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

Sincerely,

Dennis Vaughn
Vice President, Marketing Operations

Baxter Healthcare Corporation

Baxter, PRIMENE, PREMASOL and VIAFLEX are trademarks of Baxter International Inc.

roduct 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
mposition and redients	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
ditional ormation	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
scription	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
ications for e	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 **6% and 10% PREMASOL – sulfite-free (Amino Acid) Injection**	Import Product **Primene 10% Solution for Infusion (glass bottle)**
sage and ministration	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.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.