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.

Revised: June 2003
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.

B. Braun Medical Inc.
Irvine CA USA 92614-5895

6.9% FreAmine HBC® (Amino Acid Injection)

Protect from light until use.

DESCRIPTION **Rx only**

6.9% FreAmine HBC (Amino Acid Injection) is a sterile, nonpyrogenic, hypertonic solution containing crystalline amino acids. A 750 mL partial fill unit provides a total of 7.3 g of nitrogen in 50 g of amino acids equal to 46 grams of protein equivalent. 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 0.76 g
Leucine USP 1.37 g
Lysine 0.41 g
(added as Lysine Acetate USP 0.58 g)
Methionine USP 0.25 g
Phenylalanine USP 0.32 g
Threonine USP 0.20 g
Tryptophan USP 0.09 g
Valine USP 0.88 g

Nonessential amino acids
Alanine USP 0.40 g
Arginine USP 0.58 g
Histidine USP 0.16 g
Proline USP 0.63 g
Serine USP 0.33 g
Glycine USP 0.33 g
Cysteine <0.014 g
(as Cysteine HCl•H_2O USP <0.020 g)
Sodium Bisulfite (as an antioxidant) <0.10 g
Water for Injection USP qs
pH adjusted with Glacial Acetic Acid USP
pH: 6.5 (6.0-7.0)
Calculated Osmolarity: 620 mOsmol/liter

Concentration of Electrolytes (mEq/liter): Sodium 10; Chloride <3; Acetate Approx. 59.3 (provided as acetic acid and Iysine acetate).

CLINICAL PHARMACOLOGY

6.9% FreAmine HBC solution provides a mixture of biologically utilizable essential and nonessential crystalline amino acids in concentrated form for protein synthesis. 6.9% FreAmine HBC contains a high concentration of the branched chain amino acids isoleucine, leucine, and valine relative to other general purpose amino acid injections. This amino acid solution,

appropriately mixed with a concentrated calorie source such as hypertonic dextrose, with or without fat emulsion, and supplemented with electrolytes, vitamins, and minerals, provides total parenteral nutrition for the severely compromised patient. 6.9% FreAmine HBC solution may also be administered peripherally with minimal caloric supplementation in order to conserve lean body mass in the well-nourished, mildly catabolic patient.

The concentration of branched chain amino acids in 6.9% FreAmine HBC has been increased because these amino acids have been reported to be especially active metabolically in the compromised patient.

It is thought that the acetate from lysine 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.

The amounts of sodium and chloride present are not of clinical significance.

INDICATIONS AND USAGE

Parenteral nutrition with 6.9% FreAmine HBC® (Amino Acid Injection) is indicated to prevent nitrogen loss or treat negative nitrogen balance in adults where (1) the alimentary tract, by the oral, gastrostomy, or jejunostomy route, cannot or should not be used, or adequate protein intake is not feasible by these routes; (2) gastrointestinal absorption of protein is impaired; or (3) nitrogen homeostasis is substantially impaired as with severe trauma or sepsis. Dosage, route of administration, and concomitant infusion of non-protein calories are dependent on various factors, such as nutritional and metabolic status of the patient, anticipated duration of parenteral nutritional support, and vein tolerance.

See **DOSAGE AND ADMINISTRATION**.

Central Venous Nutrition

Central venous infusion should be considered when amino acid solutions are to be admixed with hypertonic dextrose to promote protein synthesis in hypercatabolic or severely depleted patients, or those requiring long-term parenteral nutrition.

Peripheral Parenteral Nutrition

For moderately catabolic or depleted patients in whom the central venous route is not indicated, diluted amino acid solutions with minimal caloric supplementation may be infused by peripheral vein, supplemented, if desired, with fat emulsion. In pediatric patients, the final solution should not exceed twice normal serum osmolarity (718 mOsmol/L).

CONTRAINDICATIONS

6.9% FreAmine HBC is contraindicated in patients with anuria, hepatic coma, inborn errors of amino acid metabolism, especially those involving branched chain amino acid metabolism such as Maple Syrup Urine Disease and Isovaleric Acidemia, or hypersensitivity to one or more amino acids present in the solution.

WARNINGS

This product contains sodium bisulfite, 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 and effective use of central venous nutrition requires a knowledge of nutrition 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 central venous 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.

Administration of amino acids in the presence of impaired renal function or gastrointestinal bleeding may augment an already elevated blood urea nitrogen. Patients with azotemia from any cause should not be infused with amino acids without regard to total nitrogen intake.

Administration of amino acid solutions that have not been specifically formulated to treat patients 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.

PRECAUTIONS

General

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation. Significant deviations from normal concentrations may require the use of additional electrolyte supplements.

Strongly hypertonic nutrient solutions should be administered through an indwelling intravenous catheter with the tip located in the superior vena cava.

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.

Special care must be taken when giving hypertonic dextrose to a diabetic or prediabetic patient. To prevent severe hyperglycemia in such patients, insulin may be required.

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.

After appropriate dilution, if 6.9% FreAmine HBC® (Amino Acid Injection) is to be administered by peripheral vein, care should be taken to assure proper placement of the infusion device within the lumen of the vein. The venipuncture site should be inspected frequently for signs of infiltration. If venous thrombosis or phlebitis occurs, discontinue infusions or change infusion site and initiate appropriate treatment.

Extraordinary electrolyte losses such as may occur during protracted nasogastric suction, vomiting, diarrhea or gastrointestinal fistula drainage may necessitate additional electrolyte supplementation.

Metabolic acidosis can be prevented or readily controlled by adding a portion of the cations in the electrolyte mixture as acetate salts and in the case of hyperchloremic acidosis, by keeping the total chloride content of the infusate to a minimum. 6.9% FreAmine HBC contains less than 3 mEq chloride per liter.

6.9% FreAmine HBC contains no added phosphorus. Patients, especially those with hypophosphatemia, may require the addition of phosphate. To prevent hypocalcemia, calcium supplementation should always accompany phosphate administration. To assure adequate intake, serum levels should be monitored frequently.

When the solution is subjected to changes in temperature, crystallization of amino acids may occur. If crystals appear redissolve by addition of the dextrose solution followed by gentle agitation. Alternatively, redissolve crystals by warming the unopened unit to 40°C followed by gentle agitation for about one minute. If the amino acids do not completely redissolve, the bottle must be rejected.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility
No *in vitro* or *in vivo* carcinogenesis, mutagenesis, or fertility studies have been conducted with 6.9% FreAmine HBC® (Amino Acid Injection).

Pregnancy - Teratogenic Effects - Pregnancy Category C
Animal reproduction studies have not been conducted with 6.9% FreAmine HBC (Amino Acid Injection). It is also not known whether 6.9% FreAmine HBC can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. 6.9% FreAmine HBC 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 6.9% FreAmine HBC (Amino Acid Injection) 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 6.9% FreAmine HBC (Amino Acid Injection) 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.**

Special Precautions for Central Venous Nutrition
Administration by central venous catheter should be used only by those familiar with this technique and its complications.

Central venous nutrition may be associated with complications which can be prevented or minimized by careful attention to all aspects of the procedure including solution preparation, administration, and patient monitoring. **It is essential that a carefully prepared protocol, based on current medical practices, be followed, preferably by an experienced team.**

Although a detailed discussion of the complications of central venous nutrition is beyond the scope of this insert, the following summary lists those based on current literature:

Technical
The placement of a central venous catheter should be regarded as a surgical procedure. One should be fully acquainted with various techniques of catheter insertion as well as recognition and treatment of complications. For details of techniques and placement sites, consult the medical literature. X-ray is the best means of verifying catheter placement. Complications known to occur from the placement of central venous catheters are pneumothorax, hemothorax, hydrothorax, artery puncture and transection, injury to the brachial plexus, malposition of the catheter, formation of arterio-venous fistula, phlebitis, thrombosis, and air and catheter embolus.

Septic
The constant risk of sepsis is present during central venous nutrition. Since contaminated solutions and infusion catheters are potential sources of infection, it is imperative that the preparation of parenteral nutrition solutions and the placement and care of catheters be accomplished under controlled aseptic conditions.

Solutions should ideally be prepared in the hospital pharmacy in a laminar flow hood. The key factor in their preparation is careful aseptic technique to avoid inadvertent touch contamination during mixing of solutions and subsequent admixtures.

Parenteral nutrition solutions should be used promptly after mixing. Any storage should be under refrigeration for as brief a time as possible. Administration time for a single bottle and set should never exceed 24 hours.

Consult the medical literature for a discussion of the management of sepsis during central venous nutrition. In brief, typical management includes replacing the solution being administered with a fresh container and set, and culturing the remaining contents for bacterial or fungal contamination. If sepsis persists and another source of infection is not identified, the catheter is removed, the proximal tip cultured, and a new catheter reinserted when the fever has subsided. Non-specific, prophylactic antibiotic treatment is not recommended. Clinical experience indicates that the catheter is likely to be the prime source of infection as opposed to aseptically prepared and properly stored solutions.

Metabolic
The following metabolic complications have been reported: metabolic acidosis, hypophosphatemia, alkalosis, hyperglycemia and glycosuria, osmotic diuresis and dehydration, rebound hypoglycemia, elevated liver enzymes, hypo-and hypervitaminosis, electrolyte imbalances, and hyperammonemia in pediatric patients. Frequent clinical evaluation and laboratory determinations are necessary, especially during the first few days of central venous nutrition, to prevent or minimize these complications.

ADVERSE REACTIONS
See **"Warnings"** and **"*Special Precautions for Central Venous Nutrition*."**
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.

If electrolyte supplementation is required during peripheral infusion, it is recommended that additives be administered throughout the day in order to avoid possible venous irritation. Irritating additive medications may require injection at another site and should not be added directly to the amino acid infusate.

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.

DOSAGE AND ADMINISTRATION
The total daily dose of 6.9% FreAmine HBC® (Amino Acid Injection) depends on daily protein requirements and on the patient's metabolic and clinical response. The determination of nitrogen balance and accurate daily body weights, corrected for fluid balance, are probably the best means of assessing individual protein requirements.

While Recommended Dietary Allowances of protein are approximately 0.8 g/kg of body weight for a healthy adult, it must be recognized that protein as well as caloric requirements in traumatized or malnourished patients may be substantially increased. Daily amino acid doses of approximately 1.5 g/kg of body weight for adults with adequate calories are generally sufficient to satisfy protein needs and promote positive nitrogen balance. Higher doses may be required in severely catabolic states. Such higher doses must be accompanied by frequent laboratory evaluation. Fat emulsion may be supplied to help meet energy requirements.

Fat emulsion coadministration should be considered when prolonged (more than 5 days) parenteral nutrition is required in order to prevent essential fatty acid deficiency (E.F.A.D.). Serum lipids should be monitored for evidence of E.F.A.D. in patients maintained on fat free TPN.

The provision of sufficient intracellular electrolytes, principally potassium, magnesium, and phosphate, is also required for optimum utilization of amino acids. Approximately 60 – 180 mEq of potassium, 10 – 30 mEq of magnesium, and 20 – 80 mEq of phosphate per day appear necessary to achieve optimum metabolic response. In addition, sufficient quantities of the major extracellular electrolytes (sodium, calcium, and chloride) must be given. In patients with

hyperchloremic or other metabolic acidoses, sodium and potassium may be added as the acetate or lactate salts to provide bicarbonate precursor. The electrolyte content of 6.9% FreAmine HBC must be considered when calculating daily electrolyte intake. Serum electrolytes, including magnesium and phosphorus, should be monitored frequently.

If a patient's nutritional intake is primarily parenteral, vitamins, especially the water soluble vitamins, and trace elements should also be provided.

Central Venous Nutrition

For severely catabolic, depleted patients or those requiring long-term total parenteral nutrition, central venous nutrition should be considered. Total parenteral nutrition may be started with infusates containing lower concentrations of dextrose; dextrose content may be gradually increased to estimated caloric needs as the patient's glucose tolerance increases.

In adults, strongly hypertonic mixtures of amino acids and dextrose may be safely administered only by continuous infusion through a central venous catheter with the tip located in the vena cava. A mixture of 750 mL 6.9% FreAmine HBC® (Amino Acid Injection) solution, and 250 mL 70% Dextrose, supplemented with electrolytes, and vitamins may be administered over an 8-hour period. If administration rate should fall behind schedule, no attempt to "catch up" to planned intake should be made. In addition to meeting protein needs, the administration rate is also governed, especially during the first few days of therapy by the patient's glucose tolerance. Daily intake of amino acids and dextrose should be increased gradually to the maximum required dose as indicated by frequent determination of urine and blood sugar levels. In many patients, provision of adequate calories in the form of hypertonic dextrose may require the administration of exogenous insulin to prevent hyperglycemia and glycosuria. To prevent rebound hypoglycemia, a solution containing 5% Dextrose should be administered when hypertonic dextrose infusions are abruptly discontinued.

Peripheral Parenteral Nutrition

For moderately catabolic, depleted patients requiring parenteral nutrition in whom the central venous route is not indicated, diluted 6.9% FreAmine HBC with minimal caloric supplementation may be infused by peripheral vein, supplemented, if desired, with fat emulsion. In pediatric patients, the final solution should not exceed twice normal serum osmolarity (718 mOsmol/L).

Fat provides approximately 9 kcal per gram and parenteral fat emulsion may be administered along with amino acid-dextrose solutions through a Y-type administration set to supplement caloric intake. Fat, however, should not provide more than 60% of the total caloric intake.

Pediatric Use

Use of 6.9% FreAmine HBC 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.

6.9% FreAmine HBC may be admixed with solutions which contain phosphate or which have been supplemented with phosphate. The presence of calcium and magnesium ions in an additive solution should be considered when phosphate is also present, in order to avoid precipitation.

Care must be taken to avoid incompatible admixtures. Consult with pharmacist.

HOW SUPPLIED

6.9% FreAmine HBC is supplied sterile and nonpyrogenic in 750 mL partial-fill 1000 mL glass intravenous infusion containers with solid stoppers, packaged 6 per case.

Container	**NDC**	**Cat. No.**	**Size**	**Fill**
6.9% FreAmine HBC (Amino Acid Injection)				
	0264-9350-55	S9350-58SS	1000 mL	750 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.
Revised: June 2003
6.9% FreAmine HBC 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.

B. Braun Medical Inc.
Irvine CA USA 92614-5895

8.5% FreAmine® III (Amino Acid Injection) with Electrolytes

Protect from light until use.

DESCRIPTION **Rx only**

8.5% FreAmine III (Amino Acid Injection) with Electrolytes is a sterile, nonpyrogenic, hypertonic solution containing crystalline amino acids and electrolytes. A 500 mL unit provides a total of 6.5 g of nitrogen (41 g of protein equivalent) in 41 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 0.59 g
Leucine USP 0.77 g
Lysine 0.62 g
(added as Lysine Acetate USP 0.87 g)
Methionine USP 0.45 g
Phenylalanine USP 0.48 g
Threonine USP 0.34 g
Tryptophan USP 0.13 g
Valine USP 0.56 g

Nonessential amino acids

Alanine USP 0.60 g
Arginine USP 0.81 g
Histidine USP 0.24 g
Proline USP 0.95 g
Serine USP 0.50 g
Glycine USP 1.19 g
Cysteine <0.014 g
(as Cysteine HCl•H_2O USP <0.020 g)
Sodium Acetate•$3H_2O$ USP 0.69 g
Magnesium Acetate•$4H_2O$ 0.11 g
Potassium Acetate USP 0.01 g
Potassium Chloride USP 0.44 g
Phosphoric Acid NF 0.23 g
Sodium Bisulfite (as an antioxidant) <0.1 g
Water for Injection USP qs
pH adjusted with Glacial Acetic Acid USP
pH: 6.5 (6.0-7.0)
Calculated Osmolarity: 1045 mOsmol/liter

Concentration of Electrolytes (mEq/liter): Sodium 60; Potassium 60; Magnesium 10; Chloride 60; Phosphate ($HPO^{=}_4$) 40 (20 mmole P/liter); Acetate 125*

*Acetate provided as inorganic acetate salts (62 mEq/l), Glacial Acetic Acid USP (21 mEq/l), and Lysine Acetate USP (42 mEq/l).

CLINICAL PHARMACOLOGY

8.5% FreAmine III with Electrolytes provides a physiological ratio of biologically utilizable amino acids in concentrated form for protein synthesis along with maintenance electrolytes. Used with concentrated calorie sources such as hypertonic dextrose or fat emulsion, and vitamins and minerals, it provides total parenteral nutrition. Administered peripherally alone as an isotonic solution (3%) or with minimal caloric supplementation such as 5% dextrose, it provides nutritional support and spares body protein.

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

Parenteral nutrition with 8.5% FreAmine® III (Amino Acid Injection) with Electrolytes is indicated to prevent nitrogen loss or treat negative nitrogen balance in adults and pediatric patients, where (1) the alimentary tract, by the oral, gastrostomy, or jejunostomy route, cannot or should not be used, or adequate protein intake is not feasible by these routes; (2) gastrointestinal absorption of protein is impaired; or (3) protein requirements are substantially increased as with extensive burns. Dosage, route of administration, and concomitant infusion of non-protein calories are dependent on various factors, such as nutritional metabolic status of the patient, anticipated duration of parenteral nutritional support, and vein tolerance. See **WARNINGS, PRECAUTIONS, *Pediatric Use*,** and **DOSAGE AND ADMINISTRATION**.

Central Venous Nutrition
Central venous infusion should be considered when amino acid solutions are to be admixed with hypertonic dextrose to promote protein synthesis in hypercatabolic or severely depleted patients, or those requiring long-term parenteral nutrition.

Peripheral Parenteral Nutrition
For moderately catabolic or depleted patients in whom the central venous route is not indicated, diluted amino acid solutions mixed with 5% dextrose solutions may be infused by peripheral vein, supplemented, if desired, with fat emulsion. In pediatric patients, the final solution should not exceed twice normal serum osmolarity (718 mOsmol/L).

Protein Sparing
In well-nourished, mildly catabolic patients such as routine postsurgical patients who require only short-term parenteral nutrition, protein sparing can be achieved by peripheral infusion of diluted amino acid solutions with or without dextrose.

CONTRAINDICATIONS
8.5% FreAmine III with Electrolytes is contraindicated in patients with untreated anuria, hepatic coma or encephalopathy, inborn errors of amino acid metabolism, or hypersensitivity to one or more amino acids present in the solution.

This solution is also contraindicated where the administration of sodium, potassium, magnesium, chloride, phosphate or acetate could be clinically detrimental.

WARNINGS
This product contains sodium bisulfite, 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 and 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 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 acids in the presence of impaired renal function or gastrointestinal bleeding may augment an already elevated blood urea nitrogen. Patients with azotemia from any cause should not be infused with amino acids without regard to total nitrogen intake.

Administration of amino acid solutions to a patient with hepatic insufficiency may result in plasma amino acid imbalances, hyperammonemia, prerenal azotemia, stupor and coma. Hyperammonemia is of **special significance in infants** as its occurrence in the syndrome caused by genetic metabolic defects is sometimes associated, although not necessarily in a causal relationship, with mental retardation. This reaction appears to be dose related and is more likely to develop during prolonged therapy. It is essential that blood ammonia be measured frequently in infants. The mechanisms of this reaction are not clearly defined but may involve genetic defects and immature or subclinically impaired liver function.

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.

Solutions containing acetate should be used with great care in patients with metabolic or respiratory alkalosis, or in conditions where there is an impaired utilization of acetate.

Care must be taken to avoid incompatible electrolyte mixtures. Calcium and additional phosphate may be added to alternate bottles. If additions are made, the admixture must be inspected for solution clarity when mixed, before dispensing from the pharmacy, and immediately before and periodically during administration.

PRECAUTIONS

General

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation. Significant deviations from normal concentrations may require the use of additional electrolyte supplements.

Strongly hypertonic nutrient solutions should be administered through an indwelling intravenous catheter with the tip located in the superior vena cava.

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.

Blood sugar levels should be monitored frequently in diabetic patients.

Special care must be taken when giving hypertonic dextrose to a diabetic or prediabetic patient. To prevent severe hyperglycemia in such patients, insulin may be required.

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.

After appropriate dilution, if 8.5% FreAmine® III (Amino Acid Injection) with Electrolytes is to be administered by peripheral vein, care should be taken to assure proper placement of the needle within the lumen of the vein. 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.

Extraordinary electrolyte losses such as may occur during protracted nasogastric suction, vomiting, diarrhea or gastrointestinal fistula drainage may necessitate additional electrolyte supplementation.

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 8.5% FreAmine® III (Amino Acid Injection) with Electrolytes.

Pregnancy - Teratogenic Effects - Pregnancy Category C

Animal reproduction studies have not been conducted with 8.5% FreAmine III with Electrolytes. It is also not known whether 8.5% FreAmine III with Electrolytes can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. 8.5% 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 8.5% 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 **INDICATIONS AND USAGE, WARNINGS,** and **DOSAGE AND ADMINISTRATION.**

Geriatric Use
Clinical studies of 8.5% FreAmine lll (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**.

Special Precautions for Central Venous Nutrition
Administration by central venous catheter should be used only by those familiar with this technique and its complications.
Central venous nutrition may be associated with complications which can be prevented or minimized by careful attention to all aspects of the procedure including solution preparation, administration, and patient monitoring**. It is essential that a carefully prepared protocol, based on current medical practices, be followed, preferably by an experienced team.**
Although a detailed discussion of the complications of central venous nutrition is beyond the scope of this insert, the following summary lists those based on current literature:

Technical
The placement of a central venous catheter should be regarded as a surgical procedure. One should be fully acquainted with various techniques of catheter insertion as well as recognition and treatment of complications. For details of techniques and placement sites, consult the medical literature. X-ray is the best means of verifying catheter placement. Complications known to occur from the placement of central venous catheters are pneumothorax, hemothorax, hydrothorax, artery puncture and transection, injury to the brachial plexus, malposition of the catheter, formation of arterio-venous fistula, phlebitis, thrombosis, and air and catheter embolus.

Septic
The constant risk of sepsis is present during central venous nutrition. Since contaminated solutions and infusion catheters are potential sources of infection, it is imperative that the preparation of parenteral nutrition solutions and the placement and care of catheters be accomplished under controlled aseptic conditions.

Solutions should ideally be prepared in the hospital pharmacy in a laminar flow hood. The key factor in their preparation is careful aseptic technique to avoid inadvertent touch contamination during mixing of solutions and subsequent admixtures.

Parenteral nutrition solutions should be used promptly after mixing. Any storage should be for as brief a time as possible, under refrigeration, and protected from light. Administration time for a single bottle and set should never exceed 24 hours.

Consult the medical literature for a discussion of the management of sepsis during central venous nutrition. In brief, typical management includes replacing the solution being administered with a fresh container and set, and the remaining contents are cultured for bacterial or fungal contamination. If sepsis persists and another source of infection is not identified, the catheter is removed, the proximal tip cultured, and a new catheter reinserted when the fever has subsided. Non-specific, prophylactic antibiotic treatment is not recommended. Clinical experience indicates that the catheter is likely to be the prime source of infection as opposed to aseptically prepared and properly stored solutions.

Metabolic
The following metabolic complications have been reported: metabolic acidosis, hypophosphatemia, alkalosis, hyperglycemia and glycosuria, osmotic diuresis and dehydration, rebound hypoglycemia, elevated liver enzymes, hypo-and hypervitaminosis, electrolyte imbalances, and hyperammonemia in pediatric patients. Frequent clinical evaluation and laboratory determinations are necessary, especially during the first few days of central venous nutrition, to prevent or minimize these complications.

ADVERSE REACTIONS
See **Warnings** and ***Special Precautions for Central Venous Nutrition.***
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
The total daily dose of 8.5% FreAmine® III (Amino Acid Injection) with Electrolytes depends on daily protein requirements and on the patient's metabolic and clinical response. The

determination of nitrogen balance and accurate daily body weights, corrected for fluid balance, are probably the best means of assessing individual protein requirements.

Recommended Dietary Allowances of protein are approximately 0.9 g/kg of body weight for a healthy adult and 1.4 to 2.2 g/kg for healthy growing infants and pediatric patients. It must be recognized, however, that protein as well as caloric requirements in traumatized or malnourished patients may be substantially increased. Daily amino acid doses of approximately 1.0 to 1.5 g/kg of body weight for adults and 2 to 3 g/kg of body weight for infants with adequate calories are generally sufficient to satisfy protein needs and promote positive nitrogen balance in such patients, although higher doses may be required in severely catabolic states. Such higher doses, especially in infants, must be accompanied by frequent laboratory evaluation.

For protein sparing in well-nourished patients not receiving significant additional calories, amino acid dosages of 1.0 to 1.7 g/kg/day significantly reduce nitrogen losses and spare body protein. If rises in BUN exceed 20 mg% in 48 hours, amino acid infusion should be discontinued or rate of administration reduced.

Fat emulsion coadministration should be considered when prolonged (more than 5 days) parenteral nutrition is required in order to prevent essential fatty acid deficiency (E.F.A.D.). Serum lipids should be monitored for evidence of E.F.A.D. in patients maintained on fat free TPN.

When 8.5% FreAmine III with Electrolytes is diluted the resulting diluted electrolyte concentrations must be considered when estimating the patient's daily electrolyte requirement. Additional electrolyte supplementation may be needed.

The electrolyte content of 8.5% FreAmine III with Electrolytes must be considered when calculating daily electrolyte intake. Serum electrolytes, including magnesium and phosphate, should be monitored frequently.

If a patient's nutritional intake is primarily parenteral, vitamins, especially the water soluble vitamins, should also be provided.

Central Venous Nutrition
For severely catabolic, depleted patients or those requiring long-term total parenteral nutrition, central venous nutrition should be considered. Calorie-to-nitrogen ratios of at least 100 to 150 non-protein calories per gram of nitrogen have been recommended to achieve positive nitrogen balance in such patients. These ratios are easily and conveniently attained with the use of concentrated dextrose solutions, supplemented if desired with parenteral fat emulsion.

Total parenteral nutrition may be started with infusates containing lower concentrations of dextrose; dextrose content may be gradually increased to estimated caloric needs as the patient's glucose tolerance increases.

In adults, strongly hypertonic mixtures of amino acids and dextrose may be safely administered only by continuous infusion through a central venous catheter with the tip located in the vena

cava. For optimal nitrogen utilization, 500 mL of 8.5% FreAmine® III (Amino Acid Injection) with Electrolytes appropriately mixed with concentrated dextrose, and vitamins are typically administered over an 8-hour period. If administration rate should fall behind schedule, no attempt to "catch up" to planned intake should be made. In addition to meeting protein needs, the administration rate is also governed, especially during the first few days of therapy by the patient's glucose tolerance. Daily intake of amino acids and dextrose should be increased gradually to the maximum required dose as indicated by frequent determination of urine and blood sugar levels. In many patients, provision of adequate calories in the form of hypertonic dextrose may require the administration of exogenous insulin to prevent hyperglycemia and glycosuria. To prevent rebound hypoglycemia, a solution containing 5% dextrose should be administered when hypertonic dextrose infusions are abruptly discontinued.

Peripheral Parenteral Nutrition
For moderately catabolic, depleted patients requiring parenteral nutrition in whom the central venous route is not indicated, 8.5% FreAmine III with Electrolytes can be mixed with 5% dextrose solutions and administered by peripheral vein.

For example, to prepare a solution of 4.25% FreAmine III with Electrolytes in 2.5% dextrose, aseptically transfer 500 mL of 8.5% FreAmine III with Electrolytes to a one liter intravenous bottle containing 500 mL of 5% dextrose. Each liter of the resultant solution provides 41 grams of protein equivalent and 85 carbohydrate calories with an osmolarity of approximately 650 mOsmol/liter. In pediatric patients, the final solution should not exceed twice normal serum osmolarity (718 mOsmol/L).

Fat provides approximately 9 kcal per gram and parenteral fat emulsion may be administered along with amino acid-dextrose solutions through a Y-type administration set to supplement caloric intake. Fat, however, should not be the sole caloric intake since some studies have suggested that glucose is more nitrogen sparing in the stressed patient.

Protein Sparing
For well-nourished, mildly catabolic patients who require short-term parenteral nutritional support, 8.5% FreAmine III with Electrolytes can be administered peripherally with or without parenteral carbohydrate calories. Such infusates can be prepared by dilution of 8.5% FreAmine III with Electrolytes with Sterile Water for Injection or 5% dextrose solutions to prepare isotonic or slightly hypertonic solutions which may be administered by peripheral vein. When administering diluted amino acid injections, serum electrolyte concentrations should be monitored to ensure that appropriate electrolyte levels are provided. For example, a 4.25% FreAmine III with Electrolytes solution can be prepared by the aseptic transfer of 500 mL of 8.5% FreAmine III with Electrolytes to a half-filled intravenous one liter bottle of Sterile Water for Injection. The resultant solution contains 41 grams of amino acids with an osmolarity of approximately 525 mOsmol/liter. An approximately isotonic solution of 3% FreAmine III with Electrolytes can be prepared by aseptic transfer of 350 mL of 8.5% FreAmine III with Electrolytes to a partially filled intravenous one liter bottle containing 650 mL of Sterile Water for Injection. The resultant solution will provide 29 grams of amino acids per liter with an osmolarity of approximately 365 mOsmol/liter.

Pediatric Dosage and Administration
Use of 8.5% 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 3 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).

Infants (up to 10 kg) on total parenteral nutrition generally receive 2 to 3 grams of protein, 120 to 150 calories, and 120 to 150 mL of fluid per kilogram of body weight per day. This can be provided in a solution containing approximately 2-1/8% FreAmine III with Electrolytes (diluted from 8.5% FreAmine III with Electrolytes) and 20% dextrose. Less hypertonic mixtures may be administered by peripheral vein. When administering diluted amino acid injections, serum electrolyte concentrations should be monitored to ensure that appropriate electrolyte levels are provided. Fat emulsion may be given concurrently by central or peripheral vein through a Y-type administration

set to provide essential fatty acids and increase caloric intake. Since physiological changes occur rapidly in infants, the daily dose of nutrients/electrolytes should initially be increased slowly with frequent monitoring of pertinent clinical and metabolic parameters. Pediatric patients over 10 kilograms require fewer calories and slightly less protein; generally 50 to 80 calories and 2 grams of protein per kilogram per day is sufficient.
See **INDICATIONS AND USAGE, WARNINGS,** and **precautions, *Pediatric Use***.

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

HOW SUPPLIED
8.5% FreAmine® III (Amino Acid Injection) with Electrolytes is supplied sterile and nonpyrogenic in glass intravenous infusion bottles. The 1000 mL containers are packed 6 per case; the 500 mL containers are packed 12 per case.

NDC	**Cat. No.**	**Size**
8.5% FreAmine III (Amino Acid Injection) with Electrolytes		
0264-1931-00	S9310-10	1000 mL
0264-1931-10	S9311-10	500 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.
Revised: June 2003
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 ( ) 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.

B. Braun Medical Inc.
Irvine CA USA 92614-5895

8.5% FreAmine® III (Amino Acid Injection)

Protect from light until use.

DESCRIPTION **Rx only**

8.5% FreAmine III (Amino Acid Injection) is a sterile, nonpyrogenic, hypertonic solution containing crystalline amino acids. A 500 mL unit provides a total of 6.5 g of nitrogen (41 g of protein equivalent) in 41 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 0.59 g
Leucine USP 0.77 g
Lysine 0.62 g
(added as Lysine Acetate USP 0.87 g)
Methionine USP 0.45 g
Phenylalanine USP 0.48 g
Threonine USP 0.34 g
Tryptophan USP 0.13 g
Valine USP 0.56 g

Nonessential amino acids
Alanine USP 0.60 g
Arginine USP 0.81 g
Histidine USP 0.24 g
Proline USP 0.95 g
Serine USP 0.50 g
Glycine USP 1.19 g
Cysteine <0.014 g
(as Cysteine HCl•H_2O USP <0.020 g)
Phosphoric Acid NF 0.115 g
Sodium Bisulfite (as an antioxidant) <0.1 g
Water for Injection USP qs
pH adjusted with Glacial Acetic Acid USP
pH: 6.5 (6.0-7.0)
Calculated Osmolarity: 810 mOsmol/liter

Concentration of Electrolytes (mEq/liter): Sodium 10; Phosphate ($HPO^{=}_4$) 20 (10 mmole P/liter); Acetate Approx. 72 (provided as acetic acid and lysine acetate); Chloride <3.

CLINICAL PHARMACOLOGY

8.5% FreAmine III provides a physiological ratio of biologically utilizable amino acids in concentrated form for protein synthesis. Used with concentrated calorie sources such as hypertonic dextrose or fat emulsion, and with electrolytes, vitamins and minerals, it provides total parenteral nutrition. Administered peripherally alone as an isotonic solution (3%) or with

minimal caloric supplementation such as 5% dextrose, it provides nutritional support and spares body protein.

Phosphate is a major intracellular anion which participates in providing energy for metabolism of substrates and contributes to significant metabolic and enzymatic reactions in 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.

It is thought that the acetate from lysine 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.

The amounts of sodium and chloride present are not of clinical significance.

INDICATIONS AND USAGE
Parenteral nutrition with 8.5% FreAmine® III (Amino Acid Injection) is indicated to prevent nitrogen loss or treat negative nitrogen balance in adults and pediatric patients where (1) the alimentary tract, by the oral, gastrostomy, or jejunostomy route, cannot or should not be used, or adequate protein intake is not feasible by these routes; (2) gastrointestinal absorption of protein is impaired; or (3) protein requirements are substantially increased as with extensive burns. Dosage, route of administration, and concomitant infusion of non-protein calories are dependent on various factors, such as nutritional and metabolic status of the patient, anticipated duration of parenteral nutritional support, and vein tolerance. See **WARNINGS, PRECAUTIONS, *Pediatric Use*,** and **DOSAGE AND ADMINISTRATION**.

Central Venous Nutrition
Central venous infusion should be considered when amino acid solutions are to be admixed with hypertonic dextrose to promote protein synthesis in hypercatabolic or severely depleted patients, or those requiring long-term parenteral nutrition.

Peripheral Parenteral Nutrition
For moderately catabolic or depleted patients in whom the central venous route is not indicated, diluted amino acid solutions mixed with 5% dextrose solutions may be infused by peripheral vein, supplemented, if desired, with fat emulsion. In pediatric patients, the final solution should not exceed twice normal serum osmolarity (718 mOsmol/L).

Protein Sparing
In well-nourished, mildly catabolic patients such as routine postsurgical patients who require only short-term parenteral nutrition, protein sparing can be achieved by peripheral infusion of amino acid solutions with or without dextrose.

CONTRAINDICATIONS
8.5% FreAmine III 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 the solution.

WARNINGS

This product contains sodium bisulfite, 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 and effective use of central venous nutrition requires a knowledge of nutrition 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 central venous 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.

Administration of amino acids in the presence of impaired renal function or gastrointestinal bleeding may augment an already elevated blood urea nitrogen. Patients with azotemia from any cause should not be infused with amino acids without regard to total nitrogen intake.

Administration of amino acid solutions to a patient with hepatic insufficiency may result in plasma amino acid imbalances, hyperammonemia, prerenal azotemia, stupor and coma. Hyperammonemia is of **special significance in infants** as its occurrence in the syndrome caused by genetic metabolic defects is sometimes associated, although not necessarily in a causal relationship, with mental retardation. This reaction appears to be dose related and is more likely to develop during prolonged therapy. It is essential that blood ammonia be measured frequently in infants. The mechanisms of this reaction are not clearly defined but may involve genetic defects and immature or subclinically impaired liver function.

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.

Care must be taken to avoid incompatible electrolyte mixtures. Infusate levels of 10-15 mEq/liter of phosphate, 5 mEq/liter of calcium, and 5-10 mEq/liter of magnesium are rarely incompatible when properly mixed. Higher levels must be added cautiously with adequate mixing (avoid layering) and inspection. Additional calcium and phosphate may be added to alternate bottles. Whatever the electrolyte formula, the infusion must be inspected for solution clarity at the time of mixing, before dispensing from the pharmacy, and immediately before and periodically during administration.

PRECAUTIONS

General

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation. Significant deviations from normal concentrations may require the use of additional electrolyte supplements.

Strongly hypertonic nutrient solutions should be administered through an indwelling intravenous catheter with the tip located in the superior vena cava.

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.

Special care must be taken when giving hypertonic dextrose to a diabetic or prediabetic patient. To prevent severe hyperglycemia in such patients, insulin may be required.

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.

After appropriate dilution, if 8.5% FreAmine® III (Amino Acid Injection) is to be administered by peripheral vein, care should be taken to assure proper placement of the needle within the lumen of the vein. The venipuncture site should be inspected frequently for signs of infiltration. If venous thrombosis or phlebitis occurs, discontinue infusions or change infusion site and initiate appropriate treatment.

Extraordinary electrolyte losses such as may occur during protracted nasogastric suction, vomiting, diarrhea or gastrointestinal fistula drainage may necessitate additional electrolyte supplementation.

Metabolic acidosis can be prevented or readily controlled by adding a portion of the cations in the electrolyte mixture as acetate salts and in the case of hyperchloremic acidosis, by keeping the total chloride content of the infusate to a minimum. 8.5% FreAmine III contains less than 3 mEq chloride per liter.

8.5% FreAmine III contains 10 mmole phosphorus per liter. Some patients, especially those with hypophosphatemia, may require additional phosphate. To prevent hypocalcemia, calcium supplementation should always accompany phosphate administration. To assure adequate intake, serum levels should be monitored frequently.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility
No *in vitro* or *in vivo* carcinogenesis, mutagenesis, or fertility studies have been conducted with 8.5% FreAmine® (Amino Acid Injection).

Pregnancy - Teratogenic Effects - Pregnancy Category C
Animal reproduction studies have not been conducted with 8.5% FreAmine III (Amino Acid Injection). It is also not known whether 8.5% FreAmine III can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. 8.5% FreAmine III 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 8.5% FreAmine III (Amino Acid Injection) 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 **INDICATIONS AND USAGE, WARNINGS,** and **DOSAGE AND ADMINISTRATION**.

Geriatric Use
Clinical studies of 8.5% FreAmine lll 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.**

Special Precautions for Central Venous Nutrition
Administration by central venous catheter should be used only by those familiar with this technique and its complications.
Central venous nutrition may be associated with complications which can be prevented or minimized by careful attention to all aspects of the procedure including solution preparation, administration, and patient monitoring.
It is essential that a carefully prepared protocol, based on current medical practices, be followed, preferably by an experienced team.
Although a detailed discussion of the complications of central venous nutrition is beyond the scope of this insert, the following summary lists those based on current literature:

Technical
The placement of a central venous catheter should be regarded as a surgical procedure. One should be fully acquainted with various techniques of catheter insertion as well as recognition and treatment of complications. For details of techniques and placement sites, consult the medical literature. X-ray is the best means of verifying catheter placement. Complications known to occur from the placement of central venous catheters are pneumothorax, hemothorax,

hydrothorax, artery puncture and transection, injury to the brachial plexus, malposition of the catheter, formation of arteriovenous fistula, phlebitis, thrombosis, and air and catheter embolus.

Septic
The constant risk of sepsis is present during central venous nutrition. Since contaminated solutions and infusion catheters are potential sources of infection, it is imperative that the preparation of parenteral nutrition solutions and the placement and care of catheters be accomplished under controlled aseptic conditions.

Solutions should ideally be prepared in the hospital pharmacy in a laminar flow hood. The key factor in their preparation is careful aseptic technique to avoid inadvertent touch contamination during mixing of solutions and subsequent admixtures. Various studies have shown that solutions containing casein or fibrin hydrolysates are better microbial growth media than solutions containing 8.5% FreAmine® III (Amino Acid Injection).

Parenteral nutrition solutions should be used promptly after mixing. Any storage should be under refrigeration for as brief a time as possible. Administration time for a single bottle and set should never exceed 24 hours.

Consult the medical literature for a discussion of the management of sepsis during central venous nutrition. In brief, typical management includes replacing the solution being administered with a fresh container and set, and the remaining contents are cultured for bacterial or fungal contamination. If sepsis persists and another source of infection is not identified, the catheter is removed, the proximal tip cultured, and a new catheter reinserted when the fever has subsided. Non-specific, prophylactic antibiotic treatment is not recommended. Clinical experience indicates that the catheter is likely to be the prime source of infection as opposed to aseptically prepared and properly stored solutions.

Metabolic
The following metabolic complications have been reported: metabolic acidosis, hypophosphatemia, alkalosis, hyperglycemia and glycosuria, osmotic diuresis and dehydration, rebound hypoglycemia, elevated liver enzymes, hypo- and hypervitaminosis, electrolyte imbalances, and hyperammonemia in pediatric patients. Frequent clinical evaluation and laboratory determinations are necessary, especially during the first few days of central venous nutrition, to prevent or minimize these complications.

ADVERSE REACTIONS
See **"Warnings"** and **"*Special Precautions for Central Venous Nutrition*."**
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.

If electrolyte supplementation is required during peripheral infusion, it is recommended that additives be administered throughout the day in order to avoid possible venous irritation. Irritating additive medications may require injection at another site, and should not be added directly to the amino acid infusion.

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.

DOSAGE AND ADMINISTRATION
The total daily dose of 8.5% FreAmine III depends on daily protein requirements and on the patient's metabolic and clinical response. The determination of nitrogen balance and accurate daily body weights, corrected for fluid balance, are probably the best means of assessing individual protein requirements.

Recommended Dietary Allowances of protein are approximately 0.9 g/kg of body weight for a healthy adult and 1.4 to 2.2 g/kg for healthy growing infants and pediatric patients. It must be recognized, however, that protein as well as caloric requirements in traumatized or malnourished patients may be substantially increased. Daily amino acid doses of approximately 1.0 to 1.5 g/kg of body weight for adults and 2 to 3 g/kg of body weight for infants with adequate calories are generally sufficient to satisfy protein needs and promote positive nitrogen balance in such patients, although higher doses may be required in severely catabolic states. Such higher doses, especially in infants, must be accompanied by frequent laboratory evaluation.

For protein sparing in well-nourished patients not receiving significant additional calories, amino acid dosages of 1.0 to 1.7 g/kg/day significantly reduce nitrogen losses and spare body protein. If rises in BUN exceed 20 mg% in 48 hours, amino acid infusion should be discontinued or rate of administration reduced.

Fat emulsion coadministration should be considered when prolonged (more than 5 days) parenteral nutrition is required in order to prevent essential fatty acid deficiency (E.F.A.D.).

Serum lipids should be monitored for evidence of E.F.A.D. in patients maintained on fat free TPN.

The provision of sufficient intracellular electrolytes, principally potassium, magnesium, and phosphate, is also required for optimum utilization of amino acids. Approximately 60-180 mEq of potassium, 10-30 mEq of magnesium, and 20-80 mEq of phosphate per day appear necessary to achieve optimum metabolic response. In addition, sufficient quantities of the major extracellular electrolytes (sodium, calcium, and chloride) must be given. In patients with hyperchloremic or other metabolic acidoses, sodium and potassium may be added as the acetate or lactate salts to provide bicarbonate precursor. The electrolyte content of 8.5% FreAmine® III (Amino Acid Injection) must be considered when calculating daily electrolyte intake. Serum electrolytes, including magnesium and phosphorus, should be monitored frequently.
If a patient's nutritional intake is primarily parenteral, vitamins, especially the water soluble vitamins, should also be provided.

Central Venous Nutrition
For severely catabolic, depleted patients or those requiring long-term total parenteral nutrition, central venous nutrition should be considered. Calorie-to-nitrogen ratios of at least 100 to 150 nonprotein calories per gram of nitrogen have been recommended to achieve positive nitrogen balance in such patients. These ratios are easily and conveniently attained with the use of concentrated dextrose solutions, supplemented if desired with parenteral fat emulsion.

Total parenteral nutrition may be started with infusates containing lower concentrations of dextrose; dextrose content may be gradually increased to estimated caloric needs as the patient's glucose tolerance increases.

In adults, strongly hypertonic mixtures of amino acids and dextrose may be safely administered only by continuous infusion through a central venous catheter with the tip located in the vena cava. For optimal nitrogen utilization, 500 mL of 8.5% FreAmine III appropriately mixed with concentrated dextrose, electrolytes, and vitamins are typically administered over an 8-hour period. If administration rate should fall behind schedule, no attempt to "catch up" to planned intake should be made. In addition to meeting protein needs, the administration rate is also governed, especially during the first few days of therapy by the patient's glucose tolerance. Daily intake of amino acids and dextrose should be increased gradually to the maximum required dose as indicated by frequent determination of urine and blood sugar levels. In many patients, provision of adequate calories in the form of hypertonic dextrose may require the administration of exogenous insulin to prevent hyperglycemia and glycosuria. To prevent rebound hypoglycemia, a solution containing 5% dextrose should be administered when hypertonic dextrose infusions are abruptly discontinued.

Peripheral Parenteral Nutrition
For moderately catabolic, depleted patients requiring parenteral nutrition in whom the central venous route is not indicated, 8.5% FreAmine III can be mixed with 5% dextrose solutions and administered by peripheral vein.

For example, to prepare a solution of 4.25% FreAmine III in 2.5% dextrose, aseptically transfer 500 mL of 8.5% FreAmine III to a one liter intravenous bottle containing 500 mL of 5% dextrose. Each liter of the resultant solution provides 41 grams of protein equivalent and 85

carbohydrate calories with an osmolarity of approximately 530 mOsmol/liter. In pediatric patients, the final solution should not exceed twice normal serum osmolarity (718 mOsmol/L). Fat provides approximately 9 kcal per gram and parenteral fat emulsion may be administered along with amino acid-dextrose solutions through a Y-type administration set to supplement caloric intake. Fat, however, should not be the sole caloric intake since some studies have suggested that glucose is more nitrogen sparing in the stressed patient.

Protein Sparing
For well-nourished, mildly catabolic patients who require short-term parenteral nutritional support, 8.5% FreAmine® III (Amino Acid Injection) can be administered peripherally with or without parenteral carbohydrate calories. Such infusates can be prepared by dilution of 8.5% FreAmine III with Sterile Water for Injection or 5% Dextrose solutions to prepare isotonic or slightly hypertonic solutions which may be administered by peripheral vein. For example, a 4.25% FreAmine III solution can be prepared by the aseptic transfer of 500 mL of 8.5% FreAmine III to a half-filled intravenous one liter bottle of Sterile Water for Injection. The resultant solution contains 41 grams of amino acids with an osmolarity of approximately 405 mOsmol/liter. An approximately isotonic solution of 3% FreAmine III can be prepared by aseptic transfer of 350 mL of 8.5% FreAmine III to a partially filled intravenous one liter bottle containing 650 mL of Sterile Water for Injection. The resultant solution will provide 29 grams of amino acids per liter with an osmolarity of approximately 285 mOsmol/liter.

Pediatric Dosage and Administration
Infants (up to 10 kg) on total parenteral nutrition generally receive 2 to 3 grams of protein, 120 to 150 calories, and 120 to 150 mL of fluid per kilogram of body weight per day. This can be provided in a solution containing approximately 2-1/8% FreAmine III (diluted from 8.5% FreAmine III) and 20% dextrose. Less hypertonic mixtures may be administered by peripheral vein. Fat emulsion may be given concurrently by central or peripheral vein through a Y-type administration set to provide essential fatty acids and increase caloric intake. Since physiological changes occur rapidly in small infants, the daily dose of nutrients should initially be increased slowly with frequent monitoring of pertinent clinical and metabolic parameters. Pediatric patients over 10 kilograms require fewer calories and slightly less protein; generally 50 to 80 calories and 2 grams of protein per kilogram per day is sufficient.

Use of 8.5% FreAmine III 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 **INDICATIONS AND USAGE, 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

8.5% FreAmine III (Amino Acid Injection) is supplied sterile and nonpyrogenic in glass intravenous infusion bottles with solid stoppers; the 500 mL packed 12 per case, and 1000 mL packed 6 per case.

NDC	Cat. No.	Size
8.5% FreAmine III (Amino Acid Injection)		
0264-9030-55	S9030-SS	1000 mL
0264-9031-55	S9031-SS	500 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.
Revised: June 2003
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.

B. Braun Medical Inc.
Irvine CA USA 92614-5895

Y36-002-488
Package Insert

10% FreAmine® III (Amino Acid Injection)

Protect from light until use. **Rx only**

DESCRIPTION

10% FreAmine III (Amino Acid Injection) is a sterile, nonpyrogenic, hypertonic solution containing crystalline amino acids. Each 1000 mL provides a total of 15.3 g of nitrogen in 97 g of amino acids equal to 95.6 grams of protein equivalent. 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 0.69 g
Leucine USP 0.91 g
Lysine 0.73 g
(added as Lysine Acetate USP 1.02 g)
Methionine USP 0.53 g
Phenylalanine USP 0.56 g
Threonine USP 0.40 g
Tryptophan USP 0.15 g
Valine USP 0.66 g

Nonessential amino acids
Alanine USP 0.71 g
Arginine USP 0.95 g
Histidine USP 0.28 g
Proline USP 1.12 g
Serine USP 0.59 g
Glycine USP 1.40 g
Cysteine <0.016 g
(as Cysteine HCl•H_2O USP <0.024 g)
Phosphoric Acid NF 0.12 g
Sodium Bisulfite (as an antioxidant) <0.10 g
Water for Injection USP qs
pH adjusted with Glacial Acetic Acid USP
pH: 6.5 (6.0-7.0)
Calculated Osmolarity: 950 mOsmol/liter

Concentration of Electrolytes (mEq/liter): Sodium 10; Phosphate ($HPO^{=}_4$) 20 (10 mmole P/liter); Acetate Approx. 89 (provided as acetic acid and lysine acetate); Chloride <3.

CLINICAL PHARMACOLOGY

10% FreAmine III provides a physiological ratio of biologically utilizable amino acids in concentrated form for protein synthesis. Used with concentrated calorie sources such as

hypertonic dextrose or fat emulsion, and with electrolytes, vitamins and minerals, it provides total parenteral nutrition. Administered peripherally as an isotonic solution (3%) without nonprotein calories or with minimal caloric supplementation such as 5% dextrose, it provides nutritional support and spares body protein.

Phosphate is a major intracellular anion which participates in providing energy for metabolism of substrates and contributes to significant metabolic and enzymatic reactions in 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.

It is thought that the acetate from lysine 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.

The amounts of sodium and chloride present are not of clinical significance.

INDICATIONS AND USAGE
Parenteral nutrition with 10% FreAmine® III (Amino Acid Injection) is indicated to prevent nitrogen loss or treat negative nitrogen balance in adults and pediatric patients where (1) the alimentary tract, by the oral, gastrostomy, or jejunostomy route, cannot or should not be used, or adequate protein intake is not feasible by these routes; (2) gastrointestinal absorption of protein is impaired; or (3) protein requirements are substantially increased as with extensive burns. Dosage, route of administration, and concomitant infusion of nonprotein calories are dependent on various factors, such as nutritional and metabolic status of the patient, anticipated duration of parenteral nutritional support, and vein tolerance. See **WARNINGS, PRECAUTIONS,** ***Pediatric Use*****,** and **DOSAGE AND ADMINISTRATION**.

Central Venous Nutrition
Central venous infusion should be considered when amino acid solutions are to be admixed with hypertonic dextrose to promote protein synthesis in hypercatabolic or severely depleted patients, or those requiring long-term parenteral nutrition.

Peripheral Parenteral Nutrition
For moderately catabolic or depleted patients in whom the central venous route is not indicated, diluted amino acid solutions mixed with 5% dextrose solutions may be infused by peripheral vein, supplemented, if desired, with fat emulsion. In pediatric patients, the final solution should not exceed twice normal serum osmolarity (718 mOsmol/L).

Protein Sparing
In well-nourished, mildly catabolic patients such as routine postsurgical patients who require only short-term parenteral nutrition, protein sparing can be achieved by peripheral infusion of amino acid solutions with or without dextrose.

CONTRAINDICATIONS
10% FreAmine III is contraindicated in patients with anuria, hepatic coma, inborn errors of amino acid metabolism, or hypersensitivity to one or more amino acids present in the solution.

WARNINGS
This product contains sodium bisulfite, 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 and effective use of central venous nutrition requires a knowledge of nutrition 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 central venous 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.

Administration of amino acids in the presence of impaired renal function or gastrointestinal bleeding may augment an already elevated blood urea nitrogen. Patients with azotemia from any cause should not be infused with amino acids without regard to total nitrogen intake.

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

Hyperammonemia is of **special significance in infants** as its occurrence in the syndrome caused by genetic metabolic defects is sometimes associated, although not necessarily in a causal relationship, with mental retardation. This reaction appears to be dose related and is more likely to develop during prolonged therapy. It is essential that blood ammonia be measured frequently

in infants. The mechanisms of this reaction are not clearly defined but may involve genetic defects and immature or subclinically impaired liver function.

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.

PRECAUTIONS

General

Clinical evaluation and periodic laboratory determinations are necessary to monitor changes in fluid balance, electrolyte concentrations, and acid-base balance during prolonged parenteral therapy or whenever the condition of the patient warrants such evaluation. Significant deviations from normal concentrations may require the use of additional electrolyte supplements.

Strongly hypertonic nutrient solutions should be administered through an indwelling intravenous catheter with the tip located in the superior vena cava.

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.

Special care must be taken when giving hypertonic dextrose to a diabetic or prediabetic patient. To prevent severe hyperglycemia in such patients, insulin may be required.

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.

After appropriate dilution, if 10% FreAmine® III (Amino Acid Injection) is to be administered by peripheral vein, care should be taken to assure proper placement of the infusion device within the lumen of the vein. The venipuncture site should be inspected frequently for signs of infiltration. If venous thrombosis or phlebitis occurs, discontinue infusions or change infusion site and initiate appropriate treatment.

Extraordinary electrolyte losses such as may occur during protracted nasogastric suction, vomiting, diarrhea or gastrointestinal fistula drainage may necessitate additional electrolyte supplementation.

Metabolic acidosis can be prevented or readily controlled by adding a portion of the cations in the electrolyte mixture as acetate salts and in the case of hyperchloremic acidosis, by keeping the total chloride content of the infusate to a minimum. 10% FreAmine III contains less than 3 mEq chloride per liter.

10% FreAmine III contains phosphorus. Patients, especially those with hypophosphatemia, may require additional phosphate. To prevent hypocalcemia, calcium supplementation should always accompany phosphate administration. To assure adequate intake, serum levels should be monitored frequently.

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

Carcinogenesis, Mutagenesis, Impairment of Fertility
No *in vitro* or *in vivo* carcinogenesis, mutagenesis, or fertility studies have been conducted with 10% FreAmine® III (Amino Acid Injection).

Pregnancy - Teratogenic Effects - Pregnancy Category C
Animal reproduction studies have not been conducted with 10% FreAmine III (Amino Acid Injection). It is also not known whether 10% FreAmine III can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. 10% FreAmine III 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 10% FreAmine III (Amino Acid Injection) 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 **INDICATIONS AND USAGE, WARNINGS,** and **DOSAGE AND ADMINISTRATION**.

Geriatric Use
Clinical studies of 10% FreAmine lll (Amino Acid Injection) 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**

Special Precautions for Central Venous Nutrition
Administration by central venous catheter should be used only by those familiar with this technique and its complications.
Central venous nutrition may be associated with complications which can be prevented or minimized by careful attention to all aspects of the procedure including solution preparation, administration, and patient monitoring. **It is essential that a carefully prepared protocol, based on current medical practices, be followed, preferably by an experienced team.**
Although a detailed discussion of the complications of central venous nutrition is beyond the scope of this insert, the following summary lists those based on current literature:

Technical
The placement of a central venous catheter should be regarded as a surgical procedure. One should be fully acquainted with various techniques of catheter insertion as well as recognition and treatment of complications. For details of techniques and placement sites, consult the medical literature. X-ray is the best means of verifying catheter placement. Complications known to occur from the placement of central venous catheters are pneumothorax, hemothorax, hydrothorax, artery puncture and transection, injury to the brachial plexus, malposition of the catheter, formation of arteriovenous fistula, phlebitis, thrombosis, and air and catheter embolus.

Septic
The constant risk of sepsis is present during central venous nutrition. Since contaminated solutions and infusion catheters are potential sources of infection, it is imperative that the preparation of parenteral nutrition solutions and the placement and care of catheters be accomplished under controlled aseptic conditions.

Solutions should ideally be prepared in the hospital pharmacy in a laminar flow hood. The key factor in their preparation is careful aseptic technique to avoid inadvertent touch contamination during mixing of solutions and subsequent admixtures.

Parenteral nutrition solutions should be used promptly after mixing. Any storage should be under refrigeration for as brief a time as possible. Administration time for a single bottle and set should never exceed 24 hours.

Consult the medical literature for a discussion of the management of sepsis during central venous nutrition. In brief, typical management includes replacing the solution being administered with a fresh container and set, and the remaining contents are cultured for bacterial or fungal contamination. If sepsis persists and another source of infection is not identified, the catheter is removed, the proximal tip cultured, and a new catheter reinserted when the fever has subsided. Non-specific, prophylactic antibiotic treatment is not recommended. Clinical experience indicates that the catheter is likely to be the prime source of infection as opposed to aseptically prepared and properly stored solutions.

Metabolic
The following metabolic complications have been reported: metabolic acidosis, hypophosphatemia, alkalosis, hyperglycemia and glycosuria, osmotic diuresis and dehydration, rebound hypoglycemia, elevated liver enzymes, hypo- and hypervitaminosis, electrolyte imbalances, and hyperammonemia in pediatric patients. Frequent clinical evaluation and laboratory determinations are necessary, especially during the first few days of central venous nutrition, to prevent or minimize these complications.

ADVERSE REACTIONS
See **"Warnings"** and **"*Special Precautions for Central Venous Nutrition*."**
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.

If electrolyte supplementation is required during peripheral infusion, it is recommended that additives be administered throughout the day in order to avoid possible venous irritation. Irritating additive medications may require injection at another site and should not be added directly to the amino acid infusate.

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.

DOSAGE AND ADMINISTRATION
The total daily dose of 10% FreAmine® III (Amino Acid Injection) depends on daily protein requirements and on the patient's metabolic and clinical response. The determination of nitrogen balance and accurate daily body weights, corrected for fluid balance, are probably the best means of assessing individual protein requirements.

While Recommended Dietary Allowances of protein are approximately 0.8 g/kg of body weight for a healthy adult and 1.4 to 2.2 g/kg for healthy growing infants and pediatric patients. It must be recognized that protein as well as caloric requirements in traumatized or malnourished patients may be substantially increased. Daily amino acid doses of approximately 1.5 g/kg of body weight for adults and 2 to 3 g/kg of body weight for infants with adequate calories are generally sufficient to satisfy protein needs and promote positive nitrogen balance. Higher doses may be required in severely catabolic states. Such higher doses, especially in infants, must be accompanied by frequent laboratory evaluation. Fat emulsion may be supplied to help meet energy requirements.

Fat emulsion coadministration should be considered when prolonged (more than 5 days) parenteral nutrition is required in order to prevent essential fatty acid deficiency (E.F.A.D.). Serum lipids should be monitored for evidence of E.F.A.D. in patients maintained on fat free TPN.

For protein sparing in well-nourished patients not receiving significant additional calories, amino acid dosages of 1.0 to 1.7 g/kg/day significantly reduce nitrogen losses and spare body protein. If rises in BUN exceed 20 mg% in 48 hours, amino acid infusion should be discontinued or rate of administration reduced.

The provision of sufficient intracellular electrolytes, principally potassium, magnesium, and phosphate, is also required for optimum utilization of amino acids. Approximately 60-180 mEq of potassium, 10-30 mEq of magnesium, and 20-80 mEq of phosphate per day appear necessary

to achieve optimum metabolic response. In addition, sufficient quantities of the major extracellular electrolytes (sodium, calcium, and chloride) must be given. In patients with hyperchloremic or other metabolic acidoses, sodium and potassium may be added as the acetate or lactate salts to provide bicarbonate precursor. The electrolyte content of 10% FreAmine® III (Amino Acid Injection) must be considered when calculating daily electrolyte intake. Serum electrolytes, including magnesium and phosphorus, should be monitored frequently.
If a patient's nutritional intake is primarily parenteral, vitamins, especially the water soluble vitamins, and trace elements should also be provided.

Central Venous Nutrition
For severely catabolic, depleted patients or those requiring long-term total parenteral nutrition, central venous nutrition should be considered. Calorie-to-nitrogen ratios of at least 100 to 150 nonprotein calories per gram of nitrogen have been recommended to achieve positive nitrogen balance in such patients. These ratios are easily and conveniently attained with the use of concentrated dextrose solutions, supplemented if desired with parenteral fat emulsion.
Total parenteral nutrition may be started with infusates containing lower concentrations of dextrose; dextrose content may be gradually increased to estimated caloric needs as the patient's glucose tolerance increases.

In adults, strongly hypertonic mixtures of amino acids and dextrose may be safely administered only by continuous infusion through a central venous catheter with the tip located in the vena cava. For optimal nitrogen utilization, 500 mL of 10% FreAmine III appropriately mixed with concentrated dextrose, electrolytes, and vitamins are typically administered over an 8-hour period. If administration rate should fall behind schedule, no attempt to "catch up" to planned intake should be made. In addition to meeting protein needs, the administration rate is also governed, especially during the first few days of therapy by the patient's glucose tolerance. Daily intake of amino acids and dextrose should be increased gradually to the maximum required dose as indicated by frequent determination of urine and blood sugar levels. In many patients, provision of adequate calories in the form of hypertonic dextrose may require the administration of exogenous insulin to prevent hyperglycemia and glycosuria. To prevent rebound hypoglycemia, a solution containing 5% dextrose should be administered when hypertonic dextrose infusions are abruptly discontinued.

Peripheral Parenteral Nutrition
For moderately catabolic, depleted patients requiring parenteral nutrition in whom the central venous route is not indicated, 10% FreAmine III can be mixed with 5% dextrose solutions and administered by peripheral vein. In pediatric patients, the final solution should not exceed twice normal serum osmolarity (718 mOsmol/L).

Fat provides approximately 9 kcal per gram and parenteral fat emulsion may be administered along with amino acid-dextrose solutions through a Y-type administration set to supplement caloric intake. Fat, however, should not be the sole caloric intake since some studies have suggested that glucose is more nitrogen sparing in the stressed patient.

Protein Sparing
For well-nourished, mildly catabolic patients who require short-term parenteral nutritional support, 10% FreAmine III can be administered peripherally with or without parenteral carbohydrate calories. Such infusates can be prepared by dilution of 10% FreAmine III with

Sterile Water for Injection USP or 5% Dextrose Injection USP solutions to prepare isotonic or slightly hypertonic solutions which may be administered by peripheral vein.

Pediatric Dosage and Administration
Use of 10% FreAmine III 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).

Infants (up to 10 kg) on total parenteral nutrition generally receive 2 to 3 grams of protein, 120 to 150 calories, and 120 to 150 mL of fluid per kilogram of body weight per day. This can be provided in a solution containing approximately 2-1/8% FreAmine III (diluted from 10% FreAmine® III (Amino Acid Injection) and 20% dextrose. Less hypertonic mixtures may be administered by peripheral vein. Fat emulsion may be given concurrently by central or peripheral vein through a Y-type administration set to provide essential fatty acids and increase caloric intake. Since physiological changes occur rapidly in small infants, the daily dose of nutrients should initially be increased slowly with frequent monitoring of pertinent clinical and metabolic parameters. Pediatric patients over 10 kilograms require fewer calories and slightly less protein; generally 50 to 80 calories and 2 grams of protein per kilogram per day is sufficient.
See **INDICATIONS AND USAGE, 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
10% FreAmine III is supplied sterile and nonpyrogenic in glass intravenous infusion bottles with solid stoppers. The 1000 mL containers are packed 6 per case; the 500 mL containers are packed 12 per case.

NDC	**Cat. No.**	**Size**
10% FreAmine III (Amino Acid Injection)		
0264-9010-55	S9010-SS	1000 mL
0264-9011-55	S9011-SS	500 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.
Revised: June 2003
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.

B. Braun Medical Inc.
Irvine CA USA 92614-5895