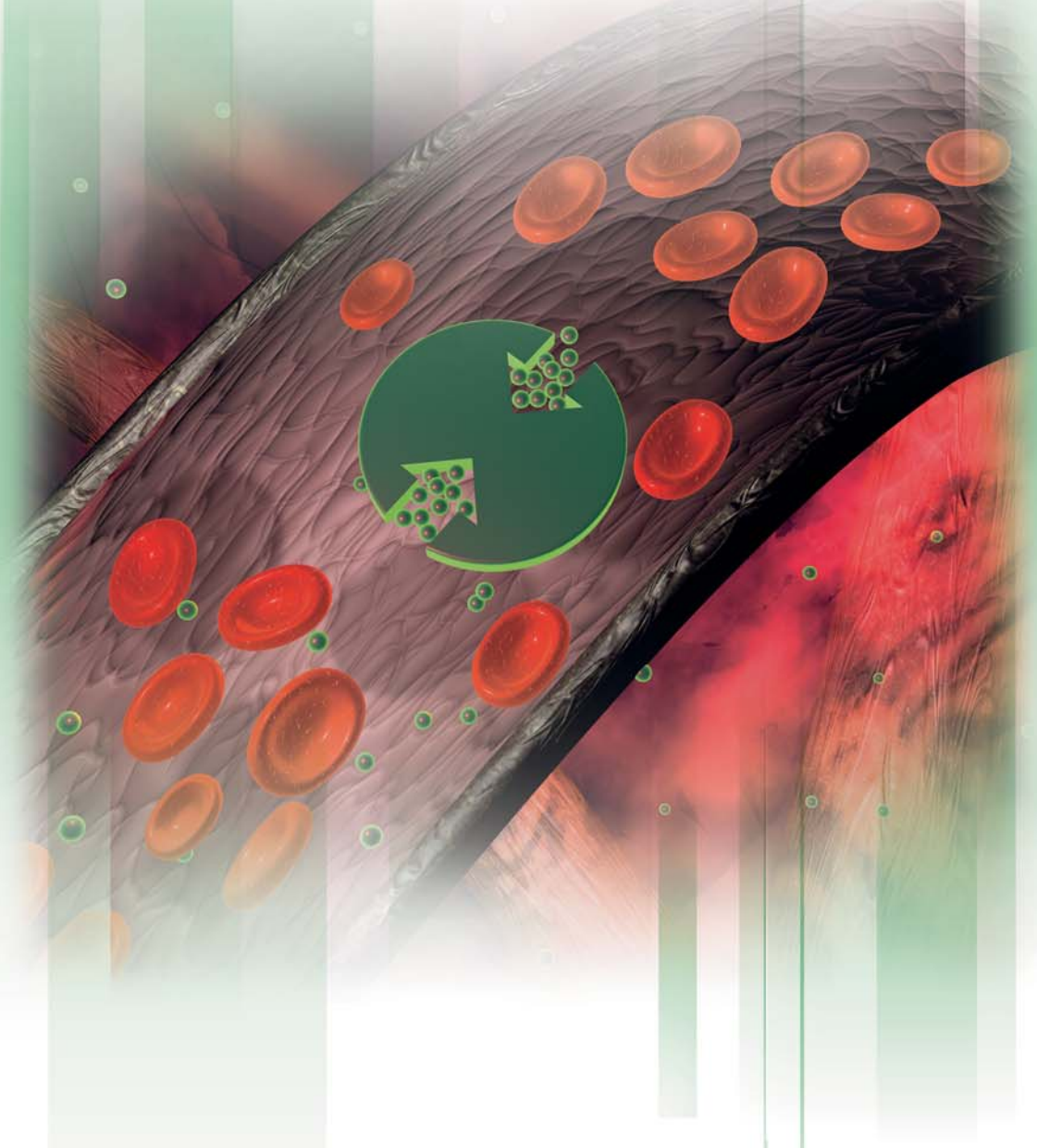
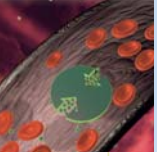
Biotest

From Nature for Life

Human Albumin Biotest

For patients needing
more than fluid resuscitation





Human Albumin Biotest

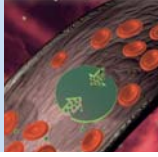
Human albumin is the most widespread plasma protein in the animal kingdom and also one of the oldest in phylogenetic terms. It occurs in almost all the more highly developed species. On the evolutionary scale, the oldest of these are the teleosts and lampreys. By comparison with all other plasma proteins albumin also occupies a prime position with regard to quantity. Its great age in the history of evolution and the quantity present in the organism are an indication of the importance of this protein, though this is often underestimated.

The presence of a substance in large quantities does not mean that its loss can be tolerated more readily. On the contrary, it is the albumin level that provides valuable indications relating to the condition of the individual. These indications are particularly meaningful in view of the fact that albumin is a protein with a long half-life and therefore shows pronounced changes only in the event of chronic defects.

In progressive malignant disease, for example, the albumin level is of high prognostic value, a fact that has been recognised for more than 50 years but is still not fully appreciated. The assumption that this protein deficit is simply a consequence of anorexia has not been confirmed. A low albumin level cannot simply be raised by means of parenteral nutrition, though this is sufficient to achieve weight gain.

The lack of albumin may be due to a number of causes. This brochure highlights the main pathological conditions that can benefit from albumin replacement.

The latest use for this versatile substance is in the extracorporal removal of toxins in liver disease, also known as albumin dialysis. Use is made here of the high capacity of albumin to bind and transport a wide variety of substances. This procedure, known as MARS (Molecular Adsorbent Recirculating System) has a great future in prospect.



…for patients needing more than fluid resuscitation

- Human albumin, a natural molecule, is of greater physiological value to the critically ill patient than fluid resuscitation alone.
- This is demonstrated in infants and children, in surgical patients, in the critically ill and in patients with cirrhosis, where the properties of this natural molecule permit rapid attainment of resuscitation endpoints, with lower risks of pulmonary oedema, renal and electrolytic complications.
- In some circumstances, substitution of non-albumin products may increase costs by increasing the probability of peri-operative adverse events.

Human albumin is a natural colloid with a unique capacity to act as a carrier molecule for fatty acids, hormones, enzymes, trace metals and drugs[1-3].

A natural colloid that can bind and inactivate toxic products generated during inflammatory disease states, bilirubin and free fatty acids, scavenge free radicals and prevent lipid peroxidation[4-8].

Albumin has a critical role in regulating the permeability of the endothelium[9, 10].

…is effective

Albumin increases intravascular oncotic pressure and so expands intravascular volume.

Albumin restores plasma volume without producing water overload or overexpanding the interstitial water[11].

Based on relative oncotic pressures, markedly smaller volumes of albumin, compared with crystalloids, are required to produce a given amount of intravascular volume expansion[11-13].

Resuscitation endpoints may be reached more rapidly and blood pressure better maintained over time when patients receive albumin rather than crystalloid infusions[11].

…of outstanding clinical experience

Over 100 million average doses were supplied until today[14].

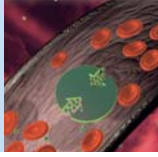
…is well tolerated

A natural constituent of human blood:

Adverse reactions to human albumin are very rare: the incidence of suspected severe allergic reactions is calculated as 0.00013 %[15].

"… lack of complications make human albumin solution superior to human plasma for exchange transfusion in neonatal polycythaemia"[16].

Albumin is prepared from human plasma; despite many millions of doses being administered, no viral transmission has ever been demonstrated[14].



…for paediatrics and neonatology

In hyperbilirubinaemia of the newborn ”crystalloids and non-protein colloids do not have bilirubin-binding properties and should not be considered as alternatives to albumin“[17].

”Laboratory and clinical data suggest that 4.5 % albumin is the optimal resuscitation fluid currently available“ for children with meningococcal septicaemia[18].

Albumin has been recommended as the colloid of choice in intraoperative management of small infants[19].

An isotonic albumin preparation has been reported superior to polygeline 3.5 % in maintaining plasma volume, albumin levels and colloid osmotic pressure over time[20].

Albumin and packed red cell injection into the fetal abdominal cavity ”is an effective procedure for in utero treatment of non-immunologic hydrops fetalis without pleural effusion“[21].

Lack of metabolic, infectious or gastrointestinal complications in neonates with polycythaemia led to the conclusion that 5 % human albumin is superior to human plasma and a recommendation for its use in neonatal polycythaemia and hyperviscosity[16].

Isotonic human albumin – effective for resuscitation and management of the critically ill child.

…effective during surgery

Albumin protects against haemolysis caused by mechanical trauma[22].

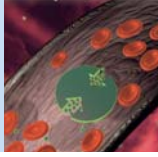
”Timely replacement with albumin“ during extensive surgery can prevent the slide into multiple organ failure and death[23].

Albumin solutions are ”useful for all acute situations of hypovolemia accompanied by hypoalbuminemia during and after surgery“[24].

In recipients of renal transplants, high-dose albumin infusion produces ”intravascular volume expansion and achieves a prompt restoration of blood flow, minimizes hypoxic injury and helps preserve renal tissue“[25].

In cardiothoracic surgery, substitution of other colloids for albumin, for cost-saving reasons, may result in greater frequency of haemorrhagic complications. ”Efforts to save money by substituting less expensive products inadvertently may increase costs by increasing the probability of perioperative adverse events“[26].

During surgery, use of concentrated human albumin minimizes hyperoxic injury, maintains intravascular volume and corrects hypoalbuminaemia.



…for the critically ill patient

There is a significant benefit for critically ill patients when albumin is infused as has been shown in a meta-analysis by Vincent et al.[27]. This meta-analysis included 71 randomized, controlled clinical trials comprising 3782 patients. For patients in intensive care units, the incidence of complications was significantly lower when albumin was infused as compared to crystalloid solutions. 1884 patients of the albumin group had 1568 complications. In 1898 patients of the control group 1719 suffered from complications.

The authors noted, the interpretation of earlier studies to clarify the effect of albumin as compared to saline infusions did not consider two decisive aspects and thus unnecessarily question the value of albumin for critically ill patients:

1. When patient mortality in clinical groups vary between 10 and 17 %, the parameter „patient mortality“ is by far too insensitive to evaluate the albumin effect.

Therefore the authors of the present meta-analysis focused on the parameter „incidence of patient morbidity“ (incidence of complications) as this parameter enables the demonstration of group differences due to its size.

2. Irrespective of the genuine study design, many studies did not clearly differentiate between the albumin group and the group with pure crystalloid solution. In many cases the control group did receive either albumin directly or via blood products post-operatively.

Conclusion of meta-analysis
In comparison to control groups, albumin significantly reduces the morbidity rate.

…for the critically ill patient, further aspects

The albumin level has prognostic importance with respect to pulmonary pathology – the risk of pneumonia increased threefold with an albumin level of less than 3 g/dL compared to normo-albuminaemic patients[28].

Platelet hyperaggregatability associated with hypoalbuminaemia is reversed by administration of exogenous albumin[29, 30].

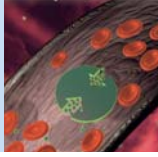
”Human albumin is the preferred first-line volume therapy in patients at risk for coagulation disorders“[31].

The interstitial oedema associated with hypoalbuminaemia may make tissues more at risk for damage and interferes with reparative mechanisms[32].

Albumin may protect the lung and other organs from edema by preserving microvascular integrity[33, 34].

Patients with sepsis receiving albumin have a significantly lower incidence of pulmonary oedema compared with those receiving crystalloid hydration[35].

For the critically ill patient use of human albumin reduces the risk of pulmonary pathology.



For patients in hypovolaemic shock, two to four times the volume of saline, compared with albumin, was required to achieve similar haemodynamic endpoints and resulted in a significantly higher incidence of pulmonary edema[35].

For patients with nephrotic syndrome . . . "Short-term albumin use in conjunction with diuretic therapy, is appropriate for patients with acute, severe peripheral or pulmonary edema"[17].

Continuous monitoring of haemodynamics and oxymetrics with electrical bioimpedance revealed albumin significantly better than crystalloids for improving blood pressure, cardiac output and tissue perfusion in critically ill patients[36].

In patients with subarachnoid haemorrhage, the properties of albumin may limit the amount of total fluid required to maintain a given [central venous pressure] value and hence may minimize the frequency of pulmonary edema[37].

Preclinical studies indicate a "striking neuroprotective effect of albumin therapy in focal cerebral ischaemia"[38].

For the critically ill patient use of human albumin is the product of choice and improves haemodynamic endpoints more rapidly than crystalloids.

…for the elderly

The plasma volume-expanding properties of human albumin may be of special value in the elderly.

"... albumin may be useful in the elderly population requiring volume expansion, since these patients may not tolerate the large volume of colloid solutions often needed for resuscitation"[39].

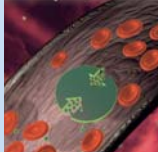
…for patients with cirrhosis

"In patients with cirrhosis and spontaneous bacterial peritonitis, treatment with intravenous albumin in addition to antibiotics reduces the incidence of renal impairment and death in comparison with treatment with an antibiotic alone"[40].

In patients with tense ascites, who are undergoing total paracentesis, albumin, at dosage of 6–8 g/l of ascitic liquid withdrawn, can prevent complication and increase the survival rate, as well as reduce renal and electrolytic complications and the activation of the endogenous vasoactive sytem[41-43].

In cirrhotic patients, the incidence of circulatory dysfunction after paracentesis was around twice as high after plasma expansion with dextran or polygeline than after plasma expansion with albumin[44].

Albumin is effective in improving the rate of response and preventing recurrence of ascites in cirrhotic patients with ascites receiving diuretics.



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Summary of Product Characteristics

1. NAME OF MEDICINAL PRODUCT

Human Albumin 20 % Biotest

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human albumin. 1000 ml solution contain 200 g human plasma protein of which at least 96 % is human albumin. The product has a hyperoncotic effect. For excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Restoration and maintenance of circulating blood volume where volume deficiency has been demonstrated and use of a colloid is appropriate.

The choice of albumin rather than artificial colloid will depend on the clinical situation of the individual patient, based on official recommendations.

4.2. Posology and method of administration

The concentration of the albumin preparation, dosage and the infusion-rate should be adjusted to the patient's individual requirements.

Posology

The dose required depends on the size of the patient, the severity of trauma or illness and on continuing fluid or protein losses. Measures of adequacy of circulating volume and not plasma albumin levels should be used to determine the dose required.

If human albumin is to be administered, haemodynamic performance should be monitored regularly; this may include:

- arterial blood pressure and pulse rate
- central venous pressure
- pulmonary artery wedge pressure
- urine output
- electrolyte
- haemaotcrit / haemoglobin

Method of administration

Human albumin can be directly administered by the intravenous route, or it can also be diluted in an isotonic solution (e.g. 0.9 % sodium chloride).

The infusion rate should be adjusted according to the individual circumstances and the indication.

4.3 Contraindications

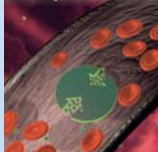
Hypersensitivity to albumin preparations or to any of the excipients.

4.4 Special warnings and special precautions for use

If allergic or anaphylactic-type reactions occur, the infusion should be stopped immediately and appropriate treatment instituted. In case of shock, the current medical standards for shock-treatment should be observed.

Albumin should be used with caution in conditions where hypervolaemia and its consequences or haemodilution could represent a special risk for the patient. Examples of such conditions are:

- decompensated cardiac insufficiency
- hypertension
- oesophageal varices



- pulmonary oedema
- haemorrhagic diathesis
- severe anaemia
- renal and post-renal anuria

The colloid-osmotic effect of human albumin 20 % is approximately four times that of blood plasma. Therefore, when concentrated albumin is administered, care must be taken to ensure adequate hydration of the patient. Patients should be monitored carefully to guard against circulatory overload and hyperhydration.

20-25 % human albumin solutions are relatively low in electrolytes compared to the 4-5 % human albumin solutions. When albumin is given, the electrolyte status of the patient should be monitored (see section 4.2) and appropriate steps taken to restore or maintain the electrolyte balance.

Albumin solutions must not be diluted with water for injections as this may cause haemolysis in recipients.

If comparatively large volumes are to be replaced, controls of coagulation and haematocrit are necessary. Care must be taken to ensure adequate substitution of other blood constituents (coagulation factors, electrolytes, platelets and erythrocytes).

Hypervolaemia may occur if the dosage and rate of infusion are not adjusted to the patient's circulatory situation. At the fist clinical signs of cardiovascular overload (headache, dys¬pnoea, jugular vein congestion), or increased blood pressure, raised venous pressure and pulmonary oedema, the infusion is to be stopped immediately.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

There are no reports of virus transmission with albumin manufactured to European Pharma¬co¬poeia specifications by established processes.

It is strongly recommended that every time that Human Albumin 20 % Biotest is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.5 Interactions with other medicinal products and other forms of interactions

No specific interactions of human albumin with other products are known.

4.6 Pregnancy and lactation

The safety of Human Albumin 20 % Biotest for use in human pregnancy has not been established in controlled clinical trials. However, clinical experience with albumin suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected.

Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or foetus, the course of gestation and peri- and postnatal development.

However, human albumin is a normal constituent of human blood.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Mild reactions such as flush, urticaria, fever and nausea occur rarely. Undesirable effects such as shivering, vomiting, erythema, drop in blood pressure with tachycardia and

dyspnoea occurred in single cases. These reactions normally disappear rapidly when the infusion rate is slowed down or the infusion is stopped. Very rarely, severe reactions as far as shock may occur. In these cases, the infusion should be stopped and an appropriate treatment should be initiated.
For safety with respect to transmissible agents, see 4.4

4.9 Overdose

Hypervolaemia may occur if the dosage and rate of infusion are too high. At the first clinical signs of cardiovascular overload (headache, dyspnoea, jugular vein congestion), or increased blood pressure, raised central venous pressure and pulmonary oedema, the infusion should be stopped immediately and the patient's haemodynamic parameters carefully monitored.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: plasma substitutes and plasma protein fractions, ATC code: B05AA01.
Human 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.
Physiochemical data: Human albumin 4-5 % is mildly hypooncotic to normal plasma. Human albumin 20 % has a corresponding hyperoncotic effect.
The most important physiological functions of albumin results from its contribution to oncotic pressure of the blood and transport function. Albumin stabilise circulating blood volume and is a carrier of hormones, enzymes, medicinal products and toxins.

5.2 Pharmacokinetic properties

Under normal situations the total exchangeable albumin pool is 4-5 g/kg body weight, of which 40-45 % is present intravascularly and 55-60 % 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 half-life of albumin is on average about 19 days. The balance between synthesis and breakdown is normally achieved by feed-back 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 the human plasma and acts like the physiological albumin.
In animals, single dose toxicity testing 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, human albumin has not been reported to be associated with embryo-foetal toxicity, oncogenic or mutagenic potential.
No signs of acute toxicity have been described in animal models.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Caprylate (16 mmol/l), N-acetyl-DL-tryptophanate (16 mmol/l), sodium ions (122 mmol/l), water for injections ad 1000 ml.

6.2 Incompatibilities

Human albumin must not be mixed with other medicinal products (except the recommended diluent), whole blood and packed red blood cells.

6.3 Shelf-life

3 years

6.4 Special precautions for storage

Do not store above 25°C. Do not freeze.

Keep the container in the outer carton in order to protect from light.

6.5 Nature and contents of container

Glass vial with 50 ml

Glass vial with 100 ml

6.6 Instructions for use and handling and disposal

The solution can be directly administered by the intravenous route, or it can be diluted in an isotonic solution (e.g. 0.9 % sodium chloride).

Albumin solutions must not be diluted with water for injections as this may cause haemolysis in recipients.

If large volumes are administered, the product should be warmed to room or body temperature before use.

The solution should be clear or slightly opalescent. Do not use solutions which are cloudy or have deposits. This may indicate that the protein is unstable or that the solution has become contaminated.

Once the container has been opened, the contents should be used immediately.

Any unused product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Biotest Pharma GmbH
Landsteinerstraße 5
63303 Dreieich
Germany

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION

10. DATE OF REVISION OF TEXT

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This brochure serves for general international use.
Local product information may differ according to local authorities regulations.

Biotest

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