AUSTRALIAN PRODUCT INFORMATION

Albumex® 20

(Human albumin) – Solution for intravenous infusion

1 NAME OF THE MEDICINE

Human albumin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human Albumin 20% (200 g/L)

It is a sterile, preservative-free 20% w/v human albumin solution. It has a nominal osmolality of 130 mOsm/kg, is hypotonic and the pH is 6.7 to 7.3. It is hyperoncotic and hypo-osmotic compared to human serum.

Albumex® 20 is manufactured from human plasma collected by Australian Red Cross Lifeblood. It is prepared using predominantly chromatographic techniques.

The composition of Albumex® 20 is as follows:

Human Albumin	200 g/L
Sodium	48–100 mmol/L
Octanoate	32 mmol/L

Albumex® 20 also contains Water for Injections.

3 PHARMACEUTICAL FORM

Solution for intravenous infusion.

Albumex® 20 is a clear, slightly viscous liquid; it is almost colourless, yellow, amber or green.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Hypoproteinaemia in the acutely ill patient

Albumex® 20 is administered when there are existing or anticipated clinical problems or complications from reduced oncotic pressure, and/or as an adjunct to diuretic therapy.

Shock

Albumex® 20 may be used for the resuscitation of patients in shock due to acute loss of blood or plasma, but 4–5% human albumin is preferred when available.

Burns

Extensive burns are followed by sequential shifts in the distribution of body water, salt and proteins, resulting in hypovolaemic shock and circulatory failure.

Initially (during the first 24 hours) there is an increased vascular permeability leading to loss of water and proteins into the extravascular compartment, and haemoconcentration. Large volumes of crystalloid solutions should be infused to restore the constricted intravascular fluid space, and smaller amounts of Albumex® 20 are required to maintain adequate plasma volume and colloid osmotic pressure.

Adult respiratory distress syndrome

The clinical syndrome is characterised by inadequate oxygenation secondary to pulmonary interstitial oedema, complicating shock and postoperative states resulting in a decreased central venous pressure, decreased plasma albumin concentration, rising blood pressure, reduced cardiac output, lowered pulse rate and a falling renal output.

The acute condition can be controlled by diuretics and Albumex® 20 in amounts sufficient to maintain vital signs.

In patients who have undergone abdominal surgery, the intravenous (IV) administration of albumin solution (20%) immediately after the operation has been shown to improve lung compliance and gaseous exchange.

Haemodialysis

Albumex® 20 may be used to assist with the rapid removal of excess extravascular fluid and to maintain perfusion pressure.

Plasma exchange

Therapeutic plasma exchange is a procedure in which approximately one plasma volume is exchanged with a colloid replacement solution. The choice of replacement fluid and its concentration are determined by the particular clinical situation and the frequency of the procedure.

Iso-oncotic albumin solution is the preferred replacement material. If the patient’s serum albumin level is not maintained, concentrated albumin (20%) may be indicated. If exchange occurs less frequently than once a week, less concentrated colloids may be appropriate.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Hypoproteinaemia in the acutely ill patient

The usual daily dose is 50–75 g human albumin (250–375 mL of Albumex® 20). The rate of administration should not exceed 2 mL per minute, as more rapid infusion may precipitate circulatory overload and pulmonary oedema.

The infusion of Albumex® 20 is not justified in hypoproteinaemic states associated with chronic cirrhosis, malabsorption, protein losing enteropathies, pancreatic insufficiency or undernutrition.

Shock

The dose should be determined by the patient's condition and response to treatment. The usual initial dose of 20 g human albumin (100 mL of Albumex® 20) may be administered as a blood volume expander at a rate of 2 to 4 mL per minute.

The rate of infusion may be increased in emergencies and repeated in 15 to 30 minutes if necessary. The total dose should not exceed the level of albumin found in the normal individual i.e. about 2 g per kg body weight in the absence of active bleeding.

If concentrated albumin (>5%) is given, it should be accompanied by the intravenous infusion of a crystalloid solution. Failure to supply this additional fluid may lead to dehydration of the tissues. The precise nature and strength of the crystalloid solution will depend on the requirements of the patient for electrolytes and fluid.

Burns

The usual dose is 20–80 g human albumin (100–400 mL of Albumex® 20) given daily at the rate of about 1 mL per minute.

Beyond 24 hours, Albumex® 20 can be used to maintain plasma colloid osmotic pressure. A reasonable goal is the maintenance of a plasma albumin concentration of 25 g/L or a colloid osmotic pressure of 20 mmHg.

The continuing need for albumin is occasioned by losses from denuded areas and decreased albumin synthesis.

Acute respiratory distress syndrome

Commence with a dose of 50 g human albumin (250 mL of Albumex® 20) over the first 24 hours together with diuretic therapy. Thereafter the dose is adjusted to maintain vital signs, particularly central venous pressure, urine output and plasma albumin concentration.

Haemodialysis

Patients with significant fluid overload prior to dialysis may benefit from the administration of 20–40 g human albumin (100–200 mL of Albumex® 20) at the end of the dialysis procedure.

Plasma exchange

Replace albumin removed on a gram-for-gram basis, e.g. removal of 2.5 L plasma should be accompanied by replacement with 125 g human albumin (625 mL of Albumex® 20), either prediluted or followed by 4–5 volumes of an appropriate crystalloid solution (see Administration - *Dilution of concentrated albumin 20%*).

Monitoring advice

It is recommended that blood pressure is monitored during administration of Albumex® 20.

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 should be monitored.

Method of administration

CAUTION: Albumex® 20 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® 20 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.

In some cases a dose of albumin is added to a suitable crystalloid solution.

Dilution of concentrated albumin 20%

Albumex® 20 can be diluted to an iso-oncotic protein concentration (4–5% albumin) prior to administration, in the proportion of 1 mL of Albumex® 20 to 4 mL of suitable crystalloid solution and administered by the usual intravenous technique. Under no circumstances should water be used since the lower tonicity will lead to intravascular haemolysis.

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® 20 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® 20 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.

The infusion of Albumex® 20 is not justified in hypoproteinaemic states associated with chronic cirrhosis, malabsorption, protein losing enteropathies, pancreatic insufficiency or undernutrition.

In chronic nephrosis, infused albumin solution (20%) is promptly excreted by the kidneys with no relief of the chronic oedema.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The sodium levels in this product are 48 to 100 mmol/L. This should be noted when the product is used in patients requiring sodium restriction.

Administration of albumin can aggravate myocardial depression when present in patients with shock. A paradoxical effect of refractory oliguria has been reported in burns patients receiving albumin, possibly because of insufficient accompanying crystalloids.

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® 20 develop, the infusion should be stopped and treatment instituted with adrenaline (epinephrine), hydrocortisone and antihistamines, as appropriate.

Circulatory overload

The colloid osmotic effect of Albumex® 20 is approximately four times that of plasma and patients should always be monitored for symptoms of circulatory overload (see Section 4.2 Dose and method of administration - Monitoring advice).

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.

In the presence of dehydration, as Albumex® 20 is hyperoncotic, it must be given with, or followed by crystalloid solution (see Section 4.2 Dose and method of administration - Administration).

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.

In chronic nephrosis, infused albumin solution (20%) is promptly excreted by the kidneys with no relief of the chronic oedema.

Albumex® 20 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® 20 in the elderly.

Paediatric use

There have been no specific clinical studies of Albumex® 20 in children.

Effects on laboratory tests

Albumin is an endogenous plasma protein so no specific effects on laboratory tests are anticipated.

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® 20 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® 20 on fertility have been conducted.

Use in pregnancy

Reproductive toxicity studies with Albumex® 20 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® 20 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® 20 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 reported 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

Although formal clinical studies with Albumex® 20 have not been conducted to determine the frequency or severity of adverse events, results from studies with Albumex® 4 and 5 (4% and 5% albumin solutions respectively) may be applicable.

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® 20 which primarily involve chills and fever. The main adverse reactions reported during routine surveillance for the current product are as follows: hypotension, hypertension, tachycardia, decreased oxygen saturation, dyspnoea, flushing, dizziness, chills, pyrexia and muscle spasms. Although true anaphylactic reactions are believed to occur rarely, no reports of anaphylaxis have been received.

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® 20 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.

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® 20 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® 20 is hyperoncotic with human serum and supplies the oncotic equivalence of approximately four times its volume of human plasma.

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 were 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 compared to 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® 20. 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® 20.

Carcinogenicity

No carcinogenicity studies have been conducted with Albumex® 20.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to Section 2 Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

The addition of other medicines to Albumex® 20 has not been evaluated.

Albumex® 20 should not be mixed with protein hydrolysates, amino acid solutions, solutions containing alcohol, or solutions containing medicines 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

10 mL: Store at 2°C to 8°C (Refrigerate. Do not freeze).

100 mL: 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® 20 is issued in glass bottles in two sizes:

- 2 g of human albumin in 10 mL of electrolyte solution
- 20 g of human albumin in 100 mL of electrolyte solution.

Albumex® 20 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

CSL Behring (Australia) Pty Ltd
ABN 48 160 734 761
189–209 Camp Road
Broadmeadows VIC 3047
Australia

For Medical/Technical Enquiries

TOLL FREE: 1800 642 865

For Customer Service Enquiries

TOLL FREE: 1800 063 892

customerservice@cslbehring.com.au

www.cslbehring.com.au

Distributed by

Australian Red Cross Lifeblood

9 DATE OF FIRST APPROVAL

4 November 1991

10 DATE OF REVISION

02 April 2020

® Registered trademark of CSL Limited

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