3052633 (Rev. 6/2018)

Albumin (Human) 25%, USP

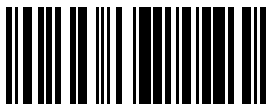
Plasbumin®-25

colors: **Black**
K/P Corporation Job No. 028453
Client: Grifols Therapeutics LLC Cat. No. 3052633
Fonts: Triumvirate Edits: reb
Date: 1/28/2019, 1/31
ID: 1,5,14 Size: 6½" x 16" (Spec 9028507 / 08937813) Proof **2**

DESCRIPTION

Albumin (Human) 25%, USP (Plasbumin®-25) is made from large pools of human venous plasma by the Cohn cold ethanol fractionation process. Part of the fractionation may be performed by another licensed manufacturer. It is prepared in accordance with the applicable requirements established by the U.S. Food and Drug Administration.

Plasbumin-25 is a 25% sterile solution of albumin in an aqueous diluent. The preparation is stabilized with 0.02 M sodium caprylate and 0.02 M acetyltryptophan. The aluminum content of the product is not more than 200 µg/L. The approximate sodium content of the product is 145 mEq/L. Plasbumin-25 is clear, slightly viscous, almost colorless to pale yellow, amber or green. It contains no preservative. Plasbumin-25 must be administered intravenously.



Each vial of Plasbumin-25 is heat-treated at 60° C for 10 hours against the possibility of transmitting the hepatitis viruses.

Additionally, the manufacturing process was investigated for its capacity to decrease the infectivity of an experimental agent of transmissible spongiform encephalopathy (TSE), considered as a model for the variant Creutzfeldt-Jakob disease (vCJD) and Creutzfeldt-Jakob disease (CJD) agents.(11-14) The production steps from Pooled Plasma to Effluent IV-1 in the Plasbumin-25 manufacturing process have been shown to decrease TSE infectivity of that experimental model agent (a total of ≥7.0 logs). These studies provide reasonable assurance that low levels of vCJD/CJD agent infectivity, if present in the starting material, would be removed.

CLINICAL PHARMACOLOGY

Each 20 mL vial of Plasbumin-25 supplies the oncotic equivalent of approximately 100 mL citrated plasma; 50 mL supplies the oncotic equivalent of approximately 250 mL citrated plasma.

When administered intravenously to an adequately hydrated subject, the oncotic (colloid osmotic) effect of 20 mL Plasbumin-25 is such that it will draw approximately a further 70 mL of fluid from the extravascular tissues into the circulation within 15 minutes,(1) thus increasing the total blood volume and reducing both hemoconcentration and whole blood viscosity. Accordingly, the main clinical indications are for hypoproteinemic states involving reduced oncotic pressure, with or without accompanying edema.(2) Plasbumin-25 can also be used as a plasma volume expander.

Albumin is a transport protein and it may be useful in severe hemolytic disease in the neonate who is awaiting exchange transfusion. The infused albumin may reduce the level of free bilirubin in the blood.(2,3) This could also be of importance in acute liver failure where albumin might serve the dual role of supporting plasma oncotic pressure, as well as binding excessive plasma bilirubin.(2)

INDICATIONS AND USAGE

Emergency Treatment of Hypovolemic Shock

Plasbumin-25 is hyperoncotic and on intravenous infusion will expand the plasma volume by an additional amount, three to four times the volume actually administered, by withdrawing fluid from the interstitial spaces, provided the patient is normally hydrated interstitially or there is interstitial edema.(1) If the patient is dehydrated, additional crystalloids must be given,(4) or alternatively, Albumin (Human) 5%, USP (Plasbumin®-5) should be used. The patient's hemodynamic response should be monitored and the usual precautions against circulatory overload observed. 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. Although Plasbumin-5 is to be preferred for the usual volume deficits, Plasbumin-25 with appropriate crystalloids may offer therapeutic advantages in oncotic deficits or in long-standing shock where treatment has been delayed.(2)

Removal of ascitic fluid from a patient with cirrhosis may cause changes in cardiovascular function and even result in hypovolemic shock. In such circumstances, the use of an albumin infusion may be required to support the blood volume.(2)

Burn Therapy

An optimal therapeutic regimen with respect to the administration of colloids, crystalloids, and water following extensive burns has not been established. During the first 24 hours after sustaining thermal injury, large volumes of crystalloids are infused to restore the depleted extracellular fluid volume. Beyond 24 hours Plasbumin-25 can be used to maintain plasma colloid osmotic pressure.

Hypoproteinemia With or Without Edema

During major surgery, patients can lose over half of their circulating albumin with the attendant complications of oncotic deficit.(2,4,5) A similar situation can occur in sepsis or intensive care patients. Treatment with Plasbumin-25 may be of value in such cases.(2)

Adult Respiratory Distress Syndrome (ARDS)(2,5)

This is characterized by deficient oxygenation caused by pulmonary interstitial edema complicating shock and postsurgical conditions. When clinical signs are those of hypoproteinemia with a fluid volume overload, Plasbumin-25 together with a diuretic may play a role in therapy.

Cardiopulmonary Bypass(2,6)

With the relatively small priming volume required with modern pumps, preoperative dilution of the blood using albumin and crystalloid has been shown to be safe and well-tolerated. Although the limit to which the hematocrit and plasma protein concentration can be safely lowered has not been defined, it is common practice to adjust the albumin and crystalloid pump prime to achieve a hematocrit of 20% and a plasma albumin concentration of 2.5 g per 100 mL in the patient.

Acute Liver Failure(2)

In the uncommon situation of rapid loss of liver function with or without coma, administration of albumin may serve the double purpose of supporting the colloid osmotic pressure of the plasma as well as binding excess plasma bilirubin.

Neonatal Hemolytic Disease(2,3)

The administration of Plasbumin-25 may be indicated prior to exchange transfusion, in order to bind free bilirubin, thus lessening the risk of kernicterus. A dosage of 1 g/kg body weight is given about 1 hour prior to exchange transfusion. Caution must be observed in hypervolemic infants.

Sequestration of Protein Rich Fluids(7)

This occurs in such conditions as acute peritonitis, pancreatitis, mediastinitis, and extensive cellulitis. The magnitude of loss into the third space may require treatment of reduced volume or oncotic activity with an infusion of albumin.

Erythrocyte Resuspension(2)

Albumin may be required to avoid excessive hypoproteinemia, during certain types of exchange transfusion, or with the use of very large volumes of previously frozen or washed red cells. About 25 g of albumin per liter of erythrocytes is commonly used, although the requirements in preexistent hypoproteinemia or hepatic impairment can be greater. Plasbumin-25 is added to the isotonic suspension of washed red cells immediately prior to transfusion.

Acute Nephrosis(2)

Certain patients may not respond to cyclophosphamide or steroid therapy. The steroids may even aggravate the underlying edema. In this situation a loop diuretic and 100 mL Plasbumin-25 repeated daily for 7 to 10 days may be helpful in controlling the edema and the patient may then respond to steroid treatment.

Renal Dialysis(2)

Although not part of the regular regimen of renal dialysis, Plasbumin-25 may be of value in the treatment of shock or hypotension in these patients. The usual volume administered is about 100 mL, taking particular care to avoid fluid overload as these patients are often fluid overloaded and cannot tolerate substantial volumes of salt solution.

Situations in Which Albumin Administration is Not Warranted(2)

In chronic nephrosis, infused albumin is promptly excreted by the kidneys with no relief of the chronic edema or effect on the underlying renal lesion. It is of occasional use in the rapid "priming" diuresis of nephrosis. Similarly, in hypoproteinemic states associated with chronic cirrhosis, malabsorption, protein losing enteropathies, pancreatic insufficiency, and undernutrition, the infusion of albumin as a source of protein nutrition is not justified.

CONTRAINDICATIONS

Certain patients, e.g., those with a history of congestive cardiac failure, renal insufficiency or stabilized chronic anemia, are at special risk of developing circulatory overload. A history of an allergic reaction to albumin is a specific contraindication to usage.

WARNINGS

Plasbumin-25 is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, and, theoretically, the Creutzfeldt-Jakob Disease (CJD) agent that can cause disease. The theoretical risk for transmission of CJD is considered extremely remote. No cases of transmission of viral diseases

or CJD have ever been identified for albumin. The risk that such products will transmit an infectious agent has been 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. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections, particularly hepatitis C. 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 Grifols Therapeutics LLC [1-800-520-2807].

The physician should discuss the risks and benefits of this product with the patient, before prescribing or administering it to the patient.

As with any hyperoncotic protein solution likely to be administered in large volumes, severe hemolysis and acute renal failure may result 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. Please refer to the **DOSAGE AND ADMINISTRATION** section for recommended diluents.

Solutions which have been frozen should not be used. Do not use if turbid. Do not begin administration more than 4 hours after the container has been entered. Partially used vials must be discarded. Vials which are cracked or which have been previously entered or damaged should not be used, as this may have allowed the entry of microorganisms. Albumin (Human) 25%, USP (Plasbumin®-25) contains no preservative.

PRECAUTIONS

General

Patients should always be monitored carefully in order to guard against the possibility of circulatory overload. Plasbumin-25 is hyperoncotic, therefore, in the presence of dehydration, albumin must be given with or followed by addition of fluids.(4)

In hemorrhage the administration of albumin should be supplemented by the transfusion of whole blood to treat the relative anemia associated with hemodilution.(8) When circulating blood volume has been reduced, hemodilution following the administration of albumin persists for many hours. In patients with a normal blood volume, hemodilution lasts for a much shorter period.(4,9,10)

The rapid rise in blood pressure which may follow the administration of a colloid with positive oncotic activity necessitates careful observation to detect and treat severed blood vessels which may not have bled at the lower blood pressure.

Drug Interactions

Plasbumin-25 is compatible with whole blood, packed red cells, as well as the standard carbohydrate and electrolyte solutions intended for intravenous use. It should, however, not be mixed with protein hydrolysates, amino acid solutions nor those containing alcohol.

Pregnancy Category C

Animal reproduction studies have not been conducted with Plasbumin-25. It is also not known whether Plasbumin-25 can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Plasbumin-25 should be given to a pregnant woman only if clearly needed.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

ADVERSE REACTIONS

Adverse reactions to albumin are rare. Such reactions may be allergic in nature or due to high plasma protein levels from excessive albumin administration. Allergic manifestations include urticaria, chills, fever, and changes in respiration, pulse and blood pressure.

DOSAGE AND ADMINISTRATION

Plasbumin-25 should always be administered by intravenous infusion. Plasbumin-25 may be administered either undiluted or diluted in 0.9% Sodium Chloride or 5% Dextrose in Water. If sodium restriction is required, Plasbumin-25 should only be administered either undiluted or diluted in a sodium-free carbohydrate solution such as 5% Dextrose in Water.

A number of factors beyond our control could reduce the efficacy of this product or even result in an ill effect following its use. These include improper storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration, and biological differences in individual patients. Because of these factors, it is important that this product be stored properly and that the directions be followed carefully during use.

Hypovolemic Shock—For treatment of hypovolemic shock, the volume administered and the speed of infusion should be adapted to the response of the individual patient.

Burns—After a burn injury (usually beyond 24 hours) there is a close correlation between the amount of albumin infused and the resultant increase in plasma colloid osmotic pressure. The aim should be to maintain the plasma albumin concentration in the region of 2.5 $\pm$ 0.5 g per 100 mL with a plasma oncotic pressure of 20 mm Hg (equivalent to a total plasma protein concentration of 5.2 g per 100 mL).(2) This is best achieved by the intravenous administration of Plasbumin-25. The duration of therapy is decided by the loss of protein from the burned areas and in the urine. In addition, oral or parenteral feeding with amino acids should be initiated, as the long-term administration of albumin should not be considered as a source of nutrition.

Hypoproteinemia With or Without Edema—Unless the underlying pathology responsible for the hypoproteinemia can be corrected, the intravenous administration of Plasbumin-25 must be considered purely symptomatic or supportive (see section **Situations in Which Albumin Administration is Not Warranted**).(2) The usual daily dose of albumin for adults is 50 to 75 g and for children 25 g. Patients with severe hypoproteinemia who continue to lose albumin may require larger quantities. Since hypoproteinemic patients usually have approximately normal blood volumes, the rate of administration of Plasbumin-25 should not exceed 2 mL per minute, as more rapid injection may precipitate circulatory embarrassment and pulmonary edema.

Other dosage recommendations are given under the specific indications referred to above.

Preparation for Administration

Remove seal to expose stopper. Always swab stopper top immediately with a suitable antiseptic prior to entering vial.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Only 16 gauge needles or dispensing pins should be used with 20 mL vial sizes and larger. Needles or dispensing pins should only be inserted within the stopper area delineated by the raised ring. The stopper should be penetrated perpendicular to the plane of the stopper within the ring.

HOW SUPPLIED

Plasbumin-25 is available in 20 mL, 50 mL, and 100 mL rubber-stoppered vials. Each single dose vial contains albumin in the following approximate amounts:

Size	Grams Albumin
20 mL	5
50 mL	12.5
100 mL	25

STORAGE

Store at room temperature not exceeding 30° C (86° F). Do not freeze. Do not use after expiration date.

CAUTION

R_x only

REFERENCES

1. Heyl JT, Gibson JG II, Janeway CA. Studies on the plasma proteins. V. The effect of concentrated solutions of human and bovine serum albumin on blood volume after acute blood loss in man. J Clin Invest. 1943;22:763-73.
2. Tullis JL. Albumin. 1. Background and use. 2. Guidelines for clinical use. JAMA. 1977;237:355-60; 460-3.
3. Comley A, Wood B. Albumin administration in exchange transfusion for hyperbilirubinaemia. Arch Dis Child. 1968;43:151-4.
4. Janeway CA, Gibson ST, Woodruff LM, Heyl JT, Bailey OT, Newhouser LR. Chemical, clinical, and immunological studies on the products of human plasma fractionation. VII. Concentrated human serum albumin. J Clin Invest. 1944;23:465-90.
5. Skillman JJ, Tanenbaum BJ. Unrecognized losses of albumin, plasma, and red cells during abdominal vascular operations. Curr Top Surg Res. 1970;2:523-33.
6. Zubiate P, Kay JH, Mendez AM, Krohn BG, Hochman R, Dunne EF. Coronary artery surgery: a new technique with use of little blood, if any. J Thorac Cardiovasc Surg. 1974;68(2):263-7.
7. Clowes GHA Jr, Vucinic M, Weidner MG. Circulatory and metabolic alterations associated with survival or death in peritonitis: clinical analysis of 25 cases. Ann Surg. 1966;163:866-85.
8. Heyl JT, Janeway CA. The use of human albumin in military medicine. I. The theoretical and experimental basis for its use. US Navy Med Bull. 1942;40:785-91.
9. Woodruff LM, Gibson ST. The clinical evaluation of human albumin. US Navy Med Bull. 1942;40:791-6.
10. Janeway CA, Berenberg W, Hutchins G. Indications and uses of blood, blood derivatives and blood substitutes. Med Clin North Am. 1945;29:1069-94.
11. Stenland CJ, Lee DC, Brown P, Petteway SR Jr, Rubenstein R. Partitioning of human and sheep forms of the pathogenic prion protein during the purification of therapeutic proteins from human plasma. Transfusion. 2002;42:1497-500.
12. Lee DC, Stenland CJ, Miller JL, Cai K, Ford EK, Gilligan KJ, et al. A direct relationship between the partitioning of the pathogenic prion protein and transmissible spongiform encephalopathy infectivity during the purification of plasma proteins. Transfusion. 2001;41:449-55.
13. Lee DC, Stenland CJ, Hartwell RC, Ford EK, Cai K, Miller JL, et al. Monitoring plasma processing steps with a sensitive Western blot assay for the detection of the prion protein. J Virol Methods. 2000;84:77-89.
14. Cai K, Miller JL, Stenland CJ, Gilligan KJ, Hartwell RC, Terry JC, et al. Solvent-dependent precipitation of prion protein. Biochim Biophys Acta. 2002;1597:28-35.

GRIFOLS

Grifols Therapeutics LLC
Research Triangle Park, NC 27709 USA

3052633
(Rev. 6/2018)