# ALBUMEX® 4

Human Albumin 4% (40 g/L)

## Product Information

### Australia

### NAME OF THE MEDICINE

Human albumin, solution for intravenous infusion.

### DESCRIPTION

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

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

### PHARMACOLOGY

Albumin accounts quantitatively for more than half of the total protein in the plasma and represents about 10 % of the protein synthesis activity of the liver. The metabolic half-life of albumin *in vivo* is about 20 days and the turnover in an adult is approximately 15 g per day. There is rapid interchange of albumin between the intra- and extravascular spaces. Albumex® 4 has two main functions: maintenance of plasma colloid osmotic pressure and carriage of intermediate products in the transport and exchange of tissue metabolites.

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

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

#### *Pharmacokinetics*

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

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

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

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

### CLINICAL TRIALS

#### *The Saline versus Albumin Fluid Evaluation Study*

The Saline versus Albumin Fluid Evaluation (SAFE) study was conducted by the Australian and New Zealand Intensive Care Society Clinical Trials Group. This large multicentre, double blind, prospective randomised controlled trial was conducted to determine the effect of fluid resuscitation with either albumin or saline on mortality in a heterogeneous population of patients in the Intensive Care Unit (ICU). The SAFE study randomised 6997 patients to receive either albumin 4 % (Albumex® 4 in blinded labelling, n=3497) or saline (n=3500). The two groups had similar baseline characteristics.

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. 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).

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

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

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

### INDICATIONS

#### *Hypovolaemia/shock*

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

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

#### *Cardiopulmonary bypass*

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

#### *Plasma exchange*

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

### CONTRAINDICATIONS

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

### PRECAUTIONS

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

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

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

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 (HAV). These procedures contribute significantly to ensure freedom from parvovirus B19.

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

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

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

### *Effects on fertility*

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

### *Use in pregnancy*

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

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

### Use in lactation

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

### *Paediatric use*

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

### *Use in the elderly*

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

### Carcinogenicity

Specific studies have not been conducted.

### *Genotoxicity*

Specific studies have not been conducted.

### *Interactions with other medicines*

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

### *Effect on laboratory tests*

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

## ADVERSE EFFECTS

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

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

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

### *Adverse events in clinical trials*

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

**Table 1: Total adverse reactions reported from the SAFE study**

| *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.

## DOSAGE AND ADMINISTRATION

### Dosage

### Hypovolaemia/shock

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

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

### *Plasma exchange*

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

### *Monitoring advice*

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

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

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

### *Administration*

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

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

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

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

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

## COMPATIBILITY WITH OTHER FLUIDS

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

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

## OVERDOSAGE

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

## PRESENTATION AND STORAGE CONDITIONS

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

2 g of human albumin in 50 mL of electrolyte solution;

10 g of human albumin in 250 mL of electrolyte solution;

20 g of human albumin in 500 mL of electrolyte solution.

### Storage

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

## NAME AND ADDRESS OF THE SPONSOR

CSL Limited ABN 99 051 588 348
Bioplasma Division
189 - 209 Camp Road
Broadmeadows VIC 3047
AUSTRALIA

Distributed by: Australian Red Cross Blood Service

## POISON SCHEDULE OF THE MEDICINE

Unscheduled

Date of Therapeutic Goods Administration approval:
23 September 2008

® Registered trademark of CSL Limited.

**For Medical/Technical Enquiries:**
TOLL FREE: 1800 067 140

**For Customer Service Enquiries:**
TOLL FREE: 1800 063 892

CSL Limited, Bioplasma Division, 189-209 Camp Road Broadmeadows Victoria Australia 3047
ABN 99 051 588 348
Internet: www.cslbioplasma.com.au

For Medical/technical inquiries: 1800 067 140 For Customer Service inquiries: 1800 063 892
Email: medicalaffairs_bioplasma@csl.com.au Email: bioplasma.customerservice@csl.com.au

Version: PI 6:00 T34500100G CSL Bioplasma 1154