

Citizen Petition
6% and 10% L-lysine HCl - remaSol™ – sulfite-free (Amino Acid)
Injections in PL 146® Plastic Container
August 9, 2000

Baxter

ATTACHMENT 2

Side-by-Side Comparison of Reference and Proposed Drug Package Inserts

Citizen Petition
 6% and 10% PremaSol™ – sulfite-free (Amino Acid)
 Injections in PL 146® Plastic Container
 August 9, 2000

Reference Drug Product Package Insert

Y36-002-361
 Package Insert

**TrophAmine®
 (Amino Acid Injections)**

Protect from light until use.

DESCRIPTION

TrophAmine (6% and 10% Amino Acid Injections) are sterile, nonpyrogenic, hypertonic solutions containing crystalline 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	6%	10%
Isoleucine USP	0.49 g	0.82 g
Leucine USP	0.84 g	1.4 g
Lysine	0.49 g	0.82 g
(added as Lysine Acetate USP)	0.69 g	1.2 g
Methionine USP	0.20 g	0.34 g
Phenylalanine USP	0.29 g	0.48 g
Threonine USP	0.25 g	0.42 g
Tryptophan USP	0.12 g	0.20 g
Valine USP	0.47 g	0.78 g
Cysteine	<0.014 g	<0.016 g
(as Cysteine HCl·H ₂ O USP)	<0.020 g	<0.024 g
Histidine USP ¹	0.29 g	0.48 g
Tyrosine ¹	0.14 g	0.24 g
(added as Tyrosine USP	0.044 g	0.044 g
and N-Acetyl-L-Tyrosine)	0.12 g	0.24 g

Side-by-Side Comparison

Black box warning
 "Pharmacy Bulk Package Not for Direct Infusion" is included per Baxter standard practice for pharmacy bulk package labeling.

"Rx only" has replaced
 "Caution: Federal (USA) law prohibits dispensing without prescription".

The statement "Protect from light until immediately prior to use" is included on the last page of the proposed product package insert. The statement does not require the same prominence of the reference drug product labeling because the proposed product is in a foil overpouch which provides a light barrier.

Some information has been reformatted consistent with Baxter standard practice (e.g., order of amino acids, inclusion of amino acid molecular formulas, etc.).

All other text is identical in content to the reference labeling with the exception of product name, manufacturer, and container information.

Proposed Drug Product Package Insert

Baxter

**6% and 10% PremaSol™ - sulfite-free
 (Amino Acid) Injections**

**Pharmacy Bulk Package
 Not for Direct Infusion**

in Viaflex® Plastic Container

Rx only

Description

6% and 10% PremaSol™ - sulfite-free (Amino Acid) Injections are sterile, nonpyrogenic, hypertonic solutions containing essential and nonessential amino acids provided in a Pharmacy Bulk Package. A Pharmacy Bulk Package is a container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for intravenous infusion.

The Viaflex® plastic container is fabricated from a specially formulated polyvinyl chloride (PL 146® Plastic). Exposure to temperatures above 25°C/77°F during transport and storage will lead to minor losses in moisture content. Higher temperatures lead to greater losses. It is unlikely that these minor losses will lead to clinically significant changes within the expiration period. The amount of water that can permeate from inside the container into the overwrap is insufficient to affect the solution significantly. Solutions in contact with the plastic container may leach out certain chemical components from the plastic in very small amounts; however, biological testing was supportive of the safety of the plastic container materials.

Each 100 mL contains:

Essential Amino Acids	6%	10%
Leucine - (CH ₃) ₂ CHCH ₂ CH (NH ₂) COOH	0.84 g	1.4 g
Isoleucine - CH ₃ CH ₂ CH (CH ₃) CH (NH ₂) COOH	0.49 g	0.82 g
Lysine (added as Lysine Acetate) - H ₂ N (CH ₂) ₄ CH (NH ₂) COOH	0.49 g	0.82 g
Valine - (CH ₃) ₂ CHCH (NH ₂) COOH	0.47 g	0.78 g
Histidine ¹ - (C ₆ H ₃ N ₂) CH ₂ CH (NH ₂) COOH	0.29 g	0.48 g
Phenylalanine - (C ₆ H ₅) CH ₂ CH (NH ₂) COOH	0.29 g	0.48 g
Threonine - CH ₃ CH (OH) CH (NH ₂) COOH	0.25 g	0.42 g
Methionine - CH ₃ S (CH ₂) ₂ CH (NH ₂) COOH	0.20 g	0.34 g
Tyrosine ¹ (added as Tyrosine and N-Acetyl-L-Tyrosine) - [C ₆ H ₄ (OH)] CH ₂ CH (NH ₂) COOH	0.14 g	0.24 g
Tryptophan - (C ₈ H ₆ N) CH ₂ CH (NH ₂) COOH	0.12 g	0.20 g
Cysteine (added as Cysteine HCl·H ₂ O) - SHCH ₂ CHNH ₂ COOH	<0.014 g	<0.016 g

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Reference Drug Product Package Insert

Essential Amino Acids

Alanine USP	0.32 g	0.54 g
Arginine USP	0.73 g	1.2 g
Proline USP	0.41 g	0.68 g
Serine USP	0.23 g	0.38 g
Glycine USP	0.22 g	0.36 g
L-Alanine	0.19 g	0.32 g
L-Aspartic Acid	0.30 g	0.50 g
L-Glutamic Acid	0.015 g	0.025 g
Taurine ¹	<0.050 g	<0.050 g
Sodium Metabisulfite NF (as an antioxidant)	qs	qs
Water for Injection USP		
pH adjusted with Glacial Acetic Acid USP		
pH: 5.5 (5.0-6.0)		
Calc. Osmolarity (mOsmol/liter)	525	875
Total Amino Acids (grams/liter)	60	100
Total Nitrogen (grams/liter)	9.3	15.5
Protein Equivalent (grams/liter)	56	97
Electrolytes (mEq/liter)		
Sodium	5	5
* Acetate (CH ₃ COO ⁻)	54.4	97
Chloride	<3	<3

¹ Provided as acetic acid and lysine acetate

² Holt LE, Snyderman SE: The amino acid requirements of infants. JAMA 1961; 175(2):124-127.

³ Rigo J, Senterre J: Is taurine essential for the neonates? Biol Neonate 1977; 32:73-76.

⁴ Gaul G, Starman JA, Raife NCR: Development of mammalian sulfur metabolism: Absence of cystothionase in human fetal tissues. Pediatr Res 1972; 6:538-547.

CLINICAL PHARMACOLOGY

TrophAmine provides a mixture of essential and nonessential amino acids as well as taurine and a soluble form of tyrosine, N-Acetyl-L-Tyrosine (NAT). This amino acid composition has been specifically formulated to provide a well tolerated nitrogen source for nutritional support and therapy for infants and young children. When administered in conjunction with cysteine hydrochloride, TrophAmine results in the normalization of the plasma amino acid concentrations to a profile consistent with that of a breast-fed infant.

The rationale for TrophAmine® (Amino Acid Injections) is based on the observation of inadequate levels of essential amino acids in the plasma of infants receiving total parenteral nutrition (TPN) using conventional amino acid solutions. The TrophAmine formula was developed through the application of specific pharmacokinetic multiple regression analysis relating amino acid intake to the resulting plasma amino acid concentrations.

Clinical studies in infants and young children who required TPN therapy showed that infusion of TrophAmine with a cysteine hydrochloride admixture resulted in a normalization of the plasma amino acid concentrations. In addition, weight gains, nitrogen balance, and serum protein concentrations were consistent with an improving nutritional status.

When infused with hypertonic dextrose as a calorie source, supplemented with cysteine hydrochloride, electrolytes, vitamins, and minerals, TrophAmine provides total parenteral nutrition in infants and young children, with the exception of essential fatty acids.

It is thought that the acetate from lysine acetate and acetic acid, under the conditions 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 in TrophAmine are not of clinical significance.

The addition of cysteine hydrochloride will contribute to the chloride load.

The electrolyte content of any additives that are introduced should be carefully considered and included in total input computations.

Side-by-Side Comparison

Use of the Viaflex® plastic packaging system obviates the need for sodium metabisulfite in the proposed product

Per Baxter standard, Water for Injection and Protein Equivalent values are not listed. Exclusion of Water for Injection on package insert is consistent with 21 CFR §201.100.

Values for total amino acids, total nitrogen and chloride are calculated for the proposed products.

Osmolarity and acetate values differ because the amount of glacial acetic acid used to adjust pH is different between the reference and proposed products.

There is no sodium in the proposed product because it does not contain sodium metabisulfite.

All other text is identical in content to the reference product package insert with the exception of product name.

Proposed Drug Product Package Insert

Nonessential Amino Acids

Arginine - H ₂ NC(NH)NH(CH ₂) ₃ CH(NH ₂)COOH	0.73 g	1.2 g
Proline - [(CH ₂) ₅ NHCH]COOH	0.41 g	0.68 g
Alanine - CH ₃ CH(NH ₂)COOH	0.32 g	0.54 g
Glutamic Acid - HOOC(CH ₂) ₂ CH(NH ₂)COOH	0.30 g	0.50 g
Serine - HOCH ₂ CH(NH ₂)COOH	0.23 g	0.38 g
Glycine - H ₂ NCH ₂ COOH	0.22 g	0.36 g
Aspartic Acid - HOOCCH ₂ CH(NH ₂)COOH	0.19 g	0.32 g
Taurine ^{2,3} - H ₂ NCH ₂ CH ₂ SO ₃ H	0.015 g	0.025 g

pH adjusted with glacial acetic acid

pH: 5.5 (5.0-6.0)

Osmolarity (mOsmol/L) (Calc.)

Total Amino Acids (grams/100 mL) (Calc.)

Total Nitrogen (grams/100 mL) (Calc.)

Acetate⁴ - (CH₃COO⁻)

Chloride (Calc.)

* Provided as acetic acid and lysine acetate.

All amino acids are added as the "L"-isomer with the exception of Glycine and Taurine, which do not have isomers.

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² Rigo J, Senterre J: Is taurine essential for the neonates? Biol Neonate 1977; 32:73-76.

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Clinical Pharmacology

6% and 10% PremaSol™ - sulfite-free (Amino Acid) injections provide a mixture of essential and nonessential amino acids as well as taurine and a soluble form of tyrosine, N-Acetyl-L-Tyrosine (NAT). This amino acid composition has been specifically formulated to provide a well tolerated nitrogen source for nutritional support and therapy for infants and young children. When administered in conjunction with cysteine hydrochloride, 6% and 10% Amino Acid Injections result in the normalization of the plasma amino acid concentrations to a profile consistent with that of a breast-fed infant.

The rationale for 6% and 10% Amino Acid Injections is based on the observation of inadequate levels of essential amino acids in the plasma of infants receiving total parenteral nutrition (TPN) using conventional amino acid solutions. These formulas were developed through the application of specific pharmacokinetic multiple regression analysis relating amino acid intake to the resulting plasma amino acid concentrations.

Clinical studies in infants and young children who required TPN therapy showed that infusion of 6% and 10% Amino Acid Injections with a cysteine hydrochloride admixture resulted in a normalization of the plasma amino acid concentrations. In addition, weight gains, nitrogen balance, and serum protein concentrations were consistent with an improving nutritional status.

When infused with hypertonic dextrose as a calorie source, supplemented with cysteine hydrochloride, electrolytes, vitamins, and minerals, PremaSol™ - sulfite-free (Amino Acid) Injections provide total parenteral nutrition in infants and young children, with the exception of essential fatty acids.

It is thought that the acetate from lysine acetate and acetic acid, under the conditions 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 amount of chloride present in PremaSol™ - sulfite-free (Amino Acid) Injections is not of clinical significance. The addition of cysteine hydrochloride will contribute to the chloride load.

The electrolyte content of any additives that are introduced should be carefully considered and included in total input computations.

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Injections in PL 146® Plastic Container
August 9, 2000

Reference Drug Product Package Insert

INDICATIONS AND USAGE

TrophAmine is indicated for the nutritional support of infants (including those of low birth weight) and young children requiring TPN via either central or peripheral infusion routes. Parenteral nutrition with TrophAmine is indicated to prevent nitrogen and weight loss or treat negative nitrogen balance in infants and young children 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 **DOSEAGE AND ADMINISTRATION** for additional information.

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 infants, 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 5-10% dextrose solutions may be infused by peripheral vein, supplemented, if desired, with fat emulsion.

CONTRAINDICATIONS

TrophAmine is contraindicated in patients with untreated anuria, hepatic coma, inborn errors of amino acid metabolism, including 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

Safe, effective use of parenteral nutrition requires a knowledge of nutrition as well as clinical expertise in recognition and treatment of the complications which can occur. Frequent evaluation and laboratory determinations are necessary for proper monitoring of parenteral nutrition. Studies should include blood sugar, serum proteins, kidney and liver function tests, electrolytes, hemogram, carbon dioxide content, serum osmolalities, blood cultures, and blood ammonia levels.

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 intravenous 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 electrolyte concentrations of the solutions. The risk of solute overload causing congested states with peripheral and pulmonary edema is directly proportional to the electrolyte concentrations of the solutions.

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

Side-by-Side Comparison

The warning "This injection is for compounding only, not for direct infusion" is included per Baxter standard practice for pharmacy bulk package labeling.

All other text is identical in content to the reference product package insert with the exception of product name.

Proposed Drug Product Package Insert

Indications and Usage

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Citizen Petition

6% and 10% PremaSol™ – sulfite-free (Amino Acid)

Injections in PL 146® Plastic Container

August 9, 2000

Reference Drug Product Package Insert

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.

This product contains sodium metabisulfite, a sulfite that may cause allergic-type reactions including anaphylactic symptoms and life-threatening or 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.

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 via an intravenous catheter placed in a central vein, preferably the superior vena cava.

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

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

Administration of glucose at a rate exceeding the patient's utilization rate 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.

Peripheral administration of TrophAmine® (Amino Acid Injections) requires appropriate dilution and provision of adequate calories. 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. TrophAmine contains less than 3 mEq chloride per liter.

Side-by-Side Comparison

All text is identical in content to the reference product package insert with the exception of product name and information related to sodium metabisulfite which is not present in the proposed product

Proposed Drug Product Package Insert

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.

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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 carbohydrates.

Peripheral administration of 6% and 10% PremaSol™ - sulfite-free (Amino Acid) Injections require appropriate dilution and provision of adequate calories. 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.

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Reference Drug Product Package Insert

TrophAmine 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.

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, the seal unbroken, and vacuum is present.

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

Usage in Pregnancy
Pregnancy Category C. Animal reproduction studies have not been conducted with TrophAmine (Amino Acid Injections). It is also not known whether TrophAmine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

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 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.

Side-by-Side Comparison

All text is identical in content to the reference product package insert with the exception of product name and exclusion of reference to vacuum in the sentence "Use only if solution is clear, the seal unbroken, and vacuum is present". The presence of a vacuum is applicable to products in glass container systems.

Proposed Drug Product Package Insert

PremaSol™ - sulfite-free (Amino Acid) Injections contain 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.

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.

Do not use unless solution is clear and seal is intact.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No *in vitro* or *in vivo* carcinogenesis, mutagenesis, or fertility studies have been conducted with 6% and 10% PremaSol™ - sulfite-free (Amino Acid) Injections.

Usage in Pregnancy
Pregnancy Category C. Animal reproduction studies have not been conducted with 6% and 10% PremaSol™ - sulfite-free (Amino Acid) Injections. It is also not known whether PremaSol™ - sulfite-free (Amino Acid) Injections can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

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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 children. Frequent clinical evaluation and laboratory determinations are necessary, especially during the first few days of venous nutrition, to prevent or minimize these complications.

ADVERSE REACTIONS

See "WARNINGS" and "Special Precautions for Central Venous Nutrition."

Reactions reported in clinical studies as a result of infusion of the parenteral fluid were water weight gain, edema, increase in BUN, and mild acidosis.

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 reaction at 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.

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.

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.

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.

Side-by-Side Comparison

The statement "Administration time for a single bottle and set should never exceed 24 hours" is not applicable. The proposed drug product is a Pharmacy Bulk Package to be used in pharmacy compounding only.

All other text is identical in content to the reference product package insert with the exception of product name.

Proposed Drug Product Package Insert

Parenteral nutrition solutions should be used promptly after mixing. Any storage should be under refrigeration and limited to a brief period of time, preferably less than 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 children. Frequent clinical evaluation and laboratory determinations are necessary, especially during the first few days of venous nutrition, to prevent or minimize these complications.

Adverse Reactions

See **Warnings and Special Precautions for Central Venous Nutrition.**

Reactions reported in clinical studies as a result of infusion of the parenteral fluid were water weight gain, edema, increase in BUN, and mild acidosis.

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 reaction at 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.

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.

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.

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.

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Citizen Petition
6% and 10% PremaSol™ – sulfite-free (Amino Acid)
Injections in PL 146® Plastic Container
August 9, 2000

Reference Drug Product Package Insert

DOSEAGE AND ADMINISTRATION

The objective of nutritional management of infants and young children is the provision of sufficient amino acid and caloric support for protein synthesis and growth.

The total daily dose of TrophAmine® (Amino Acid Injections) 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. Dosage should also be guided by the patient's fluid intake limits and glucose and nitrogen tolerances, as well as by metabolic and clinical response.

Recommendations for allowances of protein in infant nutrition have ranged from 2 to 4 grams of protein per kilogram of body weight per day (2.0 to 4.0 g/kg/day).¹ The recommended dosage of TrophAmine is 2.0 to 2.5 grams of amino acids per kilogram of body weight per day (2.0 to 2.5 g/kg/day) for infants up to 10 kilograms. For infants and young children larger than 10 kilograms, the total dosage of amino acids should include the 20 to 25 grams/day for the first 10 kg of body weight plus 1.0 to 1.25 g/day for each kg of body weight over 10 kilograms.

Typically, TrophAmine is admixed with McGaw 50% or 70% Dextrose Injection USP supplemented with electrolytes and vitamins and administered continuously over a 24 hour period.

Total daily fluid intake should be appropriate for the patient's age and size. A fluid dose of 125 mL per kilogram body weight per day is appropriate for most infants on TPN. Although nitrogen requirements may be higher in severely hypercatabolic or depleted patients, provision of additional nitrogen may not be possible due to fluid intake limits, nitrogen, or glucose intolerance.

Cysteine is considered to be an essential amino acid in infants and young children. An admixture of cysteine hydrochloride to the TPN solution is therefore recommended. Based on clinical studies, the recommended dosage is 1.0 mmole of L-cysteine hydrochloride monohydrate per kilogram of body weight per day.

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 solutions are abruptly discontinued.

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 required for optimum utilization of amino acids. 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 salts to provide bicarbonate precursor. The electrolyte content of TrophAmine® (Amino Acid Injections) must be considered when calculating daily electrolyte intake. Serum electrolytes, including magnesium and phosphorus, should be monitored frequently.

Appropriate vitamins, minerals and trace elements should also be provided.

Side-by-Side Comparison

Reference to McGaw
50% or 70% Dextrose,
USP has been replaced
with reference to
generic 50% or 70%
Dextrose, USP.

All other text is
identical in content to
the reference product
package insert with the
exception of product
name.

Proposed Drug Product Package Insert

Dosage and Administration

The objective of nutritional management of infants and young children is the provision of sufficient amino acid and caloric support for protein synthesis and growth.

The total daily dose of 6% and 10% PremaSol™ - sulfite-free (Amino Acid) Injections 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. Dosage should also be guided by the patient's fluid intake limits and glucose and nitrogen tolerances, as well as by metabolic and clinical response.

Recommendations for allowances of protein in infant nutrition have ranged from 2 to 4 grams of protein per kilogram of body weight per day (2.0 to 4.0 g/kg/day).¹ The recommended dosage of PremaSol™ - sulfite-free (Amino Acid) Injections is 2.0 to 2.5 grams of amino acids per kilogram of body weight per day (2.0 to 2.5 g/kg/day) for infants up to 10 kilograms. For infants and young children larger than 10 kilograms, the total dosage of amino acids should include the 20 to 25 grams/day for the first 10 kg of body weight plus 1.0 to 1.25 g/day for each kg of body weight over 10 kilograms.

Typically, PremaSol™ - sulfite-free (Amino Acid) Injections are admixed with 50% or 70% Dextrose Injection USP supplemented with electrolytes and vitamins and administered continuously over a 24 hour period.

Total daily fluid intake should be appropriate for the patient's age and size. A fluid dose of 125 mL per kilogram body weight per day is appropriate for most infants on TPN. Although nitrogen requirements may be higher in severely hypercatabolic or depleted patients, provision of additional nitrogen may not be possible due to fluid intake limits, nitrogen, or glucose intolerance.

Cysteine is considered to be an essential amino acid in infants and young children. An admixture of cysteine hydrochloride to the TPN solution is therefore recommended. Based on clinical studies, the recommended dosage is 1.0 mmole of L-cysteine hydrochloride monohydrate per kilogram of body weight per day.

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 solutions are abruptly discontinued.

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

The provision of sufficient intracellular electrolytes, principally potassium, magnesium, and phosphate, is required for optimum utilization of amino acids. 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 salts to provide bicarbonate precursor. The electrolyte content of 6% and 10% PremaSol™ - sulfite-free (Amino Acid) Injections must be considered when calculating daily electrolyte intake. Serum electrolytes, including magnesium and phosphorus, should be monitored frequently.

Appropriate vitamins, minerals and trace elements should also be provided.

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Citizen Petition
6% and 10% PremaSol™ – sulfite-free (Amino Acid)
Injections in PL 146® Plastic Container
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Reference Drug Product Package Insert

Central Venous Nutrition. Hypertonic mixtures of amino acids and dextrose may be safely administered by continuous infusion through a central venous catheter with the tip located in the superior vena cava. Initial infusion rates should be slow, and gradually increased to the recommended 60-125 mL per kilogram body weight per day. 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 rate of administration, particularly during the first few days of therapy, is governed 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 determinations of glucose levels in blood and urine.

Peripheral Parenteral Nutrition. For patients in whom the central venous route is not indicated and who can consume adequate calories enterally, TrophAmine may be administered by peripheral vein with or without parenteral carbohydrate calories. Such infusates can be prepared by dilution with McGaw's Sterile Water for Injection or 5%-10% Dextrose Injection to prepare isotonic or slightly hypertonic solutions for peripheral infusion. It is essential that peripheral infusion be accompanied by adequate caloric intake.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

TrophAmine 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.

⁴ Suskind RM: Textbook of Pediatric Nutrition, Raven Press, New York, 1981.

Side-by-Side Comparison

Reference to McGaw
Sterile Water for
Injection or 5-10%
Dextrose Injection has
been replaced with
reference to generic
Sterile Water for
Injection or 5-10%
Dextrose Injection.

All other text is
identical in content to
the reference product
package insert with the
exception of product
name and container
information (e.g.,
"Directions for use of
Viaflex® plastic
Pharmacy Bulk
Package container").
Some text has been
reformatted consistent
with Baxter standard
practice.

Proposed Drug Product Package Insert

Central Venous Nutrition. Hypertonic mixtures of amino acids and dextrose may be safely administered by continuous infusion through a central venous catheter with the tip located in the superior vena cava. Initial infusion rates should be slow, and gradually increased to the recommended 60-125 mL per kilogram of body weight per day. 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 rate of administration, particularly during the first few days of therapy, is governed 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 determinations of glucose levels in blood and urine.

Peripheral Parenteral Nutrition. For patients in whom the central venous route is not indicated and who can consume adequate calories enterally, PremaSol™ - sulfite-free (Amino Acid) injections may be administered by peripheral vein with or without parenteral carbohydrate calories. Such infusates can be prepared by dilution with Sterile Water for Injection or 5% -10% Dextrose Injection to prepare isotonic or slightly hypertonic solutions for peripheral infusion. It is essential that peripheral infusion be accompanied by adequate caloric intake.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

PremaSol™ - sulfite-free (Amino Acid) injections 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.

Parenteral nutrition solutions should be used promptly after mixing. Any storage should be under refrigeration and limited to a brief period of time, preferably less than 24 hours.

Directions for use of Viaflex® plastic Pharmacy Bulk Package container To Open

Tear overpouch across top at slit and remove solution container. Discard overpouch and sachet. Some opacity of the plastic due to moisture absorption during the sterilization process may be observed. This is normal and does not affect the solution quality or safety. The opacity will diminish gradually. Check for minute leaks by squeezing inner bag firmly. If leaks are found, discard solution as sterility may be impaired.

For compounding only, not for direct infusion.

Preparation for Admixing

1. The Pharmacy Bulk Package is to be used only in a suitable work area such as a laminar flow hood (or an equivalent clean air compounding area).

2. Suspend container from eyelet support.

3. Remove plastic protector from outlet port at bottom of container.

4. Attach solution transfer set. Refer to complete directions accompanying set.

Note: The closure shall be penetrated only one time with a suitable sterile transfer device or dispensing set which allows measured dispensing of the contents.

5. Viaflex® containers should not be written on directly since ink migration has not been investigated. Affix accompanying label for date and time of entry.

6. Once container closure has been penetrated, withdrawal of contents should be completed without delay. After initial entry, maintain contents at room temperature (25°C/77°F) and dispense within 4 hours.

⁴ Suskind RM: Textbook of Pediatric Nutrition, Raven Press, New York, 1981.

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Citizen Petition
 6% and 10% PremaSol™ – sulfite-free (Amino Acid)
 Injections in PL 146® Plastic Container
 August 9, 2000

Reference Drug Product Package Insert

HOW SUPPLIED

TrophAmine is supplied sterile and nonpyrogenic in 500 mL glass containers with solid stoppers.

NDC	Cat. No.	Units per Case
TrophAmine (6% Amino Acid Injection) 0264-9361-55	S9361-SS	12
TrophAmine (10% Amino Acid Injection) 0264-9341-55	S9341-SS	6

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.

Caution: Federal (U.S.A.) law prohibits dispensing without prescription.

Revised: February 1998
 U.S. Patent No. 4,491,589

Side-by-Side Comparison

“Rx only” replaced
 “Caution: Federal
 (USA) law prohibits
 dispensing without
 prescription” and is
 located on the first
 page of the proposed
 product insert.

All other text is
 identical in content to
 the reference product
 package insert with the
 exception of
 manufacturer, product
 name, code numbers,
 NDC numbers and
 statements regarding
 use of the container.

Proposed Drug Product Package Insert

How Supplied

6% and 10% PremaSol™ - sulfite-free (Amino Acid) injections are supplied in Vialtec® plastic Pharmacy Bulk Package containers in the following sizes and concentrations:

	500 mL	1000 mL	2000 mL
6%	280011 NDC 0338-1131-03		
10%		280009 NDC 0338-1130-04	280010 NDC 0338-1130-06

Exposure of pharmaceutical products to heat should be minimized. Avoid excessive heat. Protect from freezing. It is recommended the product be stored at room temperature (25°C/77°F). Brief exposure up to 40°C/104°F does not adversely affect the product.

Protect from light until immediately prior to use.

Do not remove container from overpouch until ready to use.

Do not use if overpouch has been previously opened or damaged.

Baxter Healthcare Corporation
 Clintec Nutrition Division
 Deerfield, IL 60015 USA
 Printed in USA

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 07-19-00-443
 Iss. April 2000

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6% and 10% PremaSol™ – sulfite-free (Amino Acid)
Injections in PL 146® Plastic Container
August 9, 2000

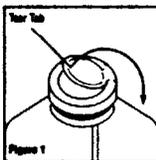
Reference Drug Product Package Insert

Directions for Use of McGraw® Glass Containers

General

Before use, perform the following checks:

1. Inspect each container. Read the label. Ensure solution is the one ordered, is within the expiration date, and that imprint on closure agrees with the label. Check the security of ball 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 sterile latex disk underneath.



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

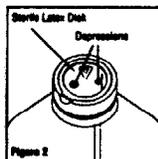
After admixture and during administration, reinspect the solution frequently. If any evidence of solution contamination or instability is found or if the patient exhibits any signs of fever, chills or other reactions not readily explainable, discontinue administration immediately and notify the physician.

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

5. Refer to Directions for Use for the administration set in use.

Products with Air Tube

1. With the sterile latex disk exposed, check for vacuum by confirming the presence of depressions in the latex disk, which should be held tightly over stopper (See Figure 2). If the latex disk is puffed or depressions cannot be seen, the vacuum has dissipated and the bottle should be rejected. The sterile latex disk provides a surface for aseptic medication addition prior to administration.



Note: When vacuum is essential for the use of the product (medication addition or transfer, etc.) the latex disk should be left in place until all additions or transfers are completed.

Medication addition or transfers should be made immediately after exposing the sterile latex disk. Identify three depressions in the latex disk prior to adding medication (See Figure 2): a triangular medication site, one large round outlet port, and one small air-inletting port.

Side-by-Side Comparison

The proposed product's "Directions for Use of Viaflex® Plastic Pharmacy Bulk Package Container" are located immediately prior to the "How Supplied" section.

Proposed Drug Product Package Insert

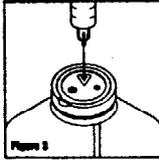
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Citizen Petition
 6% and 10% PremaSol™ – sulfite-free (Amino Acid)
 Injections in PL 146® Plastic Container
 August 9, 2000

Reference Drug Product Package Insert

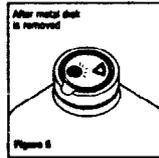
2. Before removing the latex disk, add medication through the triangular (▽) medication site (See Figure 3). The vacuum in the container will automatically draw the contents of a syringe or spiked vial into the container. Each addition/transfer will reduce the vacuum remaining in the bottle.
3. Remove the latex disk prior to inserting administration set. To remove the latex disk, grasp the lip of the disk, lift and pull up and away (See Figure 4). As the disk is lifted, and if no additions have been made, vacuum can be confirmed by an audible hiss.
4. 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.



Products with Solid Stopper

Designed for use with a vented set.

1. 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 5). 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.
2. 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. Refer to Directions for Use of air-inletting administration set to be used.
3. If admixture or set insertion is not performed immediately following removal of protective metal disk, swab stopper surface.



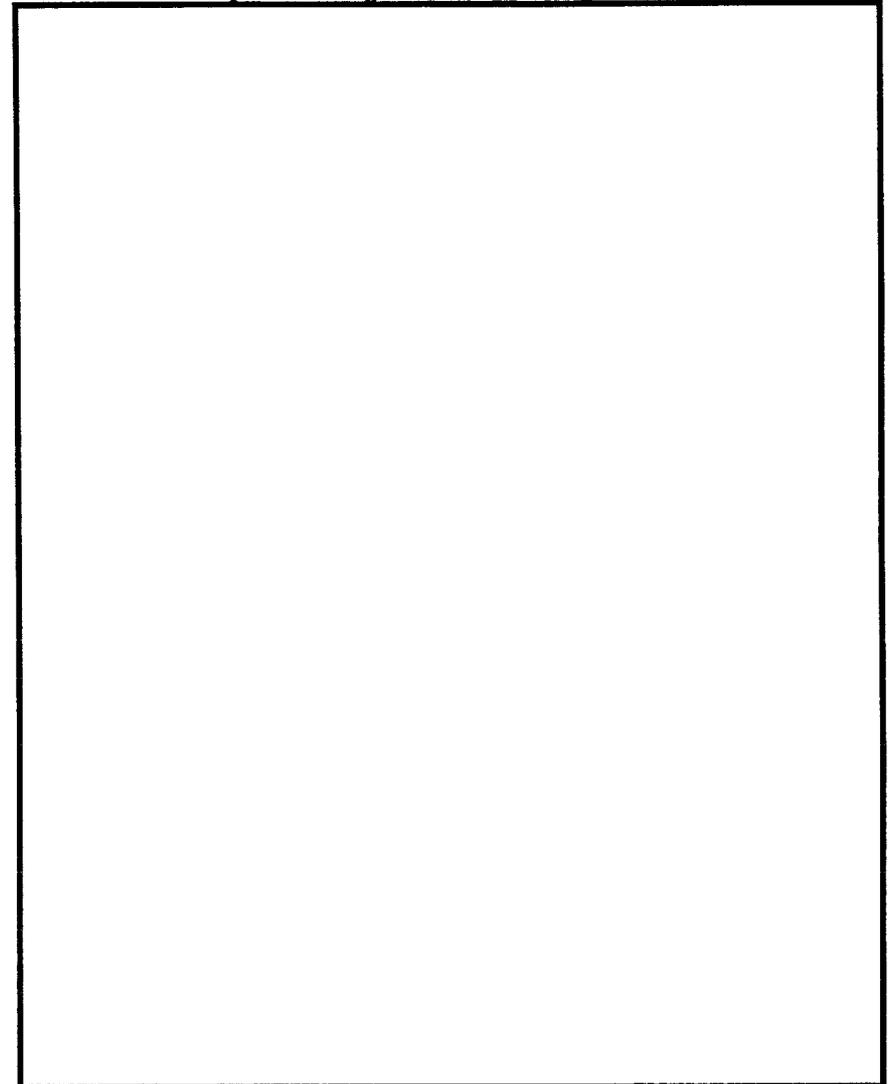
B|BRAUN
 a McGraw

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

Side-by-Side Comparison

Continuation of
 McGaw's "Directions
 for Use of Glass
 Containers."

Proposed Drug Product Package Insert



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