

FLEXBUMIN 25%, Albumin (Human), USP, 25% Solution in GALAXY Single Dose Container

DESCRIPTION

FLEXBUMIN 25% in 50 and 100 mL Galaxy plastic container is a sterile, nonpyrogenic preparation of albumin in a single dosage form for intravenous administration. Each 100 mL contains 25 g of albumin and was prepared from human venous plasma using the Cohn cold ethanol fractionation process. Source material for fractionation may be obtained from another U.S. licensed manufacturer. 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. This solution 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.

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.¹⁻³

The GALAXY plastic container is fabricated from a specially designed multilayered plastic (PL 2501). Solutions are in contact with the polyethylene layer of the container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability and safety of the plastic have been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

CLINICAL PHARMACOLOGY

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.⁴⁻⁶ Albumin is also a transport protein and binds naturally occurring, therapeutic and toxic materials in the circulation.^{5,6}

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. With patients treated for diminished blood volume, the effect of infused albumin may persist for many hours; however, in patients with normal volume, the duration will be shorter.⁷⁻⁹

Total body albumin is estimated to be 350 g for a 70 kg man and is distributed throughout the extracellular compartments; more than 60% is 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.⁵

The minimum plasma albumin level necessary to prevent or reverse peripheral edema is unknown. Some investigators recommend that plasma albumin levels be maintained at approximately 2.5 g/dL. This concentration provides a plasma oncotic value of 20 mm Hg.⁴

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 $60 \pm 0.5^\circ\text{C}$ 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 significant viral reduction. These viral reduction studies, summarized in Table 1, demonstrate viral clearance during the manufacturing process for FLEXBUMIN 25% using human immunodeficiency virus, type 1 (HIV-1) both as a target virus and as model virus 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 B 19¹⁰; hepatitis A virus (HAV), a target virus and a model for other non-enveloped RNA viruses.

These studies indicate that specific steps in the manufacture 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 is different, the overall manufacturing process of FLEXBUMIN 25% is robust in reducing viral load.

<p>TABLE 1 Summary of Viral Reduction Factor for Each Virus and Processing Step</p>
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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*	> 4.9	> 4.8	> 5.7	>5.5	>4.5	3.0
Pasteurization	> 7.8	> 6.5	n.d.	> 7.4	3.2	1.6**
Mean Cumulative Reduction Factor, log₁₀	> 12.7	> 11.3	> 5.7	> 12.9	> 7.7	4.6

n.d. = not determined

* 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 significant virus reduction capacity in *in-vitro* viral clearance studies. These process steps also contribute to the overall viral clearance robustness 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.

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

INDICATIONS AND USAGE

1. Hypovolemia

Hypovolemia is a possible indication for FLEXBUMIN 25%. Its effectiveness in reversing hypovolemia depends largely upon its ability to draw interstitial fluid into the circulation. It is most effective with patients who are well hydrated. When hypovolemia is long standing and hypoalbuminemia exists accompanied by adequate hydration or edema, 25% albumin is preferable to 5% protein solutions.^{4,6} However, in the absence of adequate or excessive hydration, 5% protein solutions should be used or 25% albumin should be diluted with crystalloid.

Although crystalloid solutions and colloid-containing plasma substitutes can be used in emergency treatment of shock, Albumin (Human) has a prolonged intravascular half-life.¹¹ When blood volume deficit is the result of hemorrhage, compatible red blood cells or whole blood should be administered as quickly as possible.

2. Hypoalbuminemia

A. General

Hypoalbuminemia is another possible indication for use of FLEXBUMIN 25%. Hypoalbuminemia can result from one or more of the following:⁵

- (1) Inadequate production (malnutrition, burns, major injury, infections, etc.)
- (2) Excessive catabolism (burns, major injury, pancreatitis, etc.)
- (3) Loss from the body (hemorrhage, excessive renal excretion, burn

exudates, etc.)

- (4) Redistribution within the body (major surgery, various inflammatory conditions, etc.)

When albumin deficit is the result of excessive protein loss, the effect of administration of albumin will be temporary unless the underlying disorder is reversed. In most cases, increased nutritional replacement of amino acids and/or protein with concurrent treatment of the underlying disorder will restore normal plasma albumin levels more effectively than albumin solutions. Occasionally hypoalbuminemia accompanying severe injuries, infections or pancreatitis cannot be quickly reversed and nutritional supplements may fail to restore serum albumin levels. In these cases, FLEXBUMIN 25% might be a useful therapeutic adjunct.

B. Burns

An optimum regimen for the use of albumin, electrolytes and fluid in the early treatment of burns has not been established, however, in conjunction with appropriate crystalloid therapy, FLEXBUMIN 25% may be indicated for treatment of oncotic deficits after the initial 24 hour period following extensive burns and to replace the protein loss which accompanies any severe burn.^{4,6}

C. Adult Respiratory Distress Syndrome (ARDS)

A characteristic of ARDS is a hypoproteinemic state, which may be causally related to the interstitial pulmonary edema. Although uncertainty exists concerning the precise indication of albumin infusion in these patients, if there is a pulmonary overload accompanied by hypoalbuminemia, 25% albumin solution may have a therapeutic effect when used with a diuretic.⁴

D. Nephrosis

FLEXBUMIN 25% may be a useful aid in treating edema in patients with severe nephrosis who are receiving steroids and/or diuretics.

3. Cardiopulmonary Bypass Surgery

FLEXBUMIN 25% has been recommended prior to or during cardiopulmonary bypass surgery, although no clear data exist indicating its advantage over crystalloid solutions.^{4,6,12}

4. Hemolytic Disease of the Newborn (HDN)

FLEXBUMIN 25% may be administered in an attempt to bind and detoxify unconjugated bilirubin in infants with severe HDN.

There is no valid reason for use of albumin as an intravenous nutrient.

CONTRAINDICATIONS

A history of allergic reactions to albumin and any of the excipients is a specific contraindication to the use of this product. FLEXBUMIN 25% is also contraindicated in severely anemic patients

and in patients with cardiac failure.

FLEXBUMIN 25% must not be diluted with Sterile Water for Injection as this may 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). Acceptable diluents include 0.9% Sodium Chloride or 5% Dextrose in Water.

WARNINGS

FLEXBUMIN 25% is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, that can cause disease. This also applies to unknown or emerging viruses and pathogens. 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 (See Description). The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV, and for the non-enveloped viruses HAV and Parvovirus B19. Despite these measures, such products can still potentially transmit disease. Based on effective donor screening and product manufacturing processes, albumin carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for 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 to Baxter Healthcare Corporation at 1-800-423-2862. The physician should discuss the risks and benefits of this product with the patient.

Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. In case of shock, standard medical treatment for shock should be implemented.

PRECAUTIONS

Hemodynamics

Do not administer FLEXBUMIN 25% without very close monitoring of hemodynamics; look for evidence of cardiac or respiratory failure, renal failure, or increasing intra-cranial pressure.

Hypervolemia/Hemodilution

FLEXBUMIN 25% should be used with caution in conditions where hypervolemia and its consequences or hemodilution could represent a special risk for the patient. Examples may include but are not limited to: decompensated cardiac insufficiency, hypertension, esophageal varices, pulmonary edema, hemorrhagic diathesis, severe anemia, renal and post-renal failure.

FLEXBUMIN 25% must be administered intravenously. The rate of administration should be adjusted according to the solution concentration and the patient's hemodynamic measurements

and should not exceed 1 mL/min to patients with normal blood volume. More rapid administration might cause circulatory overload and pulmonary edema.¹³ At the first clinical signs of cardiovascular overload (headache, dyspnea, jugular vein congestion), or increased blood pressure, raised central venous pressure and pulmonary edema, the infusion is to be stopped immediately.

Blood Pressure

A rise in blood pressure after 25% albumin infusion necessitates careful observation of the injured or post-operative patient in order to detect and treat severed blood vessels that may not have bled at a lower blood pressure.

Pregnancy–Category C, and Lactation

There are no adequate data from the use of FLEXBUMIN 25% in pregnant or lactating women. Animal reproduction studies have not been conducted with FLEXBUMIN 25%. It is not known whether FLEXBUMIN 25% can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing FLEXBUMIN 25%. FLEXBUMIN 25% should be given to a pregnant woman only if clearly needed.

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 pediatric patients.

Large Volumes

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

Electrolyte Status

When FLEXBUMIN 25% is given, the electrolyte status of the patient should be monitored and appropriate steps taken to restore or maintain the electrolyte balance.

DRUG INTERACTIONS

No interaction studies have been performed with FLEXBUMIN 25%.

ADVERSE REACTIONS

Adverse Reactions from Clinical Trials

There are no data available on adverse reactions from clinical trials conducted with

FLEXBUMIN 25%.

Post-Marketing Adverse Reactions

The following adverse reactions have been reported in the post-marketing experience. These reactions are listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity.

IMMUNE SYSTEM DISORDERS: Anaphylactic shock, Anaphylactic reactions, Hypersensitivity/Allergic reactions

NERVOUS SYSTEM DISORDERS: Headache

CARDIAC DISORDERS: Tachycardia

VASCULAR DISORDERS: Hypotension, Flushing

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS: Dyspnea

GASTROINTESTINAL DISORDERS: Vomiting, Nausea, Dysguesia

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Urticaria, Rash, Pruritis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Pyrexia, Chills

Overdose

Hypervolemia may occur if the dosage and rate of infusion are too high. (See Precautions: Hypervolemia/Hemodilution)

DOSAGE AND ADMINISTRATION

FLEXBUMIN 25% must be administered intravenously. Do not use if turbid. Do not begin administration more than 4 hours after the container has been entered. Discard unused portion.

FLEXBUMIN 25% solutions must not be diluted with Sterile Water for Injection as this may cause hemolysis in recipients (see CONTRAINDICATIONS).

Albumin solutions should not be mixed with other medicinal products including blood and blood components, but can be used concomitantly with other parenterals such as whole blood, plasma, saline, glucose or sodium lactate when deemed medically necessary. The addition of four volumes of normal saline or 5% glucose to 1 volume of FLEXBUMIN 25% gives a solution,

which is approximately isotonic and isosmotic with citrated plasma.

Albumin solutions should not be mixed with protein hydrolysates or solutions containing alcohol since these combinations may cause the proteins to precipitate.

Do not add supplementary medication.

Hypervolemia may occur if the dosage and rate of infusion are not adjusted, giving consideration to the solution concentration and the patient's clinical status. Hemodynamic parameters should be monitored in patients receiving FLEXBUMIN 25% and should be used to check for the risk of hypervolemia and cardiovascular overload. (See PRECAUTIONS).

It is strongly recommended that every time that FLEXBUMIN 25% is administered to a patient, the name and batch number of the product be recorded in order to maintain a link between the patient and the batch of the product.

Recommended Dosages

1. Hypovolemic Shock

The dosage of FLEXBUMIN 25% must be individualized. As a guideline, the initial treatment should be in the range of 100 to 200 mL for adults and 2.5 to 5 mL per kilogram body weight for children. This may be repeated after 15 to 30 minutes, if the response is not adequate. For patients with significant plasma volume deficits, albumin replacement is best administered in the form of 5% Albumin (Human).

Upon administration of additional albumin or if hemorrhage has occurred, hemodilution and a relative anemia will follow. This condition should be controlled by the supplemental administration of compatible red blood cells or compatible whole blood.

2. Burns

The optimal therapeutic regimen for administration of crystalloid and colloid solutions after extensive burns has not been established. When FLEXBUMIN 25% is administered after the first 24 hours following burns, the dose should be determined according to the patient's condition and response to treatment.

3. Hypoalbuminemia

Hypoalbuminemia is usually accompanied by a hidden extravascular albumin deficiency of equal magnitude. This total body albumin deficit must be considered when determining the amount of albumin necessary to reverse the hypoalbuminemia. When using patient's serum albumin concentration to estimate the deficit, the body albumin compartment should be calculated to be 80 to 100 mL per kg of body weight.^{5,6} Daily dose should not exceed 2 g of albumin per kilogram of body weight.

4. Hemolytic Disease of the Newborn

FLEXBUMIN 25% may be administered prior to or during exchange transfusion in a

dose of 1 g per kilogram body weight.¹⁴

Preparation for Administration

Check the GALAXY container for minute leaks prior to use by squeezing the bag firmly. If leaks are found, discard solution as sterility may be impaired. Do not add supplementary medication. Do not use unless solution is clear of particulate matter and seal is intact. 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. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

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 the fluid from the secondary container is complete.

Administration:

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 set. Make certain that the administration set contains an adequate filter (15-micron or smaller).

HOW SUPPLIED

FLEXBUMIN 25% is supplied in 50 mL (NDC 0944-0493-01) and 100 mL (NDC 0944-0493-02) in single dose GALAXY plastic container (PL 2501).

STORAGE

Store FLEXBUMIN 25% at room temperature, not to exceed 30°C (86°F). Protect from freezing.

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