Important Prescribing Information

November 30, 2017

Subject: Temporary importation of intravenous drug products to address drug shortages

Dear Healthcare Professional,

In order to address shortages of critical drug products from the aftermath of Hurricane Maria, Baxter Healthcare Corporation (Baxter) is coordinating with the U.S. Food and Drug Administration (FDA) to increase the availability of products from Baxter's manufacturing facility in Italy.

Baxter has initiated temporary importation of Primene 10% Solution for Infusion, 250 mL, in glass container, which contains amino acids and is indicated for use in children, infants, and neonates. This product is manufactured by Baxter's manufacturing facility in Italy and marketed in Europe. At this time, no other entity except Baxter is authorized by the FDA to import or distribute these products in the United States. FDA has not approved the product manufactured by Baxter's manufacturing facility in Italy.

Effective immediately, and during this temporary period, Baxter will offer the following:

Product name and description	Size	Product code	Pack factor	NDC
Primene 10% Solution for Infusion in glass container	250 mL	FCA3CG133R79D	10	0338-9577-10

It is also important to note the following:

- **Primene 10% Solution for Infusion** contains a different amino acid composition than amino acid solutions for pediatric patients marketed in the U.S. Primene 10% Solution for Infusion is sulfite-free. Please refer to the product comparison table at the end of this letter. **Primene 10% Solution for Infusion** contains L-Cysteine 0.189 g/100 mL as compared to 10% Premasol Sulfite-free (Amino Acid) Injection (<0.016 g/100 mL) and 6% Premasol Sulfite-free (Amino Acid) Injection (<0.014 g/100 mL). Consider this difference when adding additional L-Cysteine to the final parenteral nutrition solution.

- **Primene 10% Solution for Infusion** is packaged in a Type II Glass Bottle with an elastomeric stopper**.** Prior to use, it is important to visually inspect the container. Only use if the container is undamaged and the solution is clear. Discard if the container is leaking or if the solution is discolored, cloudy or contains a precipitate. Aseptic conditions must be observed throughout the preparation and use of Primene 10% Solution for Infusion. For single use only. Protect from light

- **This product has not been tested for aluminum content and this should be taken into consideration, especially when administering to preterm infants, term infants less than 1 month of age, or patients with renal impairment.**

- **Administration of solution**: **The use of a final filter is required during administration of all formulations** containing Primene and trace elements (including copper, iron, or zinc) for removal of visible particulate matter which has been observed in the infusion line for some formulations.

    - For 2-in-1 (amino acid and carbohydrate) parenteral nutrition solutions, **use a 0.2 micron filter** for removal of particulate matter that may be formed with the use of trace elements (e.g. copper).

    - For 3-in-1 (lipid, amino acid, and carbohydrate) parenteral nutrition solutions, use a **1.2 micron filter** for particulate matter removal.

  Perform visual inspections for cloudiness or precipitation of the TPN solution after compounding, prior to administration and periodically during administration. If discoloration or precipitation is noted in the filter, perform blood levels of copper (or other trace elements) where medically relevant.

- **The barcode may not register accurately on the U.S. scanning systems.** Institutions should manually input the product into their systems and confirm that barcode systems do not provide incorrect information when the product is scanned. Alternative procedures should be followed to assure that the correct drug product is being used and administered to individual patients.

There are some key differences in the labeling between the US FDA approved product 6% and 10% Premasol-Sulfite-free (Amino Acid) Injections and Primene 10% Solution for Infusion. Please see the product comparison table at the end of this letter.

Please refer to the FDA-approved package insert for the full prescribing information of 6% and 10% Premasol-Sulfite-free (Amino Acid) Injections in VIAFLEX Plastic Container at: https://www.dailymed.nlm.nih.gov/dailymed/getFile.cfm?setid=9afdcc3e-0d06-47f4-86ca-40da48b2b02b&type=pdf&name=9afdcc3e-0d06-47f4-86ca-40da48b2b02b

If you have any questions about the information contained in this letter or the use of the imported products, please contact Baxter's Medical Information Service at 1-800-933-0303.

To place an order, please contact Baxter's Center for Service by calling 1-888-229-0001.

To report product quality issues, please contact Baxter Product Surveillance at 1-800-437-5176. To report adverse events associated with these imported products, please call Baxter at 1-866-888-2472, or fax: 1-800-759-1801. Adverse events or quality problems experienced with the use of this product may also be reported to the FDA's MedWatch Adverse Event Reporting program either online, by regular mail or by fax:

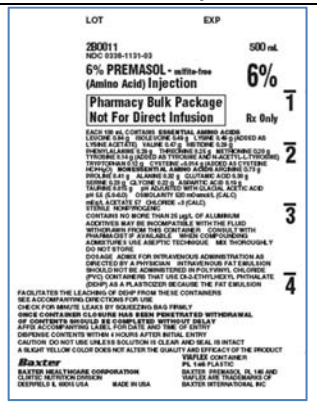
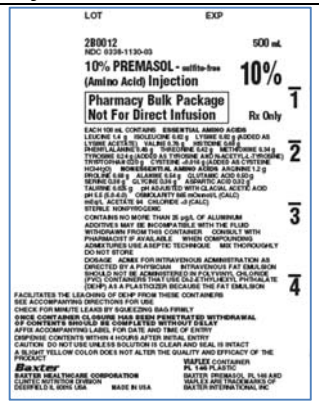
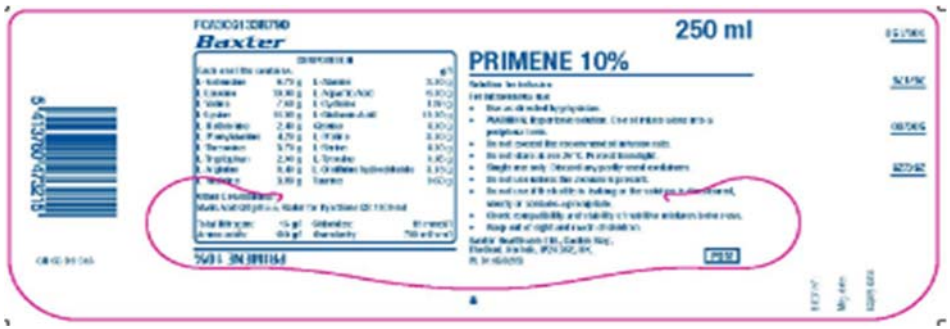
- Complete and submit the report **Online**: www.fda.gov/medwatch/report.htm
- **Regular mail or Fax**: Download form www.fda.gov/MedWatch/getforms.htm or call 1-800-332-1088 to request a reporting form, then complete and return to the address on the pre-addressed form, or submit by fax to 1-800-FDA-0178.

Sincerely,

Dennis Vaughn
Vice President, Marketing Operations

Baxter Healthcare Corporation

Product Comparison Table: Key differences in 6% and 10% Premasol – Sulfite-free Injection and Primene 10% Solution for Infusion

	US FDA Approved Product		Import Product
	6% and 10% PREMASOL – sulfite-free (Amino Acid) Injection		**Primene 10% Solution for Infusion (glass bottle)**
			Please see page 8 for a larger image 
	6% PREMASOL – sulfite-free (Amino Acid) Injection	**10% PREMASOL – sulfite-free (Amino Acid) Injection**	**Primene 10% Solution for Infusion**
Composition and Ingredients	Each 100 mL contains: **Essential Amino Acids** L-Leucine, USP 0.84 g L-Isoleucine, USP 0.49 g L-Lysine 0.49 g (as Lysine Acetate, USP) L-Valine, USP 0.47 g L-Histidine, USP 0.29 g L-Phenylalanine,USP 0.29 g L-Threonine, USP 0.25 g L-Methionine, USP 0.20 g L-Tyrosine 0.14 g (added as Tyrosine, and N-Acetyl Tyrosine, USP) L-Tryptophan, USP 0.12 g L-Cysteine <0.014 g (Added as Cysteine $HCl.H_2O$, USP) **Nonessential Amino Acids** L-Arginine, USP 0.73 g L-Proline, USP 0.41 g L-Alanine, USP 0.32 g L-Glutamic Acid, USP 0.30 g L-Serine, USP 0.23 g Glycine, USP 0.22 g L-Aspartic Acid, USP 0.19 g Taurine, USP 0.015 g USP = United States Pharmacopoeia	Each 100 mL contains: **Essential Amino Acids** L-Leucine, USP 1.4 g L-Isoleucine, USP 0.82 g L-Lysine 0.82 g (as Lysine Acetate, USP) L-Valine, USP 0.78 g L-Histidine, USP 0.48 g L-Phenylalanine, USP 0.48 g L-Threonine, USP, 0.42 g L-Methionine, USP 0.34 g L-Tyrosine 0.24 g (added as Tyrosine, and N-Acetyl-L-Tyrosine, USP) L-Tryptophan, USP 0.20 g L-Cysteine <0.016 g (Added as Cysteine $HCl.H_2O$, USP) **Nonessential Amino Acids** L-Arginine, USP 1.2 g L-Proline, USP 0.68 g L-Alanine, USP 0.54 g L-Glutamic Acid, USP 0.50 g L-Serine, USP 0.38 g Glycine, USP 0.36 g L-Aspartic Acid, USP 0.32 g Taurine, USP 0.025 g USP = United States Pharmacopoeia	Each 100 mL contains: L-Leucine, Ph. Eur. 1.00 g L-Isoleucine, Ph. Eur. 0.67 g L-Lysine, Ph. Eur. 1.10 g L-Valine, Ph. Eur 0.76 g L-Histidine, Ph. Eur. 0.38 g L-Phenylalanine, Ph. Eur 0.42 g L-Threonine, Ph. Eur. 0.37 g L-Methionine, Ph. Eur. 0.24 g L-Tyrosine, Ph. Eur. 0.045 g L-Tryptophan, Ph. Eur. 0.20 g L-Cysteine, D.A.B. 0.189 g L-Arginine, Ph. Eur. 0.84 g L-Proline, Ph. Eur. 0.30 g L-Alanine, Ph. Eur. 0.80 g L-Glutamic Acid, Ph. Eur. 1.00 g L-Serine, Ph. Eur. 0.40 g Glycine, Ph. Eur. 0.40 g L-Aspartic Acid, Ph. Eur. 0.60 g Taurine, USP 0.06 g L-Ornithine Hydrochloride, D.A.B. 0.318 g Ph.Eur.= European Pharmacopoeia; D.A.B = German Pharmacopoeia
Additional Information	Total Amino Acids 6 (grams/100 mL) (Calc.) Total Nitrogen 0.93 (grams/100 mL) (Calc.)	Total Amino Acids 10 (grams/100 mL) (Calc.) Total Nitrogen 1.55 (grams/100 mL) (Calc.)	Total Nitrogen 15 g/L Amino Acids 100 g/L
	Acetate (provided as acetic acid and lysine acetate) 57mEq/L; Chloride (Calc.) <3mEq/L PREMASOL - sulfite-free (Amino Acid) Injections contain no added phosphorus.	Acetate (provided as acetic acid and lysine acetate) 94mEq/L; Chloride (Calc.) <3mEq/L PREMASOL - sulfite-free (Amino Acid) Injections contain no added phosphorus.	Chlorides 19 mmol/L (For monovalent ions, such as sodium and chloride, the numeric value of the millimole and milliequivalent are identical.)
	pH 5.5(5.0-6.0) adjusted with glacial acetic acid Osmolarity 520 (mOsmol/L) (Calc.)	pH 5.5(5.0-6.0) adjusted with glacial acetic acid Osmolarity 865 (mOsmol/L) (Calc.)	Malic Acid QS pH 5.5 Osmolarity 780 mOsm/L Water For Injection QS 1000 mL
Description	PREMASOL - sulfite-free (Amino Acid) Injections are sterile, non-pyrogenic, hypertonic solutions containing crystalline amino acids provided in a Pharmacy Bulk Package.The finished drug product is packaged in the single port VIAFLEX (PL146) polyvinyl chloride (PVC) container closure system.		Primene 10% Solution for Infusion is a Sterile solution which contains amino acids, packaged in type II glass bottle container with nominal container size of 250 mL
Indications for Use	PREMASOL - sulfite-free (Amino Acid) Injections are 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 PREMASOL - sulfite-free (Amino Acid) Injections 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.		Primene 10% is indicated in 1) children and infants 2) neonates, at term or premature, of normal or low birth weight when oral or enteral nutrition is impossible, insufficient or contraindicated.

	US FDA Approved Product	Import Product
	6% and 10% PREMASOL – sulfite-free (Amino Acid) Injection	**Primene 10% Solution for Infusion (glass bottle)**
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).4 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 co-administration 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. **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. A slight yellow color does not alter the quality and efficacy of the product. 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.	Parenteral nutrition initiation and duration as well as dosage (dose and rate of administration) depends on a patient's • age, weight, clinical condition, • nitrogen requirements, • ability to metabolize the constituents of Primene, • additional nutrition that may be provided parenterally and/or enterally. The usual range is: 1.5 – 3.5 g amino-acids/kg/24 hours 0.230 – 0.53 g nitrogen/kg/24 hours 15 – 35 ml of Primene 10%/kg/24 hours The infusion rate should not exceed 0.05ml/kg/min. Recommended flow rates: Neonates and Infants: continuous infusion (over 24 hours). Children: continuous infusion (over 24 hours) or cyclic infusion (over about 12 hours in 24). The flow rate should be adjusted according to the dosage, the characteristics of the infusion solution, the total volume intake per 24 hours and the infusion duration. The flow rate should be increased gradually during the first hour. Method of administration: Primene is intended for intravenous use. Primene is not intended for fluid or volume replacement. Primene 10% is usually administered with a source of energy appropriate for the needs of the child, either by co-administration or as a mixture. Primene 10% may be included in the composition of nutritive mixtures combining carbohydrates, lipids, electrolytes, trace elements and vitamins to meet nutrient needs and prevent deficiencies and complications from developing, when compatibility and stability are known. Primene 10% alone should be administered in a central vein. Primene 10% in co-administration or as a mixture should be administered according to the final osmolarity of the solution infused, in a peripheral or central vein. The osmolarity of a specific infusion solution must be taken into account when peripheral administration is considered. Strongly hypertonic parenteral nutrition solutions (>900 mOsm/L) should be administered through a central venous catheter with the tip located in a large central vein. If deemed appropriate by the healthcare professional, parenteral nutrition solution may be administered peripherally in patients of all ages if the osmolarity of the formulation is ≤ 900 mOsm/L Visually inspect the container. Only use if the container is undamaged and the solution is clear. Discard if the container is leaking or if the solution is discoloured, cloudy or contains a precipitate. Aseptic conditions must be observed throughout the preparation and use of Primene 10%. For single use only. If additions are made to the container: Ensure stability and compatibility of additives. Consult with pharmacist. Prepare the injection site of the container as appropriate. Puncture the injection site and inject the additives using an injection needle or a reconstitution device/transfer set, as appropriate. Mix content of the container and the additives thoroughly. Inspect final solution for discoloration and particulate matter. Confirm the integrity of the container. Only use if the container is undamaged and the solution is clear. Any unused portion of Primene should be discarded and should not be used for subsequent admixing. Ensure proper storage requirements of additives are followed. Administration of the infusion: Allow the solution to reach room temperature before use. The **use of a final filter is required** during administration of all formulations containing Primene and trace elements (including copper, iron, or zinc) for removal of visible particulate matter which has been observed in the infusion line for some formulations. For 2 in 1 (amino acid and carbohydrate) parenteral nutrition solutions, **use a 0.2 micron filter** for removal of particulate matter that may be formed with the use of trace elements (e.g. copper). For 3 in 1 (lipid, amino acid, and carbohydrate) parenteral nutrition solutions**, use a 1.2 micron filter** for particulate matter removal. Perform visual inspections for cloudiness or precipitation of the TPN solution, infusion set, catheter and in-line filter after compounding, prior to administration and periodically during administration. If discolouration or precipitation is noted in the filter, perform blood levels of copper (or other trace elements) where medically relevant. Discard any unused contents. Do not reconnect any partially used container. Do not connect containers in series in order to avoid air embolism due to possible residual air in the primary container. Primene must not be infused through the same tubing with blood or blood components unless there is documentation that it is safe. Attach administration set. Refer to 'Instructions for Use' accompanying the set Additives may be incompatible. Do not add other medicinal products or substances without first confirming their compatibility and the stability of the resulting preparation. Excessive addition of calcium and phosphate increases the risk of the formation of calcium phosphate precipitates. The addition of trace elements may cause formation of visible particulate matter.

	US FDA Approved Product	Import Product
	6% and 10% PREMASOL – sulfite-free (Amino Acid) Injection	**Primene 10% Solution for Infusion (glass bottle)**
Contraindications	6% and 10% PREMASOL - sulfite-free (Amino Acid) Injections are 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.	Primene is contraindicated in patients with: • hypersensitivity to any of the active substances or to any of the excipients . • congenital abnormality of amino acid metabolism.
Warnings and Precautions	**See manufacturers full prescribing information for warning and precautions** **Warnings: This injection is for compounding only, not for direct infusion.** 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.** Administration of amino acids in the presence of impaired renal function or gastrointestinal bleeding may augment an already elevated blood urea nitrogen. Administration of intravenous solutions can cause fluid and/or solute overload resulting in dilution of serum electrolyte concentrations, overhydration, congested states, or pulmonary edema. 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. WARNING: This product contains aluminum that may be toxic. Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. **See manufacturers full prescribing information for warnings and precautions** **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. 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 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. PREMASOL - sulfite-free (Amino Acid) Injections contain less than 3 mEq chloride per liter. 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. Drug product contains no more than 25 μg/L of aluminum. **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. **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.	***Allergic Reactions / Hypersensitivity Reactions*** Anaphylactic/anaphylactoid reactions and other hypersensitivity/infusion reactions have been reported with amino acid solutions administered as a component of parenteral nutrition. The infusion must be stopped immediately if any signs or symptoms of a reaction develop. ***Precipitates in Patients Receiving Parenteral Nutrition*** Pulmonary vascular precipitates have been reported in patients receiving parenteral nutrition. In some cases, fatal outcomes have occurred. Excessive addition of calcium and phosphate increases the risk of the formation of calcium phosphate precipitates. Precipitates have been reported even in the absence of phosphate salt in the solution. Precipitation distal to the in line filter and suspected in vivo precipitate formation has also been reported. If signs of pulmonary distress occur, the infusion should be stopped and medical evaluation initiated. In addition to inspection of the solution, the infusion set and catheter should also periodically be checked for precipitates. ***Infectious complications*** Infection and sepsis may occur as a result of intravenous catheters used to administer parenteral formulations, poor maintenance of catheters or contaminated solutions. Immunosuppression and other factors such as hyperglycaemia, malnutrition and/or their underlying disease state may predispose patients to infectious complications. Careful symptomatic and laboratory monitoring for fever/chills, leukocytosis, technical complications with the access device, and hyperglycaemia can help recognize early infections. The occurrence of septic complications can be decreased with heightened emphasis on aseptic technique in catheter placement, maintenance, as well as aseptic technique in nutritional formula preparation. ***Refeeding Syndrome in Patients Receiving Parenteral Nutrition*** Refeeding severely undernourished patients may result in the refeeding syndrome that is characterized by the shift of potassium, phosphorus, and magnesium intracellularly as the patient becomes anabolic. Thiamine deficiency and fluid retention may also develop. Careful monitoring and slowly increasing nutrient intakes while avoiding overfeeding can prevent these complications. ***Hypertonic solutions*** Hypertonic infusion solutions may cause irritation of the vein, vein damage, and thrombosis when administered into a peripheral vein. In view of its osmolality, Primene 10% should not be infused alone into a peripheral vein. ***General Monitoring*** Monitoring should be appropriate to the patient's clinical situation and condition, and should include determinations of water and electrolyte balance, serum osmolarity, acid/base balance, blood glucose levels, blood ammonia levels, and liver and kidney function. ***Metabolic Effects*** Metabolic complications may occur if the nutrient intake is not adapted to the patient's requirements, or the metabolic capacity of any given dietary component is not accurately assessed. Adverse metabolic effects may arise from administration of inadequate or excessive nutrients or from inappropriate composition of an admixture for a particular patient's needs. ***Hepatic function*** Patients on parenteral nutrition may experience hepatic complications (including cholestasis, hepatic steatosis, fibrosis and cirrhosis, possibly leading to hepatic failure, as well as cholecystitis and cholelithiasis) and should be monitored accordingly. The etiology of these disorders is thought to be multifactorial and may differ between patients. Patients developing abnormal laboratory parameters or other signs of hepatobiliary disorders should be assessed by a clinician knowledgeable in liver diseases in order to identify possible causative and contributory factors, and possible therapeutic and prophylactic interventions. Amino acid solutions should be used with caution in patients with pre-existing liver disease or liver insufficiency. Liver function parameters should be closely monitored in these patients, and they should be monitored for possible symptoms of hyperammonaemia. Increase in blood ammonia levels and hyperammonaemia may occur in patients receiving amino acid solutions. In some patients this may indicate the presence of a congenital disorder of amino acid metabolism or hepatic insufficiency. Blood ammonia should be measured frequently in newborns and infants to detect hyperammonaemia. Depending on extent and etiology, hyperammonaemia may require immediate intervention. ***Renal effects*** Azotaemia has been reported with parenteral administration of solutions containing amino acids, and may occur in particular in the presence of renal impairment. Use with caution in patients with renal insufficiency (with e.g., uraemia). Nitrogen tolerance may be altered and dosage may have to be adjusted. Fluid and electrolyte status should be closely monitored in these patients. ***Additional precautions*** • Infusion site reactions have occurred with the use of parenteral nutrition. They include infusion site thrombophlebitis and venous irritation, as well as severe reactions (with, e.g., necrosis and blistering) when associated with extravasation. Patients should be monitored accordingly. • Severe water and electrolyte disorders, severe fluid overload states, and severe metabolic disorders should be corrected before starting the infusion. • Use with caution in patients with pulmonary oedema or heart failure. Fluid status should be closely monitored.

	US FDA Approved Product 6% and 10% PREMASOL – sulfite-free (Amino Acid) Injection	Import Product Primene 10% Solution for Infusion (glass bottle)
	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 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.	**Interaction with other medicinal products and other forms of interaction** No interaction studies have been performed. The compatibility and stability of nutritive mixtures should be confirmed before administration. **Fertility, pregnancy and lactation** There are no adequate data from the use of Primene in pregnant or lactating women. Healthcare Professionals should carefully consider the potential risks and benefits for each specific patient before administering Primene. **Effects on ability to drive and use machines** There is no information of the effects of Primene on the ability to drive or operate other heavy machinery.
Adverse Events	**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.	The adverse reactions listed below have been identified from post-marketing reports of Primene administered as a component of parenteral nutrition. The frequency of the adverse drug reactions listed in this section cannot be estimated from the available data. **Tabulated summary of adverse reactions** **System Organ Class (SOC)** / **Preferred MedDRA Term** / **frequency** IMMUNE SYSTEM DISORDERS / Hypersensitivity reaction manifested by: • Face oedema • Eyelid oedema • Rash / Not known • Adverse reactions reported with parenteral amino acid products include: Azotaemia, Hyperammonaemia. • Adverse reactions reported with parenteral nutrition to which the amino acid component may play a causal or contributory role include Anaphylactic/anaphylactoid reactions, including skin, gastrointestinal, and severe circulatory (shock) and respiratory manifestations as well as other hypersensitivity/infusion reactions, including pyrexia, chills, hypotension, hypertension, arthralgia, myalgia, urticaria, pruritus, erythema, and headache. • Hepatic failure, Hepatic cirrhosis, Hepatic fibrosis, Cholestasis, Hepatic steatosis, Blood bilirubin increased, Hepatic enzyme increased; Cholecystitis, Cholelithiasis. • Raised blood urea nitrogen in children with renal insufficiency. • Metabolic acidosis. • Pulmonary vascular precipitates. • Necrosis, blistering, swelling, scarring, skin discoloration at the infusion site associated with extravasation. • Infusion site thrombophlebitis; Venous irritation (infusion site phlebitis, pain, erythema, warmth, swelling, induration). Amino acid solutions may precipitate acute folic acid deficiency which should be corrected by supplements. Reporting of suspected adverse reactions: Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: Website: www.mhra.gov.uk/yellowcard
Overdose	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 inappropriate administration (overdose, and/or infusion rate higher than recommended), hypervolemia, electrolyte disturbances, acidosis and/or azotemia may occur. In such situations, the infusion must be stopped immediately. If medically appropriate, further intervention may be indicated to prevent clinical complications. There is no specific antidote for overdose. Emergency procedures should include appropriate corrective measures.
Storage Conditions	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.	Do not store above 25 ºC. Protect from light.
How Supplied	6% and 10% Premasol-sulfite free Amino Acid Injections are supplied in VIAFLEX plastic pharmacy Bulk Package containers in the following sizes and concentrations: 2B0011 6% PREMASOL NDC 0338-1131-03, 500 mL 2B0009 10% PREMASOL NDC 0338-1130-04, 1000mL 2B0012 10% PREMASOL NDC 0338-1130-03, 500 mL 2B0010 10% PREMASOL NDC 0338-1130-06, 2000mL	Prime 10% Solution for Infusion is supplied in glass bottle containers available in 250 mL size Product Code FCZ3CG133R79D, NDC 0338-9577-10

Product label for Primene 10% Solution for Infusion in glass container