

BUMINATE 5%, Albumin (Human), USP, 5% Solution

DESCRIPTION

BUMINATE 5%, in 250 and 500 mL glass bottles is a sterile, nonpyrogenic preparation of albumin in a single dosage form for intravenous administration. Each 100 mL contains 5 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 has been stabilized with N-acetyltryptophan (0.004 M) and sodium caprylate (0.004 M). 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. BUMINATE 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.

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 BUMINATE 5% contains no blood group isoagglutinins thereby permitting its administration without regard to the recipient's blood group.

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}

BUMINATE 5% is osmotically equivalent to an equal volume of normal human plasma and will increase circulating plasma volume by an amount approximately equal to the volume infused. 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 pressure value of 20 mm Hg.⁴

BUMINATE 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 $60 \pm 0.5^{\circ}\text{C}$ for 10 – 11 hours. This process accomplishes both purification of albumin and the reduction of viruses.

In vitro studies demonstrate that the manufacturing process for BUMINATE 5% provides for significant viral reduction. These viral reduction studies, summarized in Table 1, demonstrate viral clearance during the manufacturing process for BUMINATE 5% 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 manufacturing steps for BUMINATE 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 is different, the overall manufacturing process of BUMINATE 5% is robust in reducing viral load.

TABLE 1						
Summary of Viral Reduction Factor for Each Virus and Processing Step						
Process Step	Viral Reduction Factor (log₁₀)					
	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 Fractionation I+II+III/II+III supernatant and processing of Fractionation 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 suggests 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 use of BUMINATE 5%. 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 the 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 solutions. 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 BUMINATE 5%. 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 severe pancreatitis cannot be quickly reversed and nutritional supplements may fail to restore serum albumin levels. In these cases, BUMINATE 5% 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, BUMINATE 5% 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}

3. Cardiopulmonary Bypass Surgery

BUMINATE 5% has been recommended prior to or during cardiopulmonary bypass surgery, although no clear data exist indicating its advantage over crystalloid solutions.^{4,6,12}

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.

BUMINATE 5% is also contraindicated in severely anemic patients and in patients with cardiac failure.

BUMINATE 5% 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

BUMINATE 5% 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

Certain components used in the packaging of this product contain natural rubber latex.

Hemodynamics

Do not administer BUMINATE 5% without very close monitoring of hemodynamics; look for evidence of cardiac or respiratory failure, renal failure, or increasing intra-cranial pressure.

Hypervolemia/Hemodilution

BUMINATE 5% 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.

BUMINATE 5% must be administered intravenously. It may be administered rapidly to individuals with reduced plasma volume with the following exception: if a patient has a history of cardiac or circulatory disease, BUMINATE 5% should be administered slowly (5 to 10 mL per minute) to avoid too rapid a rise in the blood pressure. The rate of administration should be adjusted according to the solution concentration and the patient's hemodynamic measurements. 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.

Patients should always be carefully monitored in order to guard against the possibility of circulatory overload.

Blood Pressure

A rise in blood pressure after 5% 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 BUMINATE 5% in pregnant or lactating women. Animal reproduction studies have not been conducted with BUMINATE 5%. It is not known whether BUMINATE 5% 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 BUMINATE 5%. BUMINATE 5% 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 BUMINATE 5% has not been evaluated in pediatric use.

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 BUMINATE 5% 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 BUMINATE 5%.

ADVERSE REACTIONS

Adverse Reactions from Clinical Trials

There are no data available on adverse reactions from clinical trials conducted with BUMINATE 5%.

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

BUMINATE 5% 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.

BUMINATE 5% 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 volume of the total dose and the rate of infusion depend on the patient's condition and response.

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 BUMINATE 5% and should be used to check for the risk of hypervolemia and cardiovascular overload. (See PRECAUTIONS: Hypervolemia/Hemodilution).

It is strongly recommended that every time that BUMINATE 5% 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. Hypovolemia

The dosage of BUMINATE 5% must be individualized. As a guideline, the initial treatment should be in the range of 250 to 500 mL for older children and adults and 12 to 20 mL per kilogram of body weight for infants and young children. This may be repeated after 30 minutes intervals if the response is not adequate.

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 BUMINATE 5% is administered after the first 24 hours following burns, an initial dose of 500 mL is recommended.

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 the patient's serum albumin concentration to estimate the deficit, the body albumin compartment should be calculated to be 80 to 100 mL per kilogram of body weight.^{5,6} Daily dose should not exceed 2 g of albumin per kilogram of body weight.

Preparation for Administration

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

1. Remove cap from bottle to expose center portion of rubber stopper.
2. Clean stopper with germicidal solution.

Administration

Follow directions for use printed on the administration set container. Make certain that the administration set contains an adequate filter (15-micron or smaller).

HOW SUPPLIED

BUMINATE 5% is supplied in 250 mL (NDC 0944-0491-01) and 500 mL (NDC 0944-0491-02) bottles.

STORAGE

Store BUMINATE 5% at room temperature, not to exceed 30°C (86°F). Avoid freezing to prevent damage to the bottle.

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