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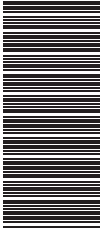
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FLEXBUMIN 25%, Albumin (Human), USP, 25% Solution

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
FLEXBUMIN 25% [Albumin (Human)] is indicated for hypovolemia, hypoalbuminemia, cardiopulmonary bypass surgery, and hemolytic disease of the newborn (HDN).

1.1 Hypovolemia
FLEXBUMIN 25% [Albumin (Human)] is indicated for reversing hypovolemia. When hypovolemia is long standing and hypoalbuminemia exists accompanied by adequate hydration or edema, 25% albumin should be used.

1.2 Hypoalbuminemia
FLEXBUMIN 25% is indicated for patients with hypoalbuminemia resulting from one or more of the following:
(1) Inadequate production (e.g., malnutrition, burns, major injury, infections)
(2) Excessive catabolism (e.g., burns, major injury, pancreatitis)
(3) Loss from the body (e.g., hemorrhage, excessive renal excretion, burn exudates)
(4) Redistribution within the body (e.g., major surgery, various inflammatory conditions)

FLEXBUMIN 25% is indicated for patients with hypoalbuminemia accompanying severe injuries, infections or severe pancreatitis that cannot be quickly reversed and nutritional supplements fail to restore serum albumin levels.

Burns
After the first 24 hours, FLEXBUMIN 25% is indicated, in conjunction with appropriate crystalloid therapy, for the treatment of oncotic deficits following extensive burns and to replace the protein loss which accompanies any severe burn.

Adult Respiratory Distress Syndrome (ARDS)
FLEXBUMIN 25% is indicated, in conjunction with diuretics, to correct interstitial pulmonary edema and hypoproteinemia associated with ARDS.

Nephrosis
FLEXBUMIN 25% is indicated for treatment of edema in patients with severe nephrosis who are receiving steroids and/or diuretics.

1.3 Cardiopulmonary Bypass Surgery
Preoperative dilution of blood using albumin and crystalloid can be used in cardiopulmonary bypass surgery. FLEXBUMIN 25% is indicated as a component of the pump priming during cardiopulmonary bypass procedures.

1.4 Hemolytic Disease of the Newborn (HDN)
FLEXBUMIN 25% is indicated for infants with severe HDN to bind and detoxify unconjugated bilirubin.

1.5 Limitations of Use
Albumin is not indicated as an intravenous nutrient.

2 DOSAGE AND ADMINISTRATION

For intravenous use only.

2.1 Dose
The dose required depends on the patient's body weight, severity of injury/illness and on continuing fluid and protein losses. Adjust the concentration, dosage and infusion rate to the patient's individual requirements. Use adequacy of circulating blood volume, not plasma albumin levels, to determine the dose required. Refer to Table 1 for recommended doses.

Do not exceed 2 g of albumin per kg of body weight for the daily dose. Do not exceed 1 mL/min for patients with normal blood volume. More rapid administration can cause circulatory overload and pulmonary edema. [See *Warnings and Precautions* (5.2)]

Table 1 Recommended Dose	
Indication	Dose
Hypovolemic Shock	Infants and young children: 2.5 to 5 mL per kg body weight. Older children and adults: initial dose 100 to 200 mL. Repeat after 15 to 30 minutes if response is not adequate.
Hypoalbuminemia	Calculate the body albumin compartment to be 80 to 100 mL per kg body weight. Do not exceed a daily dose of 2 g of albumin per kg of body weight.
Burns	The dosage should be determined according to the patient's condition and response to treatment after the first 24 hours.
Hemolytic disease in newborn	1 g per kilogram body weight prior to or during exchange transfusion.

Hypovolemia
Reversing hypovolemia depends largely upon its ability to draw interstitial fluid into the circulation. It is most effective in patients who are well hydrated. Use 5% protein solutions or dilute 25% albumin with crystalloid solutions in the absence of adequate or excessive hydration.

Hypoalbuminemia
If albumin deficit is the result of excessive protein loss, the effect of FLEXBUMIN 25% will be temporary unless the underlying disorder is reversed.

- 2.2 Administration**
- Visually inspect parenteral drug product for particulate matter and discoloration prior to administration. FLEXBUMIN 25% is a transparent or slightly opalescent solution, which may have a greenish tint or may vary from a pale straw to an amber color. Do not use unless solution is clear of particulate matter or if the solution is turbid.
 - Check the container for minute leaks prior to use by squeezing the bag firmly. If leaks are found, discard solution.
 - Do not use the bag if the tip protector is damaged, detached or missing.
 - Do not dilute with Sterile Water for Injection. Acceptable diluents include 0.9% Sodium Chloride or 5% Dextrose in Water. [See *Warnings and Precautions* (5.5)]
 - Do not mix or add with other medicinal products including blood and blood components, protein hydrolysates or solutions containing alcohol. Do not add supplementary medication.
 - Administer within 4 hours after the container has been entered.
 - Monitor hemodynamic parameters in patients receiving FLEXBUMIN 25% and check for the risk of hypervolemia and cardiovascular overload. [See *Warnings and Precautions* (5.2)]
 - Record the name and batch number of the product to maintain a link between the patient and the product.
 - Discard unused portion.

CAUTION: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before the administration of fluid from the secondary container is complete.
1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying the administration set.

3 DOSAGE FORMS AND STRENGTHS
FLEXBUMIN 25% is a solution containing 25 g of albumin per 100 mL.

- 4 CONTRAINDICATIONS**
- Patients with a history of hypersensitivity reaction to albumin preparations or to any of the excipients (N-acetyltryptophan and sodium caprylate). Reactions have included anaphylactic shock, anaphylactic reaction, or hypersensitivity/allergic reactions. [See *Warnings and Precautions* (5.1) and *Adverse Reactions* (6.2)]
 - Patients with severe anemia or cardiac failure with normal or increased intravascular volume. [See *Warnings and Precautions* (5.2)]

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions
Hypersensitivity reactions (including anaphylactic reactions) have been observed. Discontinue administration immediately if a hypersensitivity reaction (including anaphylactic type reactions) is suspected. In case of shock, implement standard medical treatment for shock.

5.2 Hypervolemia/Hemodilution
Under conditions where hypervolemia and/or hemodilution may occur, adjust dose and rate of infusion to the patient's volume status. Monitor coagulation and hematology parameters when comparatively large volumes are replaced. Ensure adequate substitution of other blood constituents (coagulation factors, platelets, and erythrocytes). Monitor electrolyte status to maintain the electrolyte balance.

Discontinue administration at the first clinical signs of cardiovascular overload (e.g., headache, dyspnea, jugular venous distention, rales and abnormal elevations in systemic or central venous blood pressure).

Conditions that pose increased risk of hypervolemia and/or hemodilution include but are not limited to:

- Heart failure
- Hypertension
- Esophageal varices
- Pulmonary edema
- Hemorrhagic diathesis
- Severe anemia
- Renal failure

5.3 Hemodynamics
Closely monitor hemodynamic parameters after administering FLEXBUMIN 25% for evidence of cardiac or respiratory failure, renal failure, or increasing intracranial pressure.

5.4 Blood Pressure
Monitor blood pressure in trauma patients and postoperative surgery patients resuscitated with FLEXBUMIN 25% in order to detect re-bleeding secondary to clot disruption.

5.5 Hemolysis
Do not dilute FLEXBUMIN 25% with Sterile Water for Injection as this can cause hemolysis in recipients. There exists a risk of potentially fatal hemolysis and acute renal failure from the use of Sterile Water for Injection as a diluent for Albumin (Human) in concentrations of 20% or higher. [See *Dosage and Administration* (2.2)]

5.6 Transmission of Infectious Agents
FLEXBUMIN 25% is a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD or vCJD, have ever been identified for licensed albumin.

All infections thought by a physician possibly to have been transmitted by this product should be reported by the physician or other healthcare provider. The physician should discuss the risks and benefits of this product with the patient.

6 ADVERSE REACTIONS

The most serious adverse reactions are hypersensitivity reaction (including anaphylactic reaction) and pulmonary edema.

6.1 Clinical Trials Experience

No sponsor initiated clinical studies have been conducted with FLEXBUMIN 25%.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of FLEXBUMIN 25%. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The following adverse reactions have been reported in the post approval use of FLEXBUMIN 25%:

- Immune System Disorders: Anaphylactic shock, anaphylactic reaction, hypersensitivity/allergic reactions
- Nervous System Disorders: Headache, dysgeusia
- Cardiac Disorders: Myocardial infarction, atrial fibrillation, tachycardia
- Vascular Disorders: Hypotension, flushing
- Respiratory, Thoracic, and Mediastinal Disorders: Pulmonary edema, dyspnea
- Gastrointestinal Disorders: Vomiting, nausea
- Skin and Subcutaneous Tissue Disorders: Urticaria, rash, pruritus
- General Disorders and Administration Site Conditions: Pyrexia, chills

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

No human or animal data are available to indicate the presence or absence of drug-associated risk. It is not known whether FLEXBUMIN 25% can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity.

8.2 Lactation

Risk Summary

No human or animal data are available to indicate the presence or absence of drug-associated risk. It is not known whether FLEXBUMIN 25% is excreted in human milk.

8.4 Pediatric Use

The safety of albumin solutions has been demonstrated in children provided the dose is appropriate for body weight; however, the safety of FLEXBUMIN 25% has not been evaluated in sponsor conducted pediatric studies.

8.5 Geriatric Use

No human or animal data.

10 OVERDOSAGE

Hypervolemia may occur if the dosage and rate of infusion are too high. [See *Warnings and Precautions* (5.2)]

11 DESCRIPTION

FLEXBUMIN 25% is a sterile, nonpyrogenic preparation of albumin in a single dosage form for intravenous administration. Each 100 mL contains 25 g of albumin. It has been adjusted to physiological pH with sodium bicarbonate and/or sodium hydroxide and stabilized with N- acetyltryptophan (0.02M) and sodium caprylate (0.02M). The sodium content is 145 ± 15 mEq/L. FLEXBUMIN 25% contains no preservative and none of the coagulation factors found in fresh whole blood or plasma. FLEXBUMIN 25% is a transparent or slightly opalescent solution which may have a greenish tint or may vary from a pale straw to an amber color and is clear of particulate matter.

FLEXBUMIN 25% is manufactured from human plasma by the modified Cohn-Oncley cold ethanol fractionation process, which includes a series of cold-ethanol precipitation, centrifugation and/or filtration steps followed by pasteurization of the final product at 60 ± 0.5°C for 10 - 11 hours. This process accomplishes both purification of albumin and reduction of viruses.

In vitro studies demonstrate that the manufacturing process for FLEXBUMIN 25% provides for effective viral reduction. These viral reduction studies, summarized in Table 2, demonstrate viral clearance during the manufacturing process for FLEXBUMIN 25%.

These studies indicate that specific steps in the manufacturing of FLEXBUMIN 25% are capable of eliminating/inactivating a wide range of relevant and model viruses. Since the mechanism of virus elimination/inactivation by fractionation and by heating steps is different, the overall manufacturing process of FLEXBUMIN 25% is effective in reducing viral load.

Table 2 Summary of Viral Reduction Factor for Each Virus and Processing Step [§]						
Process Step	Viral Reduction Factor (log ₁₀)					
	Lipid Enveloped			Non-Enveloped		
	HIV-1	Flaviviridae		PRV	HAV	Parvoviridae
		BVDV	WNV			MMV
Processing of Fraction I+II+III/II +III supernatant to Fraction IV ₄ Cuno 70C filtrate ^b	>4.9	>4.8	>5.7	>5.5	>4.5	3.0
Pasteurization	>7.8	>6.5	n.d. ^a	>7.4	3.2	1.6 ^c
Mean Cumulative Reduction Factor, log ₁₀	>12.7	>11.3	>5.7	>12.9	>7.7	4.6

[§] Human immunodeficiency virus, type 1 (HIV-1) both as a target virus and model for HIV-2 and other lipid-enveloped RNA viruses; bovine viral diarrhea virus (BVDV), a model for lipid-enveloped RNA viruses, such as hepatitis C virus (HCV); West Nile Virus (WNV), a target virus and model for other similar lipid-enveloped RNA viruses; pseudorabies virus (PRV), a model for other lipid- enveloped DNA viruses such as hepatitis B virus (HBV); mice minute virus (MMV), models for non-enveloped DNA viruses such as human parvovirus B19¹⁰; and hepatitis A virus (HAV), a target virus and a model for other non-enveloped RNA viruses.)

^a n.d. not determined

^b Other Albumin fractionation process steps (processing of cryo-poor plasma to Fraction I+II+III/II+III supernatant and processing of Fraction V suspension to Cuno 90LP filtrate) showed virus reduction capacity in *in-vitro* viral clearance studies. These process steps also contribute to the overall viral clearance effectiveness of the manufacturing process. However, since the mechanism of virus removal is similar to that of this particular process step, the viral inactivation data from other steps were not used in the calculation of the Mean Cumulative Reduction Factor.

^c Recent scientific data suggests that the actual human parvovirus B19 (B19V) is far more effectively inactivated by pasteurization than indicated by model virus data.¹⁰

The likelihood of the presence of viable hepatitis viruses has been minimized by testing the plasma at three stages: for the presence of hepatitis viruses, by fractionation steps with demonstrated virus removal capacity and by heating the product for 10 hours at 60°C. This procedure has been shown to be an effective method of inactivating hepatitis virus in albumin solutions even when those solutions were prepared from plasma known to be infective.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Albumin is responsible for 70-80% of the colloid osmotic pressure of normal plasma, thus making it useful in regulating the volume of circulating blood. Albumin is also a transport protein and binds naturally occurring, therapeutic and toxic materials in the circulation.

12.2 Pharmacodynamics

FLEXBUMIN 25% is osmotically equivalent to approximately five times its volume of human plasma. When injected intravenously, 25% albumin will draw about 3.5 times its volume of additional fluid into the circulation within 15 minutes, except when the patient is markedly dehydrated. This extra fluid reduces hemoconcentration and blood viscosity. The degree and duration of volume expansion depends upon the initial blood volume. In patients with decreased blood volume, the effect of infused albumin can persist for many hours; however, in patients with normal blood volume, the duration will be shorter.

12.3 Pharmacokinetics

Total body albumin is estimated to be 350 g for a 70 kg patient , with more than 60% located in the extravascular fluid compartment. The half-life of albumin is 15 to 20 days with a turnover of approximately 15 g per day.

The minimum plasma albumin level necessary to prevent or reverse peripheral edema is unknown. It is recommended that plasma albumin levels be maintained at approximately 2.5 g/dL. This concentration provides a plasma oncotic pressure value of 20 mmHg.

13 HOW SUPPLIED/STORAGE AND HANDLING

FLEXBUMIN 25% is supplied in a single-dose plastic container:

NDC Number	Fill Size	Grams Protein
NDC 0944-0493-01	50 mL	12.5 g
NDC 0944-0493-02	100 mL	25 g

Storage

Room temperature: not exceed 30°C (86°F). Protect from freezing.

14 MANUFACTURER

Baxalta US Inc.,
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Los Angeles, California,
90039 United States

15 REVISION DATE

Feb 2020