AUSTRALIAN PRODUCT INFORMATION

Albumex® 4

(Human albumin) – Solution for intravenous infusion

1 NAME OF THE MEDICINE

Human albumin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human Albumin 4% (40 g/L)

It is a sterile, preservative-free 4% w/v human albumin solution which is iso-oncotic with human serum. It has a nominal osmolality of 260 mOsm/kg, is approximately isotonic and the pH is 6.7 to 7.3.

Albumex® 4 is manufactured from human plasma collected by Australian Red Cross Lifeblood. It is prepared using predominantly 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® 4 also contains Water for Injections.

3 PHARMACEUTICAL FORM

Solution for intravenous infusion.

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypovolaemia/shock

Preservation of an adequate circulating blood volume should be the primary aim of therapy. The initial resuscitating fluid should not be a human blood product, but rather an alternative plasma volume expander should be used as first-line replacement. Albumex® 4 may, however, be the initial plasma expander of choice if shock is associated with significant hypoalbuminaemia (albumin concentration less than 25 g/L), or if it is clinically desirable to avoid the infusion of large volumes of crystalloid solutions.

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

Cardiopulmonary bypass

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

Plasma exchange

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

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.

Plasma exchange

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

Monitoring advice

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

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

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

Method of administration

CAUTION: Albumex® 4 contains no antimicrobial preservative. It must, therefore, be used immediately after opening the bottle. Any unused solution should be discarded appropriately. Use in one patient on one occasion only.

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 Australian Red Cross Lifeblood.

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

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

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

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

Allergic reactions

Hypersensitivity reactions occur rarely when human albumin solutions are administered because of the human origin of the product. Should an anaphylactic reaction to Albumex® 4 develop, the infusion should be stopped and treatment instituted with adrenaline (epinephrine), hydrocortisone and antihistamines as appropriate.

Hypotension

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

Circulatory overload

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

adjusted to the patient's circulatory situation. Patients should be carefully monitored for this potential complication.

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

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

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

Albumex® 4 contains trace amounts of aluminium (≤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 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 contribute significantly to ensure freedom from parvovirus B19.

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

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

Use in the elderly

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

Paediatric use

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

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 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 (see Section 6.2 Incompatibilities).

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

Use in pregnancy

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

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

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects on ability to drive and use machines have been observed. However, adverse effects of Albumex® include dizziness which could affect the ability to drive or use machines (see Section 4.8 Adverse effects (Undesirable effects)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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

Adverse reactions with albumin solutions in general include hypotension, chills, fever and allergic reactions including anaphylaxis, urticaria, skin rashes, nausea, vomiting and increased salivation. Mild reactions such as mild hypotension, flushing, urticaria, fever, and nausea normally disappear rapidly when the infusion rate is slowed down or the infusion is stopped (see Section 4.2 Dose and method of administration - Monitoring advice).

Very rarely, severe allergic reactions such as anaphylactic shock may occur. In these cases, the infusion should be stopped and an appropriate treatment should be initiated (see Section 4.4 Special warnings and precautions for use).

Adverse events in clinical trials

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

Table 1: Total adverse reactions reported from the SAFE study

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

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

Post-marketing surveillance

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

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Excess human albumin may lead to circulatory overload (see Section 4.4 Special warnings and precautions for use).

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

The manufacturing process for Albumex® 4 contains dedicated steps to reduce the possibility of virus transmission including pasteurisation (heating at 60°C for 10 hours) and incubation at low pH to inactivate viruses.

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 metabolic half-life of albumin *in vivo* is about 19 days and the turnover in an adult is approximately 15 g per day. There is rapid interchange of albumin between the intra- and extravascular spaces.

Albumex® 4 has two main functions: maintenance of plasma colloid osmotic pressure and carriage of intermediate products in the transport and exchange of tissue metabolites.

The beneficial effect of 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 trials

The Saline versus Albumin Fluid Evaluation Study

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

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

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

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

groups (p = 0.85). There was no significant difference in survival times during the first 28 days between the two groups (p = 0.96).

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

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

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

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

5.2 PHARMACOKINETIC PROPERTIES

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

Excretion

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

Genotoxicity

No genotoxicity studies have been conducted with Albumex® 4.

Carcinogenicity

No carcinogenicity studies have been conducted with Albumex® 4.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

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

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C (Do not freeze). Protect from light. Do not use after the expiry date.

6.5 NATURE AND CONTENTS OF CONTAINER

Albumex® 4 is issued in glass bottles in three sizes:

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

Albumex® 4 is packaged in latex free materials.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

CAS Number

9048-49-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI updated to the new format
2, 4.2, 7	Name changed to Australian Red Cross Lifeblood
4.7	Information added about effects on ability to drive and use machines