with standard aseptic technique. The solution is compatible with whole blood or packed red cells as well as the usual electrolyte and carbohydrate solutions intended for intravenous use. By contrast, it should not be mixed with protein hydrolysates, amino acid mixtures, or solutions containing alcohol. It is ready for use as contained in the bottle and may be given without regard to the blood group of the recipient.
The dosage of Albumin (Human) 25% is based on the principles outlined in the section on indications but should always be adapted to the individual situation. The quantities required may be underestimated because of hidden extravascular deficits, and the effect of Albumin (Human) infusion on the serum protein level should therefore be checked by laboratory analysis.

8.1 **Volume Deficit**
The appropriate Albumin (Human) dose for the treatment of a volume deficit should be estimated from the recipient's hemodynamic response (7), supplemented with the established safeguards against a circulatory overload. In the absence of active hemorrhage, the total dose should at any rate not exceed the normal circulating albumin mass, i.e. 2 g per kg body weight.

8.2 **Oncotic Deficit**
The appropriate Albumin (Human) dose in grams of protein for the correction of an oncotic deficit can, as an average, be estimated from the difference between the desired and the acutal TSP level x plasma volume (~40 ml/kg) x 2, the latter factor allowing for the hidden extravascular deficit. The individual effect is, however, variable and should be checked by measuring the postinfusion TSP level (10, 17).

8.3 **Hemolytic Disease of the Newborn**
The appropriate Albumin (Human) dose for the binding of free serum bilirubin in severely hemolytic infants is 1 g/kg body weight, to be given about one hour prior to the exchange transfusion, and caution is recommended in hypervolemic infants.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

9. How supplied

Albumin (Human) 25% is supplied in 50 ml (NDC 44206-251-05) and 100 ml (NDC 44206-251-10) vials, with circular. The package may be supplied with a disposable sterile intravenous administration set.

10. Storage

Albumin (Human) should be stored at a temperature not exceeding 30 °C (86 °F). It should not be used after the expiration date printed on the label.

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Albumin (Human)

25% Solution

Rx only

1. Description

Albumin (Human) is a sterile aqueous solution for intravenous administration containing the albumin component of human blood.
This product was prepared from venous plasma. The product has been produced by alcohol fractionation and has been heated for 10 hours at 60 °C for inactivation of infectious agents. The results of virus validation studies have shown that the manufacturing process, particularly alcohol fractionation, eliminates enveloped and non-enveloped viruses. Additionally, heat treatment at 60 °C for a period of 10 hours efficiently inactivates viruses. The solution contains 145 ±15 milliequivalents of sodium per liter (mEq/L) and the potassium content is not over 2 mEq/L. The aluminum content does not exceed 200 µg/L. The solution is stabilized with 0.08 millimole of sodium acetyltryptophanate plus 0.08 millimole of sodium caprylate per gram of albumin. The solution contains no preservative.

2. Clinical Pharmacology (13, 17)

2.1 Albumin (Human) should not be used as an intravenous nutrient because of the slow breakdown and relatively unfavorable composition of the albumin molecule with respect to its content of essential amino acids. Oral provision of proteins or an intravenous regimen providing adequate calories and a suitable amino acid mixture are the methods of choice for the treatment of protein malnutrition as such, though they do not permit the rapid correction of hypoproteinemia.

2.2 The binding properties of albumin may provide an indication for its use in severe hemolytic disease of the newborn, where it may lower the plasma concentration of free bilirubin pending an exchange transfusion. This effect is possibly also relevant in certain cases of acute liver failure with rapidly increasing levels of serum bilirubin, particularly in the presence of severe hypoproteinemia.

2.3 The colloid osmotic or oncotic properties of albumin at this moment constitute the predominant reason for its clinical use. The rationale for this is the Starling concept of the capillary balance of hydrostatic and oncotic pressure gradients across the capillary walls as the determinant of the fluid – i.e. volume – distribution between the intravascular and the interstitial compartment (16). The two main indications for the use of Albumin (Human) are therefore a plasma or blood volume deficit and the oncotic deficit resulting from hypoproteinemia. The 25% concentration is oncotically equivalent to approximately five times its volume of normal human plasma. The effective colloid osmotic pressure of the serum proteins depends very largely on the relatively small and numerous albumin molecules, which therefore play a decisive role in the maintenance of the circulating plasma volume.

3. Indications and Usage

3.1 **General Principles** (17)

3.1.1 **Volume Deficit**
Since the oncotic pressure of Albumin (Human) 25% solution is about four times higher than that of normal human serum, it will expand the plasma volume if interstitial water is available for an inflow through the capillary walls. However, many patients suffering from an acute volume deficit also have some degree of interstitial dehydration. In the absence of overhydration, the treatment of an acute volume deficit with Albumin (Human) 25% should therefore include isotonic electrolyte solutions with an albumin:electrolyte ratio of 1:3 or 1:4. By contrast, chronic volume deficits have usually been at least partially compensated for by the renal retention of sodium and water with some degree of tissue edema, and in these circumstances a trial with Albumin (Human) only is indicated. In any case, an anemia of clinically relevant magnitude requires specific treatment, and the metabolic needs of the patient with respect to fluid and electrolytes must be cared for.

3.1.2 **Oncotic Deficit**
The common causes of hypoproteinemia are protein-calorie malnutrition, defective absorption in gastro-intestinal disorders, faulty albumin synthesis in chronic hepatic failure, increased protein catabolism postoperatively or with sepsis, and abnormal renal losses of albumin with chronic kidney disease. In all these settings, the circulating albumin mass is initially maintained by a gradual transfer of extravascular albumin to the circulation, and hypoproteinemia ensues only when this compensatory potential has been exhausted. This implies that manifest hypoproteinemia is usually accompanied by a hidden extravascular albumin deficit of equal magnitude as the measurable intravascular deficit, which must be allowed for if Albumin (Human) is infused because of the capillary permeability of that protein.
The primary sequel of the oncotic deficit resulting from hypoproteinemia is a loss of plasma and a gain of interstitial volume with increased lymphatic flow. As a secondary response, the kidney retains sodium and water which distribute themselves on both sides of the capillary walls and the plasma vol-

ume may be returned almost to normal when the interstitial hydrostatic pressure increases sufficiently to compensate for the decrease of the serum oncotic pressure. This chain of events is accelerated by the infusion of crystalloid fluids. The plasma volume is maintained at the price of interstitial edema (2).
There is some evidence that a serum oncotic pressure near 20 mm Hg – equalling a total serum protein (TSP) concentration of 5.2 g/100 ml – represents a threshold, below which the risk of complications increases (17). The target organs of hypoproteinemia include the skin, the lungs, and the intestine (10). Cutaneous edema lowers the oxygen tension of wounds and may thus impair the healing process (5). An oncotic deficit favors the development of interstitial pulmonary edema (4) and the intestinal accumulation of fluids, which may progress to a paralytic ileus (9).
Relief of the basic pathology is the definitive mode of therapy for the restoration of the plasma protein content, but this process takes time to become effective, and the rapid correction of a critical oncotic deficit by the administration of Albumin (Human) 25% – possibly in conjunction with a diuretic – may therefore be indicated, particularly in high-risk patients who have undergone abdominal, cardio-vascular-thoracic, or urologic surgery or who have acute bacteremia. In notably catabolic patients, attempts to raise the TSP level above 6 g/100 ml usually prove futile, even with massive doses of Albumin (Human) (17).
It is emphasized that whereas Albumin (Human) may be necessary to prevent or treat the aforementioned acute complications of hypoproteinemia, it is **not** indicated for treatment of the chronic condition itself.

3.2 **Specific Indications** (17)

3.2.1 **Acute Circumstances in which Albumin (Human) Use is usually appropriate**

Shock
Though electrolyte solutions such as Ringer's lactate and colloid-containing plasma substitutes may be used as an emergency treatment of shock, Albumin (Human) 25% used according to the aforementioned principles has a much longer intravascular half-life and may therefore be preferable. In addition, anemia of clinically relevant magnitude requires specific therapy with red cells.

Burns
Immediate therapy during the first 24 hours is directed at the administration of large volumes of crystalloid solutions and lesser amounts of Albumin (Human) to maintain an adequate plasma volume and protein (colloid) content. For continuation of therapy beyond 24 hours, larger amounts of Albumin (Human) and lesser amounts of crystalloid are generally used (17). An optimum regimen for the use of Albumin (Human), electrolytes, and fluid in the early treatment of burns has, however, not yet been established.
With restoration of normal capillary function, a close relationship exists once again between infused albumin and resultant increase in plasma oncotic pressure. A goal should be sought of maintaining a plasma albumin concentration of about 2.5 ±0.5 g/100 ml or a plasma oncotic pressure of 20 mm Hg (equivalent to a TSP concentration of 5.2 g/100 ml) (17). In the presence of extensive granulating wounds, a daily loss of up to 30 g of albumin may continue into the late postburn period (1). Proteinrich oral feedings, or adequate parenteral nutrition should be included in the overall regimen to the fullest possible extent, though such treatment does not permit the rapid correction of an oncotic deficit.

3.2.2 **Acute Circumstances in which Albumin (Human) Use may be appropriate**

Adult Respiratory Distress Syndrome
Several factors are usually involved in the development of the state now commonly called the adult respiratory distress syndrome, one of these being a hypoproteinemic fluid overload. If present, this may be corrected by the use of Albumin (Human) 25% and a diuretic (14, 17).

Cardiopulmonary Bypass
An adequate blood volume during cardiopulmonary bypass can be maintained with crystalloids as the only pump priming fluid, but only at the price of interstitial edema. A commonly employed program is an Albumin (Human) and crystalloid pump prime adjusted so as to achieve a hematocrit of 20% and a plasma albumin level of 2.5 g/100 ml in the patient, but the level to which either may be lowered safely has not yet been defined (17).

Pre- and postoperative Hypoproteinemia
Patients undergoing major surgery may lose more than half of their circulating albumin mass (6, 9, 15), and complications attributable to an oncotic deficit may occur in such cases, as well as in septic and intensive care patients. Oncotic therapy with Albumin (Human) 25% may therefore be indicated in such patients, according to the principles outlined in 3.1.2. Temporary redistribution of protein is usually not an indication for Albumin (Human).

Third Space Problems of Infectious Origin
The sequestration of protein-rich fluid during acute peritonitis, pancreatitis, mediastinitis or extensive cellulitis may be of sufficient magnitude to require the treatment of a volume or an oncotic deficit with Albumin (Human) (3), although this occurrence is relatively rare.

Acute Liver Failure
In acute liver failure, Albumin (Human) may serve the triple purpose of stabilizing the circulation, correcting an oncotic deficit and binding excessive serum bilirubin. The therapeutic approach is guided by the individual circumstances (17).

Acute Nephrosis
Patients with acute nephrosis may prove refractory to cyclophosphamide or steroid therapy and their edema may even be aggravated initially by steroids. In such cases, a response may be elicited by combining 100 ml of 20–25% Albumin (Human) with an appropriate diuretic. This combination should be repeated daily for about one week, after which the patient may react satisfactorily to drug therapy (17).

Ascites
The use of Albumin (Human) for blood volume support may be indicated if circulatory instability follows the withdrawal of ascitic fluid.

Red Cell Resuspension Media
As a rule, the use of Albumin (Human) for resuspending red cells can be dispensed with. However, in exceptional circumstances such as certain types of exchange transfusions and the use of very large volumes of erythrocyte concentrates and frozen or washed red cells, the addition of Albumin (Human) to the resuspension medium may be indicated in order to provide sufficient volume and/or avoid excessive hypoproteinemia during the subsequent transfusion. If necessary, 20–25 g or more of Albumin (Human) per liter of red cell suspension should be added as a concentrated solution to the isotonic, electrolyte suspension of erythrocytes immediately before transfusion, the individual dosage depending on the TSP level of the recipient.

Renal Dialysis
Patients undergoing long-term hemodialysis may need Albumin (Human) for the treatment of a volume or an oncotic deficit. As a rule, the initial dose should not exceed 100 ml of a 20–25% solution, and the patients should be carefully observed for signs of a circulatory overload, to which they are particularly sensitive.

Hemolytic Disease of the Newborn
Albumin (Human) 25% may be indicated in order to bind and thus detoxify free serum bilirubin in severely hemolytic infants pending an exchange transfusion.

3.2.3 **Circumstances in which Albumin (Human) Use is not justified**
For the reasons set forth in sections 2. and 3.1, there is no valid reason for the use of Albumin (Human) as an intravenous nutrient or for treating the stabilized hypoproteinemia accompanying chronic cirrhosis, chronic nephrosis, proteinlosing enteropathy, malabsorption and pancreatic insufficiency.
If, however, a patient in this category has to cope with a superimposed acute stress, e.g. anesthesia, surgery or major infections, his hemodynamic state, oncotic deficit and fluid balance should be carefully assessed and the appropriate steps taken as indicated by the individual circumstances.

4. Contraindications

The only specific contraindication to the use of Albumin (Human) 25% is a history of an incompatibility reaction to Albumin (Human) in the individual recipient (see «Adverse Reactions»).

5. Warnings

ALBUMIN (HUMAN) 25% IS MADE FROM HUMAN PLASMA. PRODUCTS MADE FROM HUMAN PLASMA MAY CONTAIN INFECTIOUS AGENTS, SUCH AS VIRUSES, THAT CAN CAUSE DISEASE. THE RISK THAT SUCH PRODUCTS WILL TRANSMIT AN INFECTIOUS AGENT HAS BEEN EXTREMELY REDUCED BY SCREENING PLASMA DONORS FOR PRIOR EXPOSURE TO CERTAIN VIRUSES, BY TESTING FOR THE PRESENCE OF CERTAIN CURRENT VIRUS INFECTIONS, AND BY INACTIVATING AND/OR REMOVING CERTAIN VIRUSES THROUGH ALCOHOL FRACTIONATION AND THROUGH HEAT TREATMENT OF THE PRODUCT IN THE FINAL CONTAINER FOR 10 HOURS AT 60 °C. DESPITE THESE MEASURES, SUCH PRODUCTS CAN STILL POTENTIALLY TRANSMIT DISEASE. A THEORETICAL RISK FOR TRANSMISSION OF CREUTZFELDT-JAKOB DISEASE (CJD) IS CONSIDERED EXTREMELY REMOTE. NO CASES OF TRANSMISSION OF VIRAL DISEASES OR CJD HAVE EVER BEEN IDENTIFIED FOR ALBUMIN. THERE IS ALSO THE POSSIBILITY THAT UNKNOWN INFECTIOUS AGENTS MAY BE PRESENT IN SUCH PRODUCTS. ALL INFECTIONS THOUGHT BY A PHYSICIAN POSSIBLY TO HAVE BEEN TRANSMITTED BY THIS PRODUCT SHOULD BE REPORTED BY THE PHYSICIAN OR OTHER HEALTHCARE PROVIDER TO THE ZLB BIOPLASMA AG, TEL.NO: 01141 31 344 44 44. THE PHYSICIAN SHOULD DISCUSS THE RISKS AND BENEFITS OF THIS PRODUCT WITH THE PATIENT. TURBID SOLUTIONS MUST NOT BE USED. DO NOT BEGIN ADMINISTRATION MORE THAN 4 HOURS AFTER INTRODUCTION OF THE ADMINISTRATION SET. PARTIALLY USED BOTTLES MUST BE DISCARDED. THERE EXISTS A RISK OF POTENTIALLY FATAL HEMOLYSIS AND ACUTE RENAL FAILURE FROM THE INAPPROPRIATE USE OF STERILE WATER FOR INJECTION AS A DILUENT FOR ALBUMIN (HUMAN) 25%. ACCEPTABLE DILUENTS INCLUDE 0.9% SODIUM CHLORIDE OR 5% DEXTROSE IN WATER.

6. Precautions

Adequate precautions should be taken against circulatory overload and may include pulmonary auscultation or X-ray as well as monitoring the central venous or pulmonary artery wedge pressure. Special caution is indicated in patients with stabilized chronic anemia, congestive heart failure and renal insufficiency.
Pregnancy Category C. Animal reproduction studies have not been conducted with Albumin (Human). It is also not known whether Albumin (Human) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Albumin (Human) should be given to a pregnant woman only if clearly needed. There is, however, no evidence for any contraindication to the use of Albumin (Human) specifically associated with reproduction, pregnancy or the fetus.

7. Adverse Reactions

Since Albumin (Human) 25% is sterile when coming from the manufacturer, bacterial contamination with the risk of postinfusion septicemia can only occur if the container has been damaged or following puncture of the rubber cap (see WARNINGS).
Though very rare, non-septic incompatibility reactions including nausea, chills, fever, urticaria, headache and hypotension following the administration of albumin-containing preparations have been recorded (8, 11, 12, 17). A favorable response was observed to the intravenous administration of 50 to 100 mg of prednisolone (12).

8. Dosage and Administration

Albumin (Human) 25% must be administered INTRAVENOUSLY. The venipuncture site should not be infected or traumatized, and should be prepared