CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20849

FINAL PRINTED LABELING

20% ProSol™ - sulfite-free (Amino Acid) Injection

Pharmacy Bulk Package
Not for Direct Infusion

in Viaflex® Plastic Container

Description

20% ProSol™ - sulfite-free (Amino Acid) Injection is a sterile, nonpyrogenic, hypertonic solution of 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). 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 of 20% ProSol™ - sulfite-free (Amino Acid) Injection contains:

Amino Acids	20.0 g
Total Nitrogen	3.21 g
pH	6.0 (5.5 to 6.5)
(pH adjusted with glacial acetic acid.)	

Essential Amino Acids

Valine - $(CH_3)_2$ CHCH (NH_2) COOH	1.44 g
Lysine (added as Lysine Acetate) - H_2N $(CH_2)_4$ CH (NH_2) COOH	1.35 g
Histidine - $(C_3H_3N_2)$ CH_2CH (NH_2) COOH	1.18 g
Isoleucine - CH_3CH_2CH (CH_3) CH (NH_2) COOH	1.08 g
Leucine - $(CH_3)_2$ $CHCH_2CH$ (NH_2) COOH	1.08 g
Phenylalanine - (C_6H_5) CH_2 CH (NH_2) COOH	1.00 g
Threonine - CH_3CH (OH) CH (NH_2) COOH	980 mg
Methionine - CH_3S $(CH_2)_2$ CH (NH_2) COOH	760 mg
Tryptophan - (C_8H_6N) CH_2CH (NH_2) COOH	320 mg

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Nonessential Amino Acids	
Alanine - $CH_3CH(NH_2)COOH$	2.76 g
Glycine - H_2NCH_2COOH	2.06 g
Arginine - $H_2NC(NH)NH(CH_2)_3CH(NH_2)COOH$	1.96 g
Proline - $[(CH_2)_3NHCH]COOH$	1.34 g
Glutamic Acid - $HOOC(CH_2)_2CH(NH_2)COOH$	1.02 g
Serine - $HOCH_2CH(NH_2)COOH$	1.02 g
Aspartic Acid - $HOOCCH_2CH(NH_2)COOH$	600 mg
Tyrosine - $[C_6H_4(OH)]CH_2CH(NH_2)COOH$	50 mg
Anion profiles per liter*	
Acetate from Lysine Acetate and glacial acetic acid	140 mEq
*Balanced by ions from amino acids.	
Osmolarity (calc.)	1835 mOsmol/L

Clinical Pharmacology

20% ProSol™ - sulfite-free (Amino Acid) Injection administered via central vein, after appropriate dilution, will provide biologically utilizable source material for protein synthesis when used with concentrated calorie sources (such as hypertonic dextrose and/or fat emulsion), electrolytes, vitamins and minerals. Administered peripherally after appropriate dilution or with minimal calorie supplementation (such as 5% dextrose), it enhances the conservation of body protein.

Indications and Usage

20% ProSol™ - sulfite-free (Amino Acid) Injection is indicated as an adjunct in the offsetting of nitrogen loss or in the treatment of negative nitrogen balance in patients where: (1) the alimentary tract cannot or should not be used, (2) gastrointestinal absorption of protein is impaired, or (3) metabolic requirements for protein are substantially increased, as with extensive burns. 20% ProSol™ - sulfite-free (Amino Acid) Injection can be used to reduce fluid intake in patients who require both fluid restriction and total parenteral nutrition (TPN). 20% ProSol™ - sulfite-free (Amino Acid) Injection is intended to be dosed on the basis of grams of amino acids/kg body weight/day. Therefore, this more concentrated amino acid solution provides the same nutritional value (grams of total amino acids) as in a more dilute form, but with the opportunity to limit fluid intake.

Central Vein Administration: 20% ProSol™ - sulfite-free (Amino Acid) Injection is intended for use in a pharmacy admixture program and as such is restricted to the preparation of admixtures for intravenous use. Central vein infusion should be considered when amino acid solutions are to be admixed with hypertonic dextrose to promote protein synthesis such as for hypercatabolic or depleted patients or those requiring long term parenteral nutrition. **20% ProSol™ - sulfite-free (Amino Acid) Injection should never be administered undiluted.**

Peripheral Vein Administration: For patients in whom the central vein route is not indicated, amino acid solutions diluted with low dextrose concentrations may be infused by peripheral vein with or without supplemented fat emulsion. Because of the high osmolarity of 20% ProSol™ - sulfite-free (Amino Acid) Injection (1835 mOsmol/L), peripheral vein administration should be limited to dilutions below twice normal serum osmolarity (718 mOsmol/L). **20% ProSol™ - sulfite-free (Amino Acid) Injection should never be administered by peripheral vein undiluted.**

Protein-Sparing: Dilute amino acid solutions for **peripheral administration** may be used in patients who exhibit no clinically significant protein malnutrition. The purpose of the solution is to replace protein losses which occur in relation to an intercurrent phenomenon which is known or suspected to be productive of a protein loss condition for a short or moderate period of time. Protein-sparing can be achieved by peripheral infusion of dilute amino acid solutions with or without dextrose. 20% ProSol™ - sulfite-free (Amino Acid) Injection must be diluted below twice normal serum osmolarity (718 mOsmol/L).

Contraindications

Hypersensitivity to one or more amino acids

Severe liver disease or hepatic coma

Anuria

Warnings

This injection is for compounding only, not for direct infusion.

Additives may be incompatible. Consult with pharmacist, if available. When introducing additives, use aseptic techniques. Mix thoroughly. Do not store.

Because of the potential for life-threatening events, caution should be taken to ensure that precipitates have not formed in any parenteral nutrient admixture.

Caution should be exercised when admixing 20% ProSol™ - sulfite-free (Amino Acid) Injection. This solution should be used promptly after admixing. Any storage should be under refrigeration and limited to a brief period of time, preferably less than 24 hours. Reference should be made to I.V. Fat Emulsion package insert and high concentration dextrose injection from Baxter Healthcare Corporation package insert for detailed information on each component.

Proper administration of this injection requires a knowledge of fluid and electrolyte balance and nutrition as well as clinical expertise in recognition and treatment of the complications which may occur.

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

Hyperammonemia is of **special significance in infants.** This reaction appears to be related to a deficiency of the urea cycle amino acids of genetic or product origin. It is essential that blood ammonia be measured frequently in infants.

Conservative doses of this injection should be given to patients with known or suspected hepatic dysfunction. Should symptoms of hyperammonemia develop, administration should be discontinued and the patient's clinical status reevaluated.

Administration of amino acid solutions in the presence of impaired renal function presents special issues associated with retention of electrolytes.

This injection should not be administered simultaneously with blood through the same infusion set because of the possibility of pseudoagglutination.

Administration by central venous catheter should be used only by those familiar with this technique and its complications.

Precautions

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20% ProSol™ - sulfite-free (Amino Acid) Injection is a highly concentrated amino acid solution used for the preparation of sterile total parenteral nutrition admixtures (see **Dosage and Administration**). Some of the amino acids in 20% ProSol™ - sulfite-free (Amino Acid) Injection are close to their limit of solubility, and, as such, a small number of amino acid crystals may form upon storage. If amino acid crystals are present, they will re-dissolve upon dilution during admixture compounding. Do not use unless admixture is free of visible particulate. Use of a final filter is recommended during administration of all parenteral solutions where possible.

It is essential to provide adequate calories concurrently if parenterally administered amino acids are to be retained by the body and utilized for protein synthesis. Concentrated dextrose solutions are an effective source of such calories.

With the administration of 20% ProSol™ - sulfite-free (Amino Acid) Injection in combination with highly concentrated dextrose solutions, hyperglycemia, glycosuria and hyperosmolar syndrome may result. Blood and urine glucose should be monitored on a routine basis in patients receiving this therapy.

Sudden cessation in administration of a concentrated dextrose solution may result in insulin reaction due to high levels of endogenous insulin. Parenteral nutrition mixtures should be withdrawn slowly.

The metabolizable acetate anion and amino acid profile in this injection were designed to minimize or prevent occurrences of hyperchloremic metabolic acidosis and hyperammonemia. However, the physician should be aware of appropriate countermeasures if they become necessary.

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

Because of its antianabolic activity, concurrent administration of tetracycline may reduce the protein-sparing effect of infused amino acids.

Care should be taken to avoid excess fluid accumulation, particularly in patients with renal disease, pulmonary insufficiency and heart disease.

During protein-sparing therapy in the absence of supporting carbohydrate metabolism, an accumulation of ketone bodies in the blood often occurs. Correction of ketonemia usually can be accomplished by administering some carbohydrates.

Protein-sparing therapy is useful for periods up to 10 to 12 days. Patients requiring nutritional support thereafter should be placed on oral or parenteral regimens that employ adequate nonprotein calorie components.

20% ProSol™ - sulfite-free (Amino Acid) Injection is not intended for direct infusion, and, as such, should never be administered undiluted.

Laboratory Tests

Frequent clinical evaluation and laboratory determinations are necessary for proper monitoring during administration.
Laboratory tests should include blood glucose, serum electrolytes, liver and kidney function, serum osmolarity, blood ammonia, serum protein, pH, hematocrit, WBC and urinary glucose. When 20% ProSol™ - sulfite-free (Amino Acid) Injection is combined with electrolytes, care should be used in administering this solution to patients with congestive heart failure, renal failure, edema, adrenal hyperactivity, acid base imbalance and those receiving diuretics or antihypertensive therapy. Serum electrolytes should be monitored daily. When 20% ProSol™ - sulfite-free (Amino Acid) Injection is infused without adequate non-protein calories, monitoring of BUN is required.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies with 20% ProSol™ - sulfite-free (Amino Acid) Injection have not been performed to evaluate carcinogenic potential, mutagenic potential, or effects on fertility.

Pregnancy: Teratogenic Effects
Pregnancy Category C. Animal reproduction studies have not been conducted with 20% ProSol™ - sulfite-free (Amino Acid) Injection. It is also not known whether 20% ProSol™ - sulfite-free (Amino Acid) Injection can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. 20% ProSol™ - sulfite-free (Amino Acid) Injection should be given to a pregnant woman only if clearly needed.

Nursing Mothers: Caution should be exercised when 20% ProSol™ - sulfite-free (Amino Acid) Injection is administered to a nursing woman.

Pediatric Use: Safety and effectiveness of 20% ProSol™ - sulfite-free (Amino Acid) Injection in pediatric patients have not been established.

Special Precautions

Administration of 20% ProSol™ - sulfite-free (Amino Acid) Injection and other nutrients via central or peripheral venous catheter may be associated with complications which can be prevented or minimized by careful attention to all aspects of the procedure. This includes attention to 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. The physician should be fully acquainted with various techniques of catheter insertion as well as recognition and treatment of complications. For details of techniques and placement site 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, cardiac arrhythmia and catheter embolus.

Septic: The constant risk of sepsis is present during administration of parenteral nutrition solution. Since contaminated solutions and infusion catheters are potential sources of infection, it is imperative that the preparation of the solution and the placement and care of catheters be accomplished under controlled aseptic conditions. If fever develops, the solution, its delivery system and the site of the indwelling catheter should be changed.

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

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

Adverse Reactions

See **Warnings, Precautions** and **Special Precautions**

Infusion of any hypertonic solution can result in local inflammatory reactions. Policies and procedures should be established for the recognition and management of such reactions.

Overdosage

In the event of overhydration or solute overload, re-evaluate the patient and institute appropriate corrective measures. See **Contraindications** and **Warnings**

Dosage and Administration

If a patient is unable to take enteral nourishment for a prolonged period of time, institution of total parenteral nutrition (TPN) with exogenous calories should be considered.

The total daily dose of 20% ProSol™ - sulfite-free (Amino Acid) Injection depends on the patient's metabolic requirement 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 nitrogen requirements.

Recommended Dietary Allowances* of protein range from approximately 0.75 g/kg of body weight for adults to 1.68 g/kg for infants. It must be recognized, however, that protein as well as caloric requirements in traumatized or malnourished patients may be increased substantially. 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.

For the initial treatment of trauma or protein calorie malnutrition, higher doses of protein with corresponding quantities of carbohydrate may be necessary to promote adequate patient response to therapy. The severity of the illness being treated is the primary consideration in determining proper dose level. Such higher doses, especially in infants, must be accompanied by more 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 reduce nitrogen losses and spare body protein. If daily increases in BUN in the range of 10 to 15mg% for more than three days should occur, then protein-sparing therapy should be discontinued and a regimen with full nonprotein calorie substrates should be adopted.

Care should be exercised to insure the maintenance of proper levels of serum potassium. Quantities of 60 to 180 mEq of potassium per day have been used with adequate clinical effect. It may be necessary to add quantities of this electrolyte to this injection, depending primarily on the amount of carbohydrate administered to and metabolized by the patient.

Total daily fluid requirements can be met beyond the volume of amino acid solutions by supplementing with noncarbohydrate or carbohydrate-containing electrolyte solutions.

Maintenance vitamins, additional electrolytes and trace elements should be administered as required.

Fat emulsion coadministration should be considered when prolonged parenteral nutrition (more than 5 days) 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 total parenteral nutrition. Caution should be exercised in administering fat emulsions to patients with severe liver damage, pulmonary disease, anemia or blood coagulation disorders, or when there is danger of fat embolism.

Fat emulsion admixed into total parenteral formula may obscure the presence of precipitate formation.

Central Vein Administration: Hypertonic mixtures of amino acids and dextrose may be administered safely by continuous infusion through a central venous catheter with the tip located in the vena cava. In addition to meeting nitrogen needs, the administration rate is governed, especially during the first few days of therapy, by the

patient's tolerance to dextrose. Daily intake of amino acids and dextrose should be increased gradually to the maximum required dose as indicated by frequent determinations of urine and blood sugar levels.

In many patients, provision of adequate calories in the form ofhypertonic dextrose may require the administration of exogenous insulin to prevent hyperglycemia and glycosuria.

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. Sudden cessation in administration of a concentrated dextrose solution may result in insulin reaction due to high levels of endogenous insulin. Such solutions should be withdrawn slowly.

Peripheral Vein Administration: In patients requiring parenteral nutrition for whom the central vein route is not indicated, this injection can be mixed with low concentration dextrose solutions and administered by peripheral vein with or without fat emulsion.

Intravenous fat emulsion provides approximately 1.1 kcal/mL (10%) or 2.0 kcal/mL (20%) and may be administered along with amino acid-dextrose solutions by means of a short Y-connector near the infusion site to supplement caloric intake. Fat, however, should not be the sole caloric intake since studies have indicated that glucose is more nitrogen sparing in the stressed patient.

Protein-Sparing: For well nourished patients who require short-termparenteral support, this injection can be administered peripherally with or without carbohydrate calories. Such infusates can be prepared by dilution of this injection with 5% Dextrose Injection and/or Sterile Water for Injection to prepare solutions which may be administered by peripheral vein, not to exceed twice normal serumosmolarity.

Depending upon the clinical condition of the patient, approximately 3 liters of solution may be administered per 24 hour period. When usedpostoperatively, the therapy should begin with 1000 mL the first postoperative day. Thereafter, the dose may be increased to 3000 mL per day.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Use of a final filter is recommended during administration of allparenteral solutions where possible. Filters of less than 1.2 microns pore size must not be used with admixtures containing fat emulsions.

A slight yellow color does not alter the quality and efficacy of the product.

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

20% ProSol™ - sulfite-free (Amino Acid) Injection in the Pharmacy Bulk Package is intended for use in the preparatión of sterile, intravenous admixtures. Additives may be incompatible with the fluid withdrawn from this container. Complete information is not available. Those additives known to be incompatible should not be used. Consult with pharmacist, if available. When compounding admixtures, use aseptic technique. Mix thoroughly. Do not store any unused portion of 20% ProSol™ - sulfite-free (Amino Acid) Injection.

Any storage of admixtures should be under refrigeration and limited to a brief period of time, preferably less than 24 hours.

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Directions for Use of Viaflex® plastic Pharmacy Bulk Package container

To Open

Tear overpouch down side at slit and remove solution container. 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.**

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How Supplied

20% ProSol™ - sulfite-free (Amino Acid) Injection is supplied in Pharmacy Bulk Package containers in the following sizes:

2B6183	500 mL	NDC 0338-0499-03
2B6184	1000 mL	NDC 0338-0499-04
2B6186	2000 mL	NDC 0338-0499-06

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.

Do not remove container from overpouch until ready to use.

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

*Food and Nutrition Board National Academy of Sciences - National Research Council (Revised 1989)

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