NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Albumex® 20 (20%) solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Human albumin

It is a 20% w/v human albumin solution.

Albumex® 20 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 composition of Albumex® 20 is as follows:

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

Albumex® contains no preservatives.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for intravenous infusion.

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

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.

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% 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.

Therapeutic 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

Dose

Hypoproteinaemia in the acutely ill patient

The usual daily dose is 50–75 g. The rate of administration should not exceed 2 mL per minute, as more rapid infusion may precipitate circulatory overload and pulmonary oedema.

In some cases a dose of albumin is added to a suitable crystalloid solution in the proportion of 1 mL Albumex® 20 to 4 mL crystalloid solution and administered by the usual intravenous technique.

Shock

The dose should be determined by the patient's condition and response to treatment. The usual initial dose of 20 g 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 (>4–5%) 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.

The patient's haemodynamic response should be monitored and the usual precautions against circulatory overload observed.

Burns

The usual dose is 20 to 80 g human albumin 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.

Adult respiratory distress syndrome

Commence with a dose of 50 g human albumin (equivalent to 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 may benefit from the administration of 100–200 mL of Albumex® 20 at the end of the dialysis procedure.

Therapeutic plasma exchange

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

Paediatric population

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

Method of administration

Albumex® 20 should always be administered by intravenous infusion through a standard IV infusion giving set.

The following procedure is recommended for the 100 mL pack size:

- 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® 20 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.**

The following procedure is recommended for the 10 mL (paediatric) pack size:

- 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, insert the needle vertically in the stopper and draw up the product.
- Infuse the product into appropriate chamber as required e.g. infusion set.

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.

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.

In the treatment of shock, monitor blood pressure frequently. Widening of the pulse pressure is correlated with an increase in stroke volume or cardiac output.

For further instructions, see section 6.6.

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

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.

Sodium content

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.

Hypersensitivity

True anaphylactic reactions occur rarely. 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

Patients with cardiac failure, renal insufficiency or stabilised chronic anaemia often have an increased circulatory plasma volume and are therefore at special risk of developing circulatory overload.

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.

The colloid osmotic effect of Albumex® 20 is approximately four times that of plasma. Therefore, patients should always be monitored carefully in order to guard against the possibility of circulatory overload.

As Albumex® 20 is hyperoncotic, albumin must be given with or followed by crystalloid solution in the presence of dehydration.

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

Aluminium content

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 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. 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.

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.

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® 20 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

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. The Saline versus Albumin Fluid Evaluation (SAFE) study (using Albumex® 4%) was conducted by the Australian and New Zealand Intensive Care Society Clinical Trials Group.

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 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 of Albumex® preparations 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.

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® 20 in children.

Elderly population

There have been no specific clinical studies of Albumex® 20 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® 20 is hyperoncotic with human serum and supplies the oncotic equivalence of approximately four times its volume of human plasma.

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
Water for injections

6.2 Incompatibilities

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.

6.3 Shelf life

4 years

Stability after first opening:

Use in one patient on one occasion only. Albumex® 20 contains no antimicrobial preservative. It must, therefore, be used **immediately** after opening the bottle.

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.

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 10 mL of electrolyte solution
20 g of human albumin in 100 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® 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 the New Zealand Blood Service.

Any unused solution should be discarded appropriately.

7 MEDICINE SCHEDULE

General Sale Medicine

8 SPONSOR

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3 December 2018

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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.