ENG

FLEXBUMIN 20%, Albumin (Human), USP, 20% Solution
in **GALAXY Single Dose Container**

DESCRIPTION

FLEXBUMIN 20% 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 20 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 (0.016 M) and sodium caprylate (0.016M). 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 20% 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 20% is osmotically equivalent to approximately five times its volume of human plasma. When injected intravenously, 20% albumin will draw about three 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 20% 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 20% provides for significant viral reduction. These viral reduction studies, summarized in Table 1, demonstrate viral clearance during the manufacturing process for FLEXBUMIN 20% 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), model for non-enveloped DNA viruses such as human parvovirus B19[10]; and 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 20% 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 20% is robust in reducing viral load.

TABLE 1
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*	**> 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,log_{10}	**> 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 20%. 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, 20% 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 20% 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 20%.

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 20% 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 20% 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, 20% albumin solution may have a therapeutic effect when used with a diuretic.[4]

D. Nephrosis
FLEXBUMIN 20% 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 20% 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 20% 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
FLEXBUMIN 20% administration is contraindicated among patients with a history of allergic reactions to albumin and to any of the excipients. FLEXBUMIN 20% is also contraindicated in severely anemic patients.
FLEXBUMIN 20% solutions must not be diluted with water for injections as this may cause hemolysis in recipients. 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 FLEXBUMIN 20%.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

WARNINGS

Allergic Reaction/Anaphylactic Shock

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.

Transmission of Infectious Agents

Albumin 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.

PRECAUTIONS

Hemodynamics

Do not administer FLEXBUMIN 20% without very close monitoring of hemodynamics, look for evidence of cardiac or respiratory failure, renal failure, or increasing intra-cranial pressure.

Hypervolemia/Hemodilution

FLEXBUMIN 20% 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.

The rate of administration should be adjusted according to the solution concentration and the patient's hemodynamic measurements. Rapid administration might cause circulatory overload and pulmonary edema. 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.

Pediatric

The safety and efficacy of the use of FLEXBUMIN 20% solution in pediatric patients have not been established in clinical trials; however, the use of albumin solutions in the pediatric population is referenced in the medical literature.

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 20% is given, the electrolyte status of the patient should be monitored and appropriate steps taken to restore or maintain the electrolyte balance. FLEXBUMIN 20% solutions contain 130-160 mmol/l sodium. The amount of sodium in FLEXBUMIN 20% is to be taken into consideration for patients on a controlled sodium diet.

Blood pressure

A rise in blood pressure after FLEXBUMIN 20% 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.

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

No interaction studies have been performed with FLEXBUMIN 20%

PREGNANCY, LACTATION AND FERTILITY: Category C

There are no adequate data from the use of FLEXBUMIN 20% in pregnant or lactating women. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing FLEXBUMIN 20%.

The effects of Albumin on fertility have not been established in controlled clinical trials.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no information of the effects of FLEXBUMIN 20% on the ability to drive or operate an automobile or other heavy machinery.

ADVERSE REACTIONS

1. **Adverse Reactions from Clinical Trials**

There are no data available on adverse reactions from Shire-sponsored clinical trials conducted with FLEXBUMIN 20%.

2. **Post-Marketing Adverse Reactions**

The following adverse reactions have been reported in the post-marketing experience:

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

NERVOUS SYSTEM DISORDERS: Headache, Dsygeusia

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

OVERDOSE

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

DOSAGE AND ADMINISTRATION

FLEXBUMIN 20% 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 20% 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 three volumes of normal saline or 5% glucose to 1 volume of FLEXBUMIN 20% 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 20% 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 20% 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 20% must be individualized. As a guideline, the initial treatment should be in the range of 125 to 250 ml for adults and 3 to 6 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 20% 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 to100 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 20% 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 20% 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).

Nature and Contents of Container

Presence of extractables

Solutions are in contact with the polyethylene layer of the multilayered plastic GALAXY 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.

Instructions for Use, Handling, and Disposal

FLEXBUMIN 20% solutions should not be mixed with other medicinal products including blood and blood components, but can be used concomitantly when deemed medically necessary.

Do not use unless solution is clear and seal is intact. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If leaks are found, discard.

There is a risk of potentially fatal hemolysis and acute renal failure from the use of Sterile Water for Injection as a diluent for FLEXBUMIN 20% in concentrations of 20% or higher. Acceptable diluents include 0.9% Sodium Chloride or 5% Dextrose in Water.

Do not use the bag if the tip protector is damaged, detached or missing.

HOW SUPPLIED

FLEXBUMIN 20% is supplied in 50 ml and 100 ml in single dose GALAXY plastic container.

STORAGE

Store FLEXBUMIN 20% at room temperature, not to exceed 30°C (86°F). Protect from freezing.

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