Y36-002-491
Package Insert

3% FreAmine® III (Amino Acid Injection) with Electrolytes

Protect from light until use

DESCRIPTION **Rx only**

3% FreAmine III (Amino Acid Injection) with Electrolytes is a sterile, nonpyrogenic, slightly hypertonic solution containing crystalline amino acids and maintenance electrolytes. A 1000 mL unit provides a total of 4.6 g of nitrogen (29 g of protein equivalent) in 29 g of amino acids. All amino acids designated USP are the "L"-isomer, with the exception of Glycine USP which does not have an isomer.

Each 100 mL contains:

Essential amino acids
Isoleucine USP 0.21 g
Leucine USP 0.27 g
Lysine 0.22 g
(added as Lysine Acetate USP 0.31 g)
Methionine USP 0.16 g
Phenylalanine USP 0.17 g
Threonine USP 0.12 g
TRYPTOPHAN USP 0.046 G
VALINE USP 0.20 G

Nonessential amino acids
Alanine USP 0.21 g
Arginine USP 0.29 g
Histidine USP 0.085 g
Proline USP 0.34 g
Serine USP 0.18 g
Glycine USP 0.42 g
Cysteine <0.014 g
(as Cysteine HCl•H_2O USP <0.020 g)
Sodium Acetate•$3H_2O$ USP 0.20 g
Magnesium Acetate•$4H_2O$ 0.054 g
Sodium Chloride USP 0.12 g
Potassium Chloride USP 0.15 g
Phosphoric Acid NF 0.040 g
Potassium Metabisulfite NF (as an antioxidant) <0.05 g
Water for Injection USP qs
pH adjusted with Glacial Acetic Acid USP
pH: 6.8 (6.0-7.0)
Calculated Osmolarity: 405 mOsmol/liter

Concentration of Electrolytes (mEq/liter): Sodium 35; Potassium 24.5; Magnesium 5; Chloride 41; Phosphate ($HPO_4^{=}$) 7 (3.5 mmole P/liter); Acetate 44*

*Acetate provided as inorganic acetate salts (20 mEq/l), acitic acid (9 mEq/l), and lysine acetate USP (15 mEq/l).

CLINICAL PHARMACOLOGY

3% FreAmine III with electrolytes provides a physiological ratio of biologically utilizable essential and nonessential amino acids and a balanced pattern of maintenance electrolytes designed to meet adult requirements. The amino acids provide a substrate for protein synthesis as well as sparing body protein and muscle mass. Peripheral intravenous infusions of amino acids administered for short periods in selected patients promote protein anabolism and prevent protein breakdown to meet caloric requirements.

Sodium, the major cation of the extracellular fluid, functions primarily in the control of water distribution, fluid balance, and osmotic pressure of body fluids. Sodium is also associated with chloride and bicarbonate in the regulation of the acid-base equilibrium of body fluid. Potassium, the principal cation of intracellular fluid, participates in carbohydrate utilization and protein synthesis, and is critical in the regulation of nerve conduction and muscle contraction, particularly in the heart.

Chloride, the major extracellular anion, closely follows the metabolism of sodium, and changes in the acid-base balance of the body are reflected by changes in the chloride concentration. Magnesium, a principal cation of soft tissue, is primarily involved in enzyme activity associated with the metabolism of carbohydrates and protein. Magnesium is also involved in neuromuscular irritability.

Phosphate is a major intracellular anion which participates in providing energy for metabolism of substrates and contributes to significant metabolic and enzymatic reactions in almost all organs and tissues. It exerts a modifying influence on calcium levels, a buffering effect on acid-base equilibrium and has a primary role in the renal excretion of hydrogen ions.

Inorganic acetate salts serve as bicarbonate precursors. It is thought that the acetate from Iysine acetate and acetic acid, under the condition of parenteral nutrition, does not impact net acid-base balance when renal and respiratory functions are normal. Clinical evidence seems to support this thinking; however, confirmatory experimental evidence is not available.

INDICATIONS AND USAGE

3% FreAmine® III (Amino Acid Injection) with Electrolytes is designed for peripheral administration to well-nourished mildly catabolic adult patients who require only short-term parenteral nutrition. In medical or routine postsurgical patients where enteral nutrition is not desirable or cannot be tolerated, protein sparing can be achieved by the peripheral infusion of amino acid solutions with or without nonprotein calories. See **DOSAGE AND ADMINISTRATION**.

CONTRAINDICATIONS

3% FreAmine III with Electrolytes is contraindicated in patients with anuria, hepatic coma or encephalopathy, inborn errors of amino acid metabolism, or hypersensitivity to one or more amino acids present in this solution.

This solution is also contraindicated where the administration of sodium, potassium, magnesium, chloride or phosphate could be clinically detrimental. Such conditions include hyperkalemia, heart block or myocardial damage, edema due to cardiovascular, renal or hepatic failure, or acid-base imbalance.

WARNINGS

This product contains potassium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people. The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Premature neonates are particularly at risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Research indicates that patients with impaired kidney function, including premature neonates, who receive parenteral levels of aluminum at greater than 4 to 5 µg/kg/day accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.

Safe, effective use of parenteral nutrition requires a knowledge of nutrition and protein sparing as well as clinical expertise in recognition and treatment of the complications which can occur. **Frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of parenteral nutrition.** Laboratory tests should include measurement of blood sugar, electrolyte, and serum protein concentrations; kidney and liver function tests; and evaluation of acid-base balance and fluid balance. Other laboratory tests may be suggested by the patient's condition.

The intravenous administration of these solutions can cause fluid and/or solute overload resulting in dilution of serum electrolyte concentrations, overhydration, congested states or pulmonary edema. The risk of dilutional states is inversely proportional to the solute concentration of the solution infused. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the concentration of the solution.

Peripheral intravenous infusion of amino acids may cause a normal, modest rise in blood urea nitrogen (BUN) as a result of increased protein intake. The BUN may become elevated in patients with impaired renal or hepatic function. The infusion should be discontinued if the BUN levels exceed postprandial limits and continue to rise.

Administration of amino acid solutions to a patient with hepatic insufficiency may result in plasma amino acid imbalances, hyperammonemia, prerenal azotemia, stupor and coma.

Conservative doses of amino acids should be given, dictated by the nutritional status of the patient. Should symptoms of hyperammonemia develop, amino acid administration should be discontinued and the patient's clinical status reevaluated.

Solutions containing sodium ions should be used with great care, if at all, in patients with congestive heart failure, severe renal insufficiency, and in clinical states in which there is sodium retention with edema. In patients with diminished renal function, administration of solutions containing sodium or potassium ions may result in sodium or potassium retention.
Solutions containing potassium ions should be used with great care, if at all, in patients with hyperkalemia, severe renal failure, and in conditions in which potassium retention is present.

PRECAUTIONS

General

The electrolyte pattern is designed for maintenance only during protein sparing therapy in adults.

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance, whenever the condition of the patient warrants such evaluation. Significant deviations from normal concentrations may require administration of additional electrolytes.

Protein sparing therapy is intended for short-term usage only. If a patient requires an extended period of nutritional support, oral or parenteral regimens should include adequate nonprotein calorie components.

Care should be taken to avoid circulatory overload, particularly in patients with cardiac insufficiency.

In patients with myocardial infarct, infusion of amino acids should always be accompanied by dextrose, since in anoxia, free fatty acids cannot be utilized by the myocardium, and energy must be produced anaerobically from glycogen or glucose.

Administration of glucose at a rate exceeding the patient's utilization may lead to hyperglycemia, coma, and death.

Administration of amino acids without carbohydrates may result in the accumulation of ketone bodies in the blood. Correction of this ketonemia may be achieved by the administration of carbohydrate.

Blood sugar levels should be monitored frequently in diabetic patients.

During peripheral vein infusions of amino acids and electrolytes, care should be taken to assure proper placement of the needle or catheter.

The venipuncture site should be inspected frequently for signs of infiltration or inflammation. If venous thrombosis or phlebitis occurs, discontinue infusions or change infusion site and initiate appropriate treatment.

Sodium-containing solutions should be administered with caution to patients receiving corticosteroids or corticotropin, or to other salt-retaining patients. Care should be exercised in administering solutions containing sodium or potassium to patients with renal or cardiovascular insufficiency, with or without congestive heart failure, particularly if they are postoperative or elderly.

Potassium therapy should be guided primarily by serial electrocardiograms, especially in patients receiving digitalis. Serum potassium levels are not necessarily indicative of tissue potassium levels. Solutions containing potassium or magnesium should be used with caution in the presence of cardiac disease, particularly in the presence of renal disease.

To minimize the risk of possible incompatibilities arising from mixing this solution with other additives that may be prescribed, the final infusate should be inspected for cloudiness or precipitation immediately after mixing, prior to administration, and periodically during administration.

Use only if solution is clear and vacuum is present.

Drug product contains no more than 25 μg/L of aluminum.

Laboratory Tests
Frequent clinical evaluation and laboratory determinations are necessary for proper monitoring of parenteral nutrition.

Laboratory tests should include measurement of blood sugar, electrolyte, and serum protein concentrations; kidney and liver function tests; and evaluation of acid-base balance and fluid balance. Other laboratory tests may be suggested by the patient's condition.

Drug Interactions
Administration of barbiturates, narcotics, hypnotics or systemic anesthetics should be adjusted with caution in patients also receiving magnesium-containing solutions because of an additive central depressive effect.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No *in vitro* or *in vivo* carcinogenesis, mutagenesis, or fertility studies have been conducted with 3% FreAmine® III (Amino Acid Injection) with Electrolytes.

Pregnancy - Teratogenic Effects - Pregnancy Category C
Animal reproduction studies have not been conducted with 3% FreAmine III (Amino Acid Injection) with Electrolytes. It is also not known whether 3% FreAmine III with Electrolytes can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. 3% FreAmine III with Electrolytes should be given to a pregnant woman only if clearly needed.

Labor and Delivery
Information is unknown.

Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when 3% FreAmine III (Amino Acid Injection) with Electrolytes is administered to a nursing woman.

Pediatric Use
Safety and effectiveness of amino acid injections in pediatric patients have not been established by adequate and well-controlled studies. However, the use of amino acid injections in pediatric patients as an adjunct in the offsetting of nitrogen loss or in the treatment of negative nitrogen balance is well established in the medical literature. See **WARNINGS** and **DOSAGE AND ADMINISTRATION**.

Geriatric Use
Clinical studies of 3% FreAmine III (Amino Acid Injection) with Electrolytes did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. See **WARNINGS**.

ADVERSE REACTIONS
Reactions which may occur because of the solution or the technique of administration include febrile response, infection at the site of injection, venous thrombosis or phlebitis extending from the site of injection, extravasation and hypervolemia.

Local reactions of the infusion site, consisting of a warm sensation, erythema, phlebitis and thrombosis, have been reported with peripheral amino acid infusions, especially if other substances are also administered through the same site.

Generalized flushing, fever and nausea have been reported during peripheral administration of amino acids.

Symptoms may result from an excess or deficit of one or more of the ions present in the solution; therefore, frequent monitoring of electrolyte levels is essential.

Hypernatremia may be associated with edema and exacerbation of congestive heart failure due to the retention of water, resulting in an expanded extracellular fluid volume.

Reactions reported with the use of potassium-containing solutions include nausea, vomiting, abdominal pain and diarrhea. The signs and symptoms of potassium intoxication include paresthesias of the extremities, areflexia, muscular or respiratory paralysis, mental confusion, weakness, hypotension, cardiac arrhythmias, heart block, electrocardiographic abnormalities and cardiac arrest. Potassium deficits result in disruption of neuromuscular function, and intestinal ileus and dilatation.

If infused in large amounts, chloride ions may cause a loss of bicarbonate ions, resulting in an acidifying effect.

Abnormally high plasma levels of magnesium can result in flushing, sweating, hypotension, circulatory collapse, and depression of cardiac and central nervous system function. Respiratory depression is the most immediate threat to life. Magnesium deficits can result in tachycardia, hypertension, hyperirritability and psychotic behavior.

Phosphorus deficiency may lead to impaired tissue oxygenation and acute hemolytic anemia. Relative to calcium, excessive phosphorus intake can precipitate hypocalcemia with cramps, tetany and muscular hyperexcitability.

If an adverse reaction does occur, discontinue the infusion, evaluate the patient, institute appropriate therapeutic countermeasures and save the remainder of the fluid for examination if deemed necessary.

OVERDOSAGE
In the event of a fluid or solute overload during parenteral therapy, reevaluate the patient's condition and institute appropriate corrective treatment.

In the event of overdosage with potassium-containing solutions, discontinue the infusion immediately and institute corrective therapy to reduce serum potassium levels.

Treatment of hyperkalemia includes the following:

1. Dextrose Injection USP, 10% or 25%, containing 10 units of crystalline insulin per 20 grams of dextrose administered intravenously, 300 to 500 mL per hour.

2. Absorption and exchange of potassium using sodium or ammonium cycle cation exchange resin, orally and as retention enema.

3. Hemodialysis and peritoneal dialysis. The use of potassium-containing foods or medications must be eliminated. However, in cases of digitalization, too rapid a lowering of plasma potassium concentration can cause digitalis toxicity.

DOSAGE AND ADMINISTRATION

3% FreAmine® III (Amino Acid Injection) with Electrolytes is not intended for use in central vein infusions.

3% FreAmine III with Electrolytes is a convenient source of amino acids, maintenance electrolytes and water for adult patients during protein sparing therapy. Determination of nitrogen balance and accurate daily body weights, corrected for fluid balance, are probably the best means of assessing individual protein requirements.

In well-nourished, mildly catabolic adult patients who require short-term parenteral nutritional support, 3% FreAmine ® III (Amino Acid Injection) with Electrolytes can be administered peripherally with or without parenteral carbohydrate calories. For protein sparing in well-nourished patients who are not receiving significant nonprotein calories, amino acid dosages of 1.0 to 1.7 g/kg/day significantly reduce nitrogen losses and spare body protein. Approximately 3 liters per day of 3% FreAmine III with Electrolytes will provide a total of 90 g of amino acids and the recommended adult daily intake of principal intra-and extracellular electrolytes for the stable patient. Therapy should begin with one liter of 3% FreAmine III with Electrolytes on the first day (with supplemental fluids), gradually increasing the dosage until full amino acid and fluid requirements are met, to approximately 3 liters of 3% FreAmine III with Electrolytes per day.

If prolonged parenteral therapy is required, institution of total parenteral nutrition via a central vein with adequate amounts of exogenous calories is recommended.

As with all intravenous fluid therapy, the goal is to provide adequate water to cover insensible, urinary and other losses, and electrolytes for replacement and maintenance. These requirements should be determined frequently and administered appropriately.

Additional electrolytes should be administered evenly throughout the day, and irritating medications should be injected at an alternate infusion site.

Venous irritation at an infusion site can be minimized by the selection of a large peripheral vein as well as by slowing the rate of infusion. In pediatric patients, the final solution should not exceed twice normal serum osmolarity (718 mOsmol/L).

Pediatric Use

The use of amino acids alone for the intention of protein sparing therapy in pediatric patients is not recommended.

Use of 3% FreAmine III with Electrolytes in pediatric patients is governed by the same considerations that affect the use of any amino acid solution in pediatrics. The amount administered is dosed on the basis of grams of amino acids/kg of body weight/day. Two to three g/kg of body weight for infants with adequate calories are generally sufficient to satisfy protein needs and promote positive nitrogen balance. Solutions administered by peripheral vein should not exceed twice normal serum osmolarity (718 mOsmol/L).

See **WARNINGS** and **PRECAUTIONS, *Pediatric Use*.**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
Care must be taken to avoid incompatible admixtures. Consult with pharmacist.

HOW SUPPLIED
3% FreAmine III with Electrolytes is supplied sterile and nonpyrogenic in glass intravenous infusion bottles with solid stopper,
packed 6 per case.

NDC	Cat. No.	Size
3% FreAmine III (Amino Acid Injection) with Electrolytes		
0264-9040-55	S9040-SS	1000 mL

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended that the product be stored at room temperature (25°C); however, brief exposure up to 40°C does not adversely affect the product.

Protect from light until use.

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FreAmine III is a registered trademark of B. Braun Medical Inc.
Made in USA

Directions for Use of B. Braun Glass Containers with Solid Stoppers

Designed for use with a vented set.

Before use, perform the following checks:

1. Inspect each container. Read the label. Ensure solution is the one ordered and is within the expiration date. Check the security of bail and band.

2. Invert container and carefully inspect the solution in good light for cloudiness, haze, or particulate matter; check the bottle for cracks or other damage. In checking for cracks, do not be confused by normal surface marks and seams on the bottom and sides of the bottle. These are not flaws. Look for bright reflections that have depth and penetrate into the wall of the bottle. Reject any such bottle.

3. To remove the outer closure, lift the tear tab and pull up, over, and down until it is below the stopper (See Figure 1). Use a circular pulling motion on the tab until it breaks away.

4. Grasp and remove the metal disk, exercising caution not to touch the exposed sterile stopper surface.

Warning: Some additives may be incompatible. Consult with pharmacist. When introducing additives, use aseptic techniques. Mix thoroughly. Do not store.

5. Refer to Directions for Use of the set being used. Insert the set spike into the large round outlet port of the stopper and hang container.

6. After admixture and during administration, reinspect the solution frequently. If any evidence of solution contamination or instability is found or if the patient exhibits any signs of fever, chills or other reactions not readily explainable, discontinue administration immediately and notify the physician.

7. When adding medication to the container during administration, swab the triangular medication site, inject medication and mix thoroughly by gentle agitation.

8. Spiking, additions, or transfers should be made immediately after exposing the sterile stopper surface. Check for vacuum at first puncture of stopper. Admixture by needle or syringe should be made through the triangular (Δ) medication site; contents should be drawn by vacuum into the bottle. Admixture by spiked vial should be through the outlet port (See Figure 2). If contents of initial addition are not drawn into the bottle, vacuum is not present and the unit should be discarded. Each addition/transfer will reduce the vacuum remaining in the bottle.

9. If the first puncture of the stopper is the administration set spike, insert the spike fully into the outlet port of the stopper and promptly invert the bottle. Verify vacuum by observing rising air bubbles. Do not use the bottle if vacuum is not present.

10. If admixture or set insertion is not performed immediately following removal of protective metal disk, swab stopper surface.

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