HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use FLEXBUMIN 5% safely and effectively. See full prescribing information for FLEXBUMIN 5%.

FLEXBUMIN 5% Albumin (Human), USP, 5% Solution, for intravenous use
Initial U.S. Approval: 2005

INDICATIONS AND USAGE

FLEXBUMIN 5%, Albumin (Human) Solution is indicated for:
- Hypovolemia (1.1)
- Hypoalbuminemia: Burns (1.2)
- Cardiopulmonary Bypass Surgery (1.3)

Limitations of Use: Albumin is not indicated as an intravenous nutrient. (1.4)

DOSAGE AND ADMINISTRATION

For intravenous use only.
- Adjust dose and rate of infusion based on the patient's clinical status. (2.1)
- Do not exceed 2 g of albumin per kg body weight for the daily dose. (2.1)
- Do not exceed 1 mL/min for patients with normal blood volume. (2.1)
- Do not dilute with Sterile Water for Injection. (2.2)

Indication	Dose
Hypovolemic Shock	Infants and young children: 12 to 20 mL per kg body weight. Older children and adults: initial dose 250 to 500 mL. Repeat after 15 to 30 minutes if the 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.

DOSAGE FORMS AND STRENGTHS

FLEXBUMIN 5% is a solution containing 5 g of albumin per each 100 mL. (3)

CONTRAINDICATIONS

- History of hypersensitivity reaction to albumin preparations or to any of the excipients (N-acetyltryptophan and sodium caprylate). (4)
- Severe anemia or cardiac failure with normal or increased intravascular volume. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions (including anaphylactic reactions) have been observed. If hypersensitivity reaction is suspected, discontinue use and implement appropriate standard medical treatment. (5.1)
- Under conditions where hypervolemia and/or hemodilution may occur, adjust the dose and rate of infusion to the patient's volume status. When administering large volumes, monitor hemodynamic parameters and ensure adequate substitution of other blood constituents are available (coagulation factors, platelets, and erythrocytes). Monitor electrolyte balance. (5.2)
- Closely monitor hemodynamic parameters after administration for evidence of cardiac or respiratory failure, renal failure or increasing intracranial pressure. (5.3)
- Monitor blood pressure in trauma patients and postoperative surgery patients in order to detect re-bleeding secondary to clot disruption. (5.4)
- Do not dilute with Sterile Water for Injection as this can cause hemolysis in recipients. (5.5)
- This product is made from human plasma and may contain infectious agents e.g., viruses and, theoretically, the variant Creutzfeldt-Jakob disease agent. (5.6)

ADVERSE REACTIONS

The most serious adverse reactions are hypersensitivity reaction (including anaphylactic reaction) and pulmonary edema. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Takeda Pharmaceuticals U.S.A., Inc. at 1-877-TAKEDA-7 (1-877-825-3327) or contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pediatric Use: Ensure dose is appropriate for body weight. (8.4)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

FLEXBUMIN 5% [Albumin (Human)] is indicated for hypovolemia, hypoalbuminemia and cardiopulmonary bypass surgery.

1.1 Hypovolemia

FLEXBUMIN 5% [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.[4,6]

1.2 Hypoalbuminemia

FLEXBUMIN 5% is indicated for patients with hypoalbuminemia resulting from one or more of the following:[5]

(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 5% 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 5% is indicated in conjunction with appropriate crystalloid therapy, for the treatment of oncotic deficits following extensive burns and to replace protein loss which accompanies any severe burn.[4,6]

1.3 Cardiopulmonary Bypass Surgery

Preoperative dilution of blood using albumin and crystalloid can be used in cardiopulmonary bypass surgery. FLEXBUMIN 5% is indicated as a component of the pump prime during cardiopulmonary bypass procedures.[4,6]

1.4 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[11] *[see Warnings and Precautions (5.2)]*.

Table 1: Recommended Dose

Indication	Dose
Hypovolemic Shock	Infants and young children: 12 to 20 mL per kg body weight. Older children and adults: initial dose 250 to 500 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.

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 5% 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 5% 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 5% 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 5% is a solution containing 5 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), 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 5% 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 5% in order to detect re-bleeding secondary to clot disruption.

5.5 Hemolysis

Do not dilute FLEXBUMIN 5% 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) *[see Dosage and Administration (2.2)]*.

5.6 Transmission of Infectious Agents

FLEXBUMIN 5% 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 to Takeda Pharmaceuticals U.S.A., Inc. at 1-877-TAKEDA-7 (1-877-825-3327). 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 5%.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of FLEXBUMIN 5%. 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 postapproval use of FLEXBUMIN 5%:

- 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 5% 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 5% 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 5% 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 5% is a sterile, nonpyrogenic preparation of albumin in single dosage form for intravenous administration. Each 100 mL contains 5 g of albumin. It has been adjusted to physiological pH with sodium bicarbonate and/or sodium hydroxide and stabilized with N-acetyltryptophan (0.004M) and sodium caprylate (0.004M). The sodium content is 145 ± 15 mEq/L. FLEXBUMIN 5% contains no preservative and none of the coagulation factors found in fresh whole blood or plasma. FLEXBUMIN 5% 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 5% 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 to 11 hours. This process accomplishes both purification of albumin and reduction of viruses.

In vitro studies demonstrate that the manufacturing process for FLEXBUMIN 5% provides for effective viral reduction. These viral reduction studies, summarized in *Table 2*, demonstrate viral clearance during the manufacturing process for FLEXBUMIN 5%.

These studies indicate that specific steps in the manufacturing of FLEXBUMIN 5% 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 5% 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 B19[10]; 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.[1,2,3] FLEXBUMIN 5% contains no blood group isoagglutinins, thereby permitting its administration without regard to the recipient's blood group.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Albumin is responsible for 70 to 80% of the colloid osmotic pressure of normal plasma, thus making it useful in regulating the volume of circulating blood.[4,5,6] Albumin is also a transport protein and binds naturally occurring, therapeutic and toxic materials in the circulation.[5,6]

12.2 Pharmacodynamics

FLEXBUMIN 5% is osmotically equivalent to an equal volume of normal human plasma and will increase circulating plasma volume by an amount approximately equal to volume infused. 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.[7,8,9]

12.3 Pharmacokinetics

Total body albumin is estimated to be 350 g for a 70 kg patient, 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.[5]

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.[4]

15 REFERENCES

1. Cai K, Gierman T, Hotta J, et al: Ensuring the Biologic Safety of Plasma-Derived Therapeutic Proteins. Biodrugs 2005; 19 (2): 79-96.
2. Gerety R, Aronson D: Plasma derivatives and viral hepatitis. Transfusion 1982; 22 (5): 347-351.
3. Burnouf T, Padilla A: Current strategies to prevent transmission of prions by human plasma derivatives. Transfusion Clinique et Biologique 2006; 13: 320-328.
4. Tullis J: Albumin 1. Background and use Albumin 2. Guidelines for clinical use. JAMA 1977; 237 (4): 355-360, 460-463.
5. Peters T Jr: Serum albumin. The Plasma Proteins, 2nd Edition, Vol 1. Putnam FW (ed). New York, Academic Press, 1975, pp 133-181.
6. Finlayson J: Albumin products. Seminars in Thrombosis and Hemostasis 1980; 6 (2): 85-120.
7. Haynes G, Navickis R, Wilkes M: Albumin administration – what is the evidence of clinical benefit? A systematic review of randomized controlled trials. European Journal of Anesthesiology 2003; 20: 771-793.
8. Mendez C, McClain C, Marsano L, et al: Albumin Therapy in Clinical Practice. Nutrition in Clinical Practice 2005; 20: 314-320.
9. Quinlan G, Martin G, Evans T: Albumin: Biochemical Properties and Therapeutic Potential. Hepatology 2005; 41 (6): 1211-1219.
10. Blümel J, Schmidt I, Willkommen H, et al: Inactivation of parvovirus B19 during pasteurization of human serum albumin. Transfusion 2002; 42: 1011-1018.
11. Grocott M, Mythen M, Gan T: Perioperative Fluid Management and Clinical Outcomes in Adults. Anesth Analg 2005; 100: 1093-1106.

16 HOW SUPPLIED/STORAGE AND HANDLING

FLEXBUMIN 5% is supplied in a single-dose plastic container:

Plastic Container NDC Number	Carton NDC Number	Grams Protein and Fill Size
NDC 0944-0495-06 (quantity of 1)	NDC 0944-0495-05 (quantity of 2)	12.5 grams in a 250 mL plastic container

Storage

Room temperature: not to exceed 25°C (77°F). Protect from freezing.

17 PATIENT COUNSELING INFORMATION

- Inform patients of the early signs of hypersensitivity reactions, including hives, generalized urticaria, chest tightness, dyspnea, wheezing, faintness, hypotension, and anaphylaxis *[see Warnings and Precautions (5.1)]*.
- Inform patients that FLEXBUMIN 5% is made from human plasma and may contain infectious agents that can cause disease (e.g., viruses and, theoretically, the CJD agent). Explain that the risk of FLEXBUMIN 5% transmitting an infectious agent has been reduced by screening the plasma donors, by testing the donated plasma for certain virus infections, and by a process demonstrated to inactivate and/or remove certain viruses during manufacturing. Symptoms of a possible virus infection include headache, fever, nausea, vomiting, weakness, malaise, diarrhea, or, in the case of hepatitis, jaundice *[see Warnings and Precautions (5.6)]*.

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