

## **BUMINATE 25%** **Albumin (Human), USP, 25% Solution**

### **DESCRIPTION**

BUMINATE 25%, in 20, 50 and 100 mL glass bottles 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 (0.02 M). The sodium content is  $145 \pm 15$  mEq/L. This solution contains no preservative and none of the coagulation factors found in fresh whole blood or plasma. BUMINATE 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 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.<sup>1-3</sup>

### **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.<sup>4-6</sup> Albumin is also a transport protein and binds naturally occurring, therapeutic and toxic materials in the circulation.<sup>5,6</sup>

BUMINATE 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. 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.<sup>7-9</sup>

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.<sup>5</sup>

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.<sup>4</sup>

BUMINATE 25% is manufactured from human plasma by the modified Cohn-Onocley 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 BUMINATE 25% provides for effective viral reduction. These viral reduction studies, summarized in Table 1, demonstrate viral clearance during the manufacturing process for BUMINATE 25% 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<sup>10</sup>; 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 BUMINATE 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 steps is different, the overall manufacturing process of BUMINATE 25% is effective in reducing viral load.

<b>Table 1</b>						
<b>Summary of Viral Reduction Factor for Each Virus and Processing Step</b>						
<b>Process Step</b>	<b>Viral Reduction Factor (log<sub>10</sub>)</b>					
	<b>Lipid Enveloped</b>			<b>Non-Enveloped</b>		
	<b>HIV-1</b>	<b>Flaviviridae</b>		<b>PRV</b>	<b>HAV</b>	<b>Parvoviridae</b>
		<b>BVDV</b>	<b>WNV</b>			<b>MMV</b>
Processing of Fraction I+II+III/II+III supernatant to Fraction IV <sub>4</sub> 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**
<b>Mean Cumulative Reduction Factor, log<sub>10</sub></b>	<b>&gt;12.7</b>	<b>&gt;11.3</b>	<b>&gt;5.7</b>	<b>&gt;12.9</b>	<b>&gt;7.7</b>	<b>4.6</b>

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.<sup>10</sup>

## INDICATIONS AND USAGE

### *Hypovolemia*

The effectiveness of in BUMINATE 25% 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.<sup>4,6</sup> 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:<sup>5</sup>

- (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 pancreatitis cannot be quickly reversed and nutritional supplements can fail to restore serum albumin levels. BUMINATE 25% 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 25% 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.<sup>4,6</sup>

#### Adult Respiratory Distress Syndrome (ARDS)

A characteristic of ARDS is interstitial pulmonary edema, which can be causally related to hypoproteinemia. 25% albumin solution is indicated for these cases when used with a diuretic.<sup>4</sup>

#### Nephrosis

BUMINATE 25% is indicated for treatment of edema in patients with severe nephrosis who are receiving steroids and/or diuretics.

### Cardiopulmonary Bypass Surgery

BUMINATE 25% is indicated during cardiopulmonary bypass surgery as a component of the pump prime.<sup>4,6,12</sup>

### Hemolytic Disease of the Newborn (HDN)

BUMINATE 25% is indicated for infants with severe HDN to bind and detoxify unconjugated bilirubin.

## **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.

Do not administer to patients with chronic renal insufficiencies due to the potential for accumulations of aluminum. Accumulations of aluminum in patients with chronic renal insufficiencies have led to toxic manifestations such as hypercalcemia, vitamin D-refractory osteodystrophy, anemia, and severe progressive encephalopathy.<sup>11-13</sup>

## **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 25% 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 25% for evidence of cardiac or respiratory failure, renal failure, or increasing intracranial pressure.

## **Hypervolemia/Hemodilution**

Administer BUMINATE 25% 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. Do not exceed 1 mL per min for patients with normal blood volume. More rapid administration can cause circulatory overload and pulmonary edema.<sup>14</sup> 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 surgery patients resuscitated with BUMINATE 25% in order to detect rebleeding secondary to clot disruption.

## **Pregnancy –Category C**

Animal reproduction studies have not been conducted with BUMINATE 25%. It is not known whether BUMINATE 25% can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. BUMINATE 25% should be given to a pregnant woman only if clearly needed.

## **Nursing Mothers**

It is not known whether BUMINATE 25% is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BUMINATE 25% 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 25% has not been evaluated in pediatric patients.

## **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 25%.

## ADVERSE REACTIONS

### Adverse Reactions from Clinical Trials

There are no data available on adverse reactions from Baxalta-sponsored clinical trials conducted with BUMINATE 25%.

### 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 25% 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 25% 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 25% 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 BUMINATE 25% gives a solution, which is approximately isotonic and isosmotic with citrated plasma.
- 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**

#### ***Hypovolemic Shock***

The dosage of BUMINATE 25% must be individualized. Initial dosage range for adults is 100 to 200 mL and for children 2.5 to 5 mL per kilogram body weight. Repeat after 15 to 30 minutes if the response is not adequate. Administer albumin replacement in the form of 5% Albumin (Human) in patients with significant plasma volume deficits.

Upon administration of additional albumin or if hemorrhage occurs, hemodilution and 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. Determine the appropriate dose according to the patient's condition and response to treatment when BUMINATE 25% is administered after the first 24 hours following 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 kg of body weight when using the patient's serum albumin concentration to estimate the deficit.<sup>5,6</sup> Do not exceed a daily dose of 2 g of albumin per kilogram of body weight.

#### ***Hemolytic Disease of the Newborn***

Administer BUMINATE 25% prior to or during exchange transfusion at a dose of 1g per kilogram body weight.<sup>15</sup>

### **Preparation for Administration**

Visually inspect parenteral drug products for particulate matter and discoloration prior to administration. BUMINATE 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. Do not use unless solution is clear 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 25% is supplied in glass bottles:

- 20 mL NDC 0944-0490-01
- 50 mL NDC 0944-0490-02
- 100 mL NDC 0944-0490-03

### ***Storage***

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

Stability testing for BUMINATE 25% showed that aluminum concentration increased over time reaching levels that could exceed 1000 ppb over the shelf life of the product. [see

*Contraindications*].



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### **Baxalta US Inc.**

Westlake Village, CA 91362 USA  
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