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 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 and is clear of particulate matter.

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. 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.[7-9]

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 ± 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 BUMINATE 5% provides for effective 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 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 B 19[10]; and 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 steps is different, the overall manufacturing process of BUMINATE 5% is effective 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	
		Flaviviridae				Parvoviridae
	HIV-1	BVDV	WNV	PRV	HAV	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 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.

** 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

Hypovolemia

The effectiveness of BUMINATE 5% 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] Use 5% protein solutions or dilute 25% albumin with crystalloid solutions in the absence of adequate or excessive hydration. Administer compatible red blood cells or whole blood as quickly as possible when blood volume deficit is the result of hemorrhage.

Hypoalbuminemia

General

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 albumin administration will be temporary unless the underlying disorder is reversed.

There is no valid reason for use of albumin as an intravenous nutrient. 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 can fail to restore serum albumin levels. BUMINATE 5% is indicated in these cases.

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% is 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]

Cardiopulmonary Bypass Surgery

BUMINATE 5% is indicated during cardiopulmonary bypass surgery as a component of the pump prime.[6]

CONTRAINDICATIONS

- A history of allergic reactions to albumin and any of the excipients
- Severe anemia
- Heart failure

Do not dilute 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). Acceptable diluents include 0.9% Sodium Chloride or 5% Dextrose in Water.

WARNINGS

Allergic /Anaphylactic Reactions

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

Transmission of Infectious Agents

BUMINATE 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 Baxalta US Inc. at 1-800-423-2090. The physician should discuss the risks and benefits of this product with the patient.

PRECAUTIONS

Certain components used in the packaging of this product contain natural rubber latex which may cause allergic reactions.

Hemodynamics

Closely monitor hemodynamic parameters after administering BUMINATE 5% for evidence of cardiac or respiratory failure, renal failure, or increasing intracranial pressure.

Hypervolemia/Hemodilution

Administer BUMINATE 5% with caution in conditions where hypervolemia and its consequences or hemodilution could represent a special risk for the patient. Examples include but are not limited to the following: Heart failure, hypertension, esophageal varices, pulmonary edema, hemorrhagic diathesis, severe anemia, and renal failure.

Adjust the rate of administration according to the solution concentration and the patient's hemodynamic status. . Administer BUMINATE 5% slowly (5 to 10 mL per minute) to avoid too rapid a rise in blood pressure. BUMINATE 5% may be administered more rapidly to individuals with reduced plasma volume except in patients with a history of cardiovascular disease. More rapid administration can cause circulatory overload and pulmonary edema.[11] 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).

Blood Pressure

Monitor blood pressure in trauma patients and postoperative patients resuscitated with BUMINATE 5% in order to detect rebleeding secondary to clot disruption.

Pregnancy - Category C

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. BUMINATE 5% should be given to a pregnant woman only if clearly needed.

Nursing Mothers

It is not known whether BUMINATE 5% is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BUMINATE 5% is administered to a nursing woman.

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

Monitor hemodynamic parameters. Ensure adequate substitution of other blood constituents (coagulation factors, electrolytes, platelets, and erythrocytes) are available if comparatively large volumes are replaced.

Electrolyte Status

Monitor electrolyte status and ensure appropriate steps are 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 Baxalta-sponsored clinical trials conducted with BUMINATE 5%.

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, 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

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.
- Monitor hemodynamic parameters in patients receiving BUMINATE 5% and check for the risk of hypervolemia and cardiovascular overload. [see *Precautions*] Hypervolemia can occur if the dosage and rate of infusion are not adjusted, giving consideration to the solution concentration and the patient's clinical status.

- Do not dilute with Sterile Water for Injection as this can cause hemolysis in recipients [see *Contraindications*].
- Do not mix with other medicinal products including blood and blood components. BUMINATE 5% 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.
- Do not mix with protein hydrolysates or solutions containing alcohol since these combinations can cause the proteins to precipitate.
- Do not add supplementary medication.
- Record the name and batch number of the product to maintain a link between the patient and the product.
- Discard unused portion.

Recommended Dosages

Hypovolemia

The dosage of BUMINATE 5% must be individualized. Initial dosage range for older children and adults is 250 to 500 mL and for infants and young children 12 to 20 mL per kilogram of body weight. Repeat after 30 minutes intervals if the response is not adequate.

Upon administration of additional albumin or if hemorrhage occurs; hemodilution and a relative anemia can occur. Supplemental administration of compatible red blood cells or compatible whole blood may be required to treat this condition.

Burns

The optimal therapeutic regimen for administration of crystalloid and colloid solutions after extensive burns has not been established. An initial dose of 500 mL is recommended after the first 24 hours following the burns.

Hypoalbuminemia

Hypoalbuminemia is usually accompanied by a hidden extravascular albumin deficiency of equal magnitude. Consider total body albumin deficit when determining the amount of albumin necessary to reverse the hypoalbuminemia. Calculate the body albumin compartment to be 80 to 100 mL per kilogram of body weight when using the patient's serum albumin concentration to estimate the deficit.[5,6] Do not exceed a daily dose of 2 g of albumin per kilogram of body weight.

Preparation for Administration

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration. 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. Do not use unless solution is clear essentially free of particulate matter and seal is intact.

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 glass bottles:

- 250 mL NDC 0944-0491-01
- 500 mL NDC 0944-0491-02

Storage

Room temperature: Do not exceed 30°C (86°F). Avoid freezing.

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Westlake Village, CA 91362 USA
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