluation of the literature based submission provided in the Delegate's request accurately reflects the clinical status of Albunate.

CSL notes the clinical evaluator recommendation that the 5% concentration be registered in line with the SAFE study and one of the hyperoncotic concentrations. CSL reiterates the desire to register both hyperoncotic strengths of Albunate, 20% and 25%, so that there is flexibility with either presentation, depending on stock availability.

The summary of clinical efficacy provided in the Delegate's request accurately reflects the published studies regarding the clinical efficacy of Human albumin.

The summary of clinical safety provided in the Delegate's request accurately reflects the clinical safety status of Albunate.

Risk Management Plan

CSL has no comment on the RMP evaluation.

Discussion

CSL welcomes the views of the two external clinical experts who advised that albumin currently has an established place in Australian clinical practice.

[Information redacted]

Conditions of registration

CSL confirms that an updated RMP (version 3.0) has been provided to the RMP team.

CSL has noted the condition to provide samples from the first five independent batches of Albutate imported into Australia for assessment and endorsement by the TGA OLSS prior to release to the market.

Question for sponsor

The NBA manages and coordinates arrangements for the supply of blood and blood products on behalf of the Australian Government and state and territory governments. Part of their role is to assess blood supply risk and engage in contingency planning. The NBA is not in a position to provide a statement of product risk management as this is outside their jurisdiction. Therefore, CSL will not be providing a statement from the NBA as part of this response.

The issues around risk of mixing of Albumex and Albutate in the one infusion or one episode of care have already been addressed in the response provided to the first round clinical evaluation and provided within the Request for ACPM's Advice document. Additionally, as requested in review of the PI, the proposed PI has been updated to include a statement that Albutate must not be mixed with other albumins.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Albutate solution for intravenous infusion vial containing 50 g/L (5% w/v) and 200 g/L (20% w/v) of albumin to have an overall positive benefit-risk profile for the indication;

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

The choice of albumin rather than artificial colloid will depend on the clinical situation of the individual patient.

The ACPM recommended that Albutate 25 solution for intravenous infusion vial containing 250 g/L (25% w/v) (250 mL and 500 mL) of albumin should not be approved for registration.

In making this recommendation, the ACPM was concerned about confusion between the 25% and 20% solution. This should be clarified with the sponsor.

Proposed conditions of registration

The ACPM agreed with the delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the delegate to the proposed amendments to the PI and CMI and specifically advised on the following:

- Clarify with the sponsor that the Indication is based on the EMA recommendations and, in particular, why plasma exchange is not listed as an indication when it is mentioned in the dosing instructions.
- Consideration could also be given to clarifying the text under DOSAGE and ADMINISTRATION - Compatibility with other fluids.

Specific advice

The ACPM advised the following in response to the delegate's specific questions on this submission:

Advise on whether efficacy and safety have been satisfactorily established.

The ACPM advised that efficacy and safety have been established satisfactorily for the 5% and 20% strength.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Points of clarification for sponsor post ACPM from the delegate

Questions for sponsor post-ACPM

1. Albunate Registration of both 20% and 25% concentrations

Both the external clinical experts advised that only one of the 20% or 25% concentrations is needed. The sponsor agreed that there was no clinical need to have both strengths registered. However, the sponsor, still wanted to register both the 20% and 25% strengths in the event of a shortage, so that there is "flexibility to respond as quickly as possible with either registered product, depending on stock availability".

The ACPM was concerned that having both strengths registered could cause confusion. Can the sponsor clarify whether both the 20% and 25% strengths will be on the market at the same time or whether only one will be available, depending on stock availability? Also, if the 25% is provided, will the 'dear health care provider letter' (DHCPL) explain that Ablunate25% is more hyper-oncotic than the Albumex20% and therefore carries an increased risk of fluid overload.

2. Plasma exchange

The ACPM noted that plasma exchange is not included in the indication, but is included in the Dosing and Administration and the Posology/Dosing in the Core EU SmPC, as per EMA's "Guideline on the Core SPC for Human Albumin Solution (CPMP/PhVWP/BPWG/2231/99 rev.2)". The sponsor is asked to clarify.

3. Compatibility with other fluids

Albunate must not be mixed with other medicinal products, whole blood, packed cells or other albumins.

The ACPM was concerned that "other medicinal products" could be taken to include saline.

Under ADMINISTRATION, the proposed PI (based on the EU SPC) states: Albutate 20 can be directly administered by the intravenous route, or it can also be diluted in a suitable crystalloid solution.

The sponsor is asked to clarify.

4. Interactions with other medicines

The Albumex PI includes the following: Hypotension has been reported in patients given albumin who are on Angiotensin Converting Enzyme (ACE) inhibitors.

This is not in the EU SPC. The sponsor is asked to clarify.

Post ACPM response from sponsor

1. *Registration of both 20% and 25% concentrations*

CSL response:

[Information redacted] CSL plans to make available only one of the hyper-oncotic strengths at a given time, preferably the 20%. Only in the event of a shortage, would the 25% be supplied instead. There is a theoretical concern that the oncotic pressure of albumin may lead to volume overload, particularly in patients who have underlying risk factors. However, the osmolality is 258 mOsm/kg for both Albumin 20% and Albumin 25%. While there is a 50 g/L difference between the formulations, the colloid-osmotic effect of 200 to 250 g/L is not significantly different, and is approximately four times that of blood plasma.

A comprehensive search of the CSL Behring Global Safety Database for all Albumin cases (including Albumin 5%, 20%, and 25%) utilising Medical dictionary for regulatory affairs (MedDRA) and the MSSO SMQ¹⁸ haemodynamic oedema, effusions and fluid overload was performed and presented in the last submitted Albumin 5%, 20%, and 25% EU-RMP version 3.1, dated 15 December 2014.

Cumulatively from 18 September 1996 to 1 September 2013, nine case reports, the majority of which were hypersensitivity reactions, were identified. Of these 9 reports, there were 3 reports that occurred in patients with the preferred term (PT) Cardiac failure congestive and the PT Pulmonary oedema. One patient had congestive heart failure as an underlying condition and was treated for myasthenia gravis with plasma exchange using Albumin 5%. After the third plasma exchange, the patient died at home due to congestive heart failure exacerbation, which was reported to be not related to the plasma exchange procedure or albumin. The remaining two patients reported pulmonary oedema after receiving Albumin 25%. One of these 2 patients received the concomitant medication Terlipressin, the other patient received massive transfusions of blood products, and both had renal impairment which could provide additional plausible explanations for the pulmonary oedema. There were no reports of hypervolaemia in patients receiving Albumin 20%.

There is no available spontaneous data that would provide additional information regarding the risk of hypervolaemia in patients receiving Albumin 20% versus Albumin 25% and the overall reporting frequency of hypervolaemia is very rare.

CSL proposes that the PI is sufficient for the primary risk minimisation strategy regarding the potential risk of hypervolaemia and haemodilution in high risk patients. The PI for both Albumin 20% and Albumin 25% address the risk of hypervolaemia in specific patient populations, the need for adequate hydration, the need for crystalloid solution in

¹⁸ MSSO = MedDRA Maintenance and Support Services Organisation. SMQ = Standardised MedDRA Queries.

dehydrated patients, and adjustment of dose and infusion rates to the patients circulatory condition as follows:

Albunate 20% and 25% proposed PI

Albumin should be used with caution in conditions where hypervolaemia and its consequences or haemodilution could represent a special risk for the patient. Examples of such conditions are:

- decompensated cardiac insufficiency
- hypertension
- oesophageal varices
- pulmonary oedema
- haemorrhagic diathesis
- severe anaemia
- renal and post-renal anuria.

The colloid-osmotic effect of human albumin 250 g/L (for Albunate 25 and 200g/L for Albunate 20) is approximately four times that of blood plasma. Therefore, when concentrated albumin is administered, care must be taken to assure adequate hydration of the patient. Patients should be monitored carefully to guard against circulatory overload and hyperhydration.

As aligned with the most recently approved Albumin EU RMP v.3.1, no additional risk minimisation is proposed, as providers should be skilled in the use of albumin in patients at risk for volume shifts. Lastly, the same level of rigorous monitoring and management is clearly addressed in the warnings for all formulations of albumin, including albumin 5%.

Based on the above, CSL does not believe an extra statement regarding risk of fluid overload in the DHCPL is required.

2. Plasma exchange

CSL response:

Plasma exchange is a common therapeutic procedure used to treat a variety of diseases through the bulk removal of plasma. Through the bulk removal and replacement of plasma pathologic substances such as pathologic Abs, immune complexes, and cytokines can be removed.

Plasma exchange leads to a volume deficit and albumin is a common replacement fluid for therapeutic plasma exchange. As albumin is used to restore a volume deficit this is covered by the indication:

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

This is in line with the Core EU SPC, as per EMA's Guideline.¹⁹

3. Compatibility with other fluids

CSL response:

The information provided in the 'compatibility with other fluids' section is general guidance whilst the wording in the 'administration' section is very specific and provides detailed instruction on dilution with a suitable crystalloid solution. CSL believes that these two sections do not contradict.

¹⁹ Guideline on the Core SPC for Human Albumin Solution (CPMP/PhVWP/BPWG/2231/99 rev.2)

4. Interactions with other medicines

CSL response:

This statement is not in the EU SPC and CSL does not have any company information to support including it in the Albutate PI.

This interaction has been in the Albumex PI since 1995 and was relevant to previous generations of albumin manufactured in Australia by CSL, namely Stable Plasma Protein Solution (SPPS) and Normal Serum Albumin (NSA). Even though the albumin product manufactured in Australia by CSL has evolved into a much purer product with a significantly lower incidence of ADRs (refer to Che et al. 2006²⁰) this statement has remained in the Albumex PI.

Delegate's review of the response

As a result of a review of the information provided by the sponsor in their post ACPM response the Delegate decided to approve all products applied for in this submission; Albutate 5, Albutate 20 and Albutate 25.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Albutate 5 human albumin 50 g/L (5% w/v) Albutate 20 human albumin 200 g/L (20% w/v) and Albutate 25 human albumin 250 g/L (25% w/v) solution for intravenous infusion, indicated for:

Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated and use of a colloid is appropriate

The choice of albumin rather than artificial colloid will depend on the clinical situation of individual patient

Specific conditions of registration applying to these goods

- The Albutate (human albumin) EU Risk Management Plan (RMP), Version 3.1, dated 15 December 2014, as qualified by the Australian Specific Annex, Version 3.0, dated May 2015, and any subsequent revisions, as agreed with the TCA will be implemented in Australia.
- Batch Release Testing. As a minimum, the first five independent batches of
 - Albutate 5 (human albumin 50 g/L (5% w/v) 250 mL)
 - Albutate 5 (human albumin 50 g/L (5% w/v) 500 mL)
 - Albutate 20 (human albumin 200 g/L (20% w/v) 50 mL)
 - Albutate 20 (human albumin 200 g/L (20% w/v) 100 mL)
 - Albutate 25 (human albumin 250 g/L (25% w/v) 50 mL)
 - Albutate 25 (human albumin 250 g/L (25% w/v) 100 mL)

imported into Australia are not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

²⁰ Che Y et al. Impact of manufacturing improvements on clinical safety of albumin: Australian pharmacovigilance data for 1988 – 2005. *Crit Care Resusc* 2006; 8: 334–338

Attachment 1. Product Information

The PIs for Albunate 5, Albunate 20 and Albunate 25 approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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