NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Albumex® 4 (4%) solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human albumin

It is a 4% w/v human albumin solution.

Albumex® 4 is manufactured from human plasma donated by New Zealand's voluntary and non-remunerated donors. It is prepared by a combination of the Cohn cold-ethanol fractionation process and chromatographic techniques.

The nominal composition of Albumex® 4 is as follows:

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

Albumex® contains no preservatives.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for intravenous infusion.

Albumex® 4 is a clear, slightly viscous liquid; it is almost colourless, yellow, amber or green.

It has a nominal osmolality of 260 mOsm/kg, is approximately isotonic and the pH is 6.7 to 7.3.

Albumex® 4 is iso-oncotic with human serum.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypovolaemia/shock

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

Cardiopulmonary bypass

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

Plasma exchange

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

4.2 Dose and method of administration

Dose

Hypovolaemia/shock

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

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

Paediatric population

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

Method of administration

Albumex® 4 should always be administered by intravenous infusion through a standard IV infusion giving set.

The following procedure is recommended:

- Remove the plastic cover from the seal.
- Apply a suitable antiseptic to the exposed part of the rubber stopper and allow to dry.
- Stand the bottle upright and insert the air vent needle vertically in one of the indentations of the stopper. It is preferable to use a long airway needle fitted with a filter. If not available, a short needle attached to a non-wettable filter may be used.
- Clamp the tubing of the giving set and insert the perforator vertically through one of the other indentations of the stopper. **Should the stopper become dislodged, do not use this bottle and discard the solution appropriately.**
- Invert the bottle and attach the hanger to a support approximately one metre above the patient.
- Allow the tubing to fill by adjusting the clamp. Insert the giving set needle into a vein and adjust the rate of flow.

- When the bottle is empty, clamp the tubing and transfer the air vent needle and the needle at the upper end of the giving set to a further bottle of Albumex® 4 or to a bottle containing a crystalloid solution, according to requirements.
- **Should leakage become evident during administration, cease the infusion and discard the solution appropriately. Recommence the infusion with a new bottle and giving set.**

It is recommended that blood pressure is monitored during administration of Albumex® 4.

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

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

Myocardial function (in shock), serum potassium (when pretreatment concentrations are low), platelet count (when pretreatment values are low) and prothrombin times (when these are prolonged before exchange) should also be monitored.

For further instructions, see section 6.6.

4.3 Contraindications

Albumex® 4 must not be used if there is a history of allergy to this product.

Albumin is contraindicated in patients with cardiac failure, pulmonary oedema or severe anaemia.

4.4 Special warnings and precautions for use

Patients with cardiac failure, renal insufficiency, stabilised chronic anaemia or on cardiopulmonary bypass are at special risk of developing circulatory overload. When being infused with Albumex® 4 they should be carefully monitored for this potential complication.

Two potential risks when using plasma volume expanders are allergic reactions and the risk of circulatory overload. Hypersensitivity is rare when human albumin solution is used because of the human origin of the product, and circulatory overload can be avoided by monitoring the rate and volume of infusion. Should an anaphylactic reaction to Albumex® 4 develop, the infusion should be stopped and treatment instituted with adrenaline (epinephrine), hydrocortisone and antihistamines, as appropriate. Circulatory overload can be avoided by monitoring the rate and volume of infusion. Hypotension and rigors have been associated with human albumin solutions. Administration of albumin can aggravate myocardial depression when present in patients with shock.

No comparative clinical study with Albumex® 4 has been carried out. However such data exists for a similar product, Albumex® 5 which has been compared with 5% NSA in an open apheresis study carried out in five Australian apheresis clinics. Adverse experiences noted in that study are set out below as a guide to users of this product (Albumex® 4).

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

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

Hypotension

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

Aluminium content

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

Pathogen safety

This product is made from human plasma. Products made from human plasma may contain infectious agents such as viruses and theoretically Creutzfeldt-Jakob Disease (CJD) agents, that can cause disease.

The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain infectious agents and by testing for the presence of certain viral markers. In addition, virus inactivation/removal procedures are included in the manufacturing process.

The manufacturing process for Albumex® 4 contains dedicated steps to reduce the possibility of virus transmission including pasteurisation (60°C for 10 hours) and incubation at low pH to inactivate viruses. The current process and procedures applied in the manufacture of this product are effective against enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and the non-enveloped virus, hepatitis A virus (HAV). These procedures may be of limited value against the non-enveloped virus, parvovirus B19.

Despite these measures, such products may still potentially transmit disease. There is also the possibility that other known or unknown infectious agents may be present in such products. Vaccination for patients in receipt of medicinal products from human plasma should be considered where appropriate.

Effects on laboratory tests

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

4.5 Interaction with other medicines and other forms of interaction

Hypotension has been reported in patients given albumin who are on Angiotensin Converting Enzyme (ACE) inhibitors. The addition of other medicines to Albumex® 4 has not been evaluated.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials; therefore, it should be given to pregnant women only if clearly needed.

Breast-feeding

No information available.

Fertility

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

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable effects

Summary of the safety profile

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

Adverse reactions reported with human albumin solutions in general include hypotension, chills, fever and allergic reactions including anaphylaxis, urticaria, skin rashes, nausea, vomiting and increased salivation.

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

Tabulated list of adverse reactions

Adverse reactions by body system from the Saline versus Albumin Fluid Evaluation (SAFE) study comparing albumin and saline are provided in **Table 1**.

Table 1: Total adverse reactions reported from the SAFE study

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

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

Post-marketing surveillance

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

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

For safety with respect to transmissible agents and additional details on risk factors, see section 4.4.

Paediatric population

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

Elderly population

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Excess human albumin may lead to circulatory overload.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Plasma expanders substitutes and plasma protein fractions.

ATC code: B05AA01

Mechanism of action

Albumin accounts quantitatively for more than half of the total protein in the plasma and represents about 10% of the protein synthesis activity of the liver.

The most important physiological function of human albumin results from its contribution to maintenance of plasma colloid osmotic pressure of the blood within the capillaries and thus the stabilisation of the circulating blood volume. Furthermore, another important physiological role of human albumin is its carriage of intermediate products in the transport and exchange of tissue metabolites. Human albumin is a carrier of hormones, enzymes, medicinal products and toxins.

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

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

Clinical efficacy and safety

A large multicentre, double blind, randomised controlled trial was conducted to determine the effect of fluid resuscitation with either albumin or saline on mortality in a heterogeneous population of patients in the ICU. This Saline versus Albumin Fluid Evaluation (SAFE) study was a collaboration of the Australian and New Zealand Intensive Care Society Clinical Trials Group, the Australian Red Cross Blood Service and the George Institute for International Health. The trial randomised 6997 patients to receive either albumin 4% (Albumex® 4)(n = 3497) or normal (0.9%) saline (n = 3500).

The two groups had similar baseline characteristics with randomisation stratified at each centre to ensure each institution enrolled equal numbers of patients for each treatment.

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

There were also no statistically significant differences between the two groups in the secondary outcomes measured: mean (±SD) number of days spent in ICU (6.5±6.6 in the albumin group and 6.2±6.2 in the saline group, p = 0.44), days spent in hospital (15.3±9.6 and 15.6±9.6 respectively, p = 0.30), days of mechanical ventilation (4.5±6.1 and 4.3±5.7, respectively, p = 0.74) or days of renal replacement therapy (0.5±2.3 and 0.4±2.0, respectively, p = 0.41).

The proportion of patients with new single or multiple organ failure was similar in the two groups (p = 0.85).

This study concluded that in patients in the ICU, use of either 4% albumin or normal (0.9%) saline for fluid resuscitation results in similar mortality at 28 days.

5.2 Pharmacokinetic properties

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

Distribution

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

Elimination

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

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

5.3 Preclinical safety data

Human Albumin is a normal constituent of human plasma and its action does not differ from that of physiological human albumin. Single dose toxicity testing in animals is of little relevance and does not permit the evaluation of toxic or lethal doses or of a dose-effect relationship. Repeated-dose

toxicity testing is impracticable due to the development of antibodies to heterologous protein in animal models.

To date, Albumex has not been reported to be associated with embryofoetal toxicity, mutagenic, or carcinogenic potential. No signs of acute toxicity have been described in animal models.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium octanoate
Sodium chloride
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

4 years

Stability after first opening:

Use in one patient on one occasion only. Albumex® 4 contains no antimicrobial preservative. It must, therefore, be used **immediately** after opening the bottle.

6.4 Special precautions for storage

Store below 30°C (Do not freeze).

Protect from light.

6.5 Nature and contents of container

Solution in a single glass bottle, with a rubber stopper, an aluminium seal and a plastic flip-top cap.

Pack sizes:

2 g of human albumin in 50 mL of electrolyte solution
10 g of human albumin in 250 mL of electrolyte solution
20 g of human albumin in 500 mL of electrolyte solution.

Albumex® is packaged in latex free materials.

6.6 Special precautions for disposal and other handling

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

Albumex® 4 is normally clear or slightly opalescent. If it appears to be turbid by transmitted light, it must not be used and the bottle should be returned unopened to the New Zealand Blood Service.

Any unused solution should be discarded appropriately.

7 MEDICINE SCHEDULE

General Sale Medicine

8 SPONSOR

CSL Behring (NZ) Ltd
PO Box 62590
Greenlane
Auckland 1546
New Zealand

For Medical/Technical Enquiries: TOLL FREE: 0800 640 677

For Customer Service Enquiries: TOLL FREE: 0800 841 532

customerservice@cslbehring.com.au

www.cslbehring.com.au

Manufacturer

CSL Behring (Australia) Pty Ltd
189–209 Camp Road
Broadmeadows VIC 3047
Australia

Distributor

New Zealand Blood Service
71 Great South Road
Epsom
Auckland
New Zealand

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SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Data sheet reformatted to the SPC format
4.8	Clinical trial adverse reaction table and post-marketing reactions added
5.1	Further information added
5.2	Further information added
5.3	New section added
6.5	Container material information added
8	Sponsor contact information amended.