PRODUCT MONOGRAPH

PRIMENE 10%

(Amino Acid Injection 10% w/v)

Pharmacy Bulk Pack (Not for direct infusion)

Intravenous Nutritive Supplement

Baxter Corporation
Mississauga, Ontario, Canada
L5N 0C2

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PRIMENE 10%

(Amino Acid Injection)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous	10% Solution for Infusion	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

PRIMENE 10% (Amino Acid Injection 10% w/v) 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.

The purpose of the solution is to prevent nitrogen and weight loss or treat negative nitrogen balance in infants and young children 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.

CONTRAINDICATIONS

The use of PRIMENE 10% (Amino Acid Injection 10% w/v) is contraindicated in the following populations/situations:

- Known hypersensitivity to any of the active substances or excipients, or to components of the container. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.
- Patients with untreated anuria
- Hepatic coma
- Congenital abnormality of amino acid metabolism , including those involving branched chain amino acid metabolism such as maple syrup urine disease and isovaleric acidemia.

WARNINGS AND PRECAUTIONS

General

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

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

The IV administration of these solutions can lead to fluid or solute overload resulting in hyper or hypoosmolal states. The risk of hypoosmolal states is especially present in conditions associated with ADH secretion and is proportional to the infusion rate. Severe water and electrolyte disorders, severe fluid overload states, and severe metabolic disorders should be corrected before starting the infusion.

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

Administration of amino acids in the presence of impaired renal function or gastrointestinal bleeding may augment an already elevated blood urea nitrogen.

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 PRIMENE 10% (Amino Acid Injection 10% w/v) 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

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

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.

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 hyperglycemia, 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 hyperglycemia 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 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.

During administration of amino acids 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.

Peripheral administration of PRIMENE10% (Amino Acid Injection 10% w/v) requires appropriate dilution and provision of adequate calories. Hypertonic infusion solutions may cause irritation of the vein, vein damage, and thrombosis when administered into a peripheral vein (see ADVERSE REACTIONS). 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.

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. See Other Reactions. Patients should be monitored accordingly.

PRIMENE 10% (Amino Acid Injection 10% w/v) contains no added electrolytes. 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.

Unit must be used with a vented set or a non vented set with a vented spike adapter.

Administration of amino acid solutions 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 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 areterio-venous fistula, phlebitis, thrombosis, cardiac arrhythmia and catheter embolus.

PRIMENE 10% (Amino Acid Injection 10% w/v) must not be infused through the same tubing with blood or blood components unless there is documentation that it is safe because of the possibility of pseuodoagglutination.
Do not connect containers in series in order to avoid air embolism due to possible residual air contained in the primary container.

Use of a final filter is required during administration of formulations containing Primene and trace elements (including copper, iron, or zinc), because for some formulations visible particulate matter has been observed in the infusion line.

Use a 0.22 micron filter for 2 in 1 (amino acids and carbohydrates) parenteral nutrition solutions and a 1.2 micron filter for 3 in 1 (lipid, amino acids, and carbohydrates) parenteral nutrition solutions, as the addition of lipids requires a larger filter.

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 discoloration or precipitation is noted in the filter, perform blood levels of copper (or other trace elements) where medically relevant.

Light exposure of solutions for intravenous parenteral nutrition, after admixture with trace elements and/or vitamins, may have adverse effects on clinical outcome in neonates, due to generation of peroxides and other degradation products. When used in neonates and children below 2 years, PRIMENE 10% (Amino Acid Injection 10% w/v) should be protected from ambient light after admixture until administration is complete.

Cardiovascular
Use with caution in patients with pulmonary edema or heart failure. Fluid status should be closely monitored.

Endocrine and Metabolism
Sudden cessation in administration of a concentrated dextrose solution may result in insulin reaction due to continued endogenous production. Parenteral nutrition mixtures should be withdrawn slowly.

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.

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 hyper vitaminosis, 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.

Hepatic/Biliary/Pancreatic
Administration of amino acid solutions to a patient with hepatic insufficiency may result in serum amino acid imbalances, prerenal azotemia, stupor and coma.

Parenteral nutrition in general as well as amino acid solutions should be used with caution in patients with preexisting liver disease or liver insufficiency.

Liver function parameters should be closely monitored in these patients, and they should be monitored for possible symptoms of hyperammonemia. Should symptoms of hyperammonemia develop, administration should be discontinued and the patient's clinical status should be reevaluated.

Increase in blood ammonia levels and hyperammonemia may occur in patients receiving amino acid solutions. In some patients this may indicate the presence of a congenital disorder of amino acid metabolism (see CONTRAINDICATIONS) or hepatic insufficiency.

Blood ammonia should be measured frequently in newborns and infants until at least 2 years of age to detect hyperammonemia. Potential symptoms (e.g. lethargy, irritability, poor feeding, hyperventilation, and seizures), which can result in complications including developmental delay and intellectual disability may be difficult to identify in this age group.

Depending on extent and etiology, hyperammonemia may require immediate intervention. Hepatobiliary disorders including cholestasis, hepatic steatosis, fibrosis and cirrhosis, possibly leading to hepatic failure, as well as cholecystitis and cholelithiasis are known to develop in some patients on parenteral nutrition. 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.

Conservative doses of this injection should be given to patients with known or suspected hepatic dysfunction.

Immune
Anaphylactic/anaphylactoid reactions and other hypersensitivity/infusion reactions have been reported with amino acid solutions administered as a component of parenteral nutrition (see

CONTRAINDICATIONS and ADVERSE REACTIONS). The infusion must be stopped immediately if any signs or symptoms of a reaction develop.

Renal
Use with caution in patients with renal insufficiency (with e.g., uremia). Nitrogen tolerance may be altered and dosage may have to be adjusted. Fluid and electrolyte status should be closely monitored in these patients.

Azotemia has been reported with parenteral administration of solutions containing amino acids, and may occur in particular in the presence of renal impairment. Patients with azotemia from any cause should not be infused with amino acids without regard to total nitrogen intake.

Respiratory
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.

Special Populations
Pregnant Women:
There are no adequate data on the use of PRIMENE 10% (Amino Acid Injection 10% w/v) in pregnant women. Healthcare professionals should carefully consider the potential risks and benefits for each specific patient before prescribing the product.

Nursing Women:
There are no adequate data on the use of PRIMENE 10% (Amino Acid Injection 10% w/v) in nursing women. Healthcare professionals should carefully consider the potential risks and benefits for each specific patient before administering the product.

Pediatrics:
The product is specifically indicated for the pediatric population.

Monitoring and Laboratory Tests
Monitoring should be appropriate to the patient's clinical situation and condition, and may include determinations of fluid balance, water and electrolyte balance, serum osmolarity, and acid / base balance, blood glucose, serum proteins, blood ammonia levels, kidney and liver function tests, electrolytes, hemogram, arterial blood gases, and blood cultures.

ADVERSE REACTIONS

Adverse Drug Reaction Overview
Adverse reaction information is based on postmarketing experiences.

Post-Market Adverse Drug Reactions

The adverse reactions listed below have been identified from post-marketing reports of PRIMENE 10% (Amino Acid Injection) administered as a component of parenteral nutrition. They are listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity, where feasible.

IMMUNE SYSTEM DISORDERS:
Hypersensitivity reaction:
- Face edema
- Eyelid edema
- Rash

Other adverse reactions reported with parenteral amino acid products include:
RENAL AND URINARY DISORDERS:
- Azotemia

METABOLISM AND NUTRITION DISORDERS:
- Hyperammonemia
- Adverse reactions reported with parenteral nutrition to which the amino acid component may play a causal or contributory role include:

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS:

- Chills
- Infusion site discolouration
- Injection site erythema
- Infusion site extravasation
- Infusion site induration
- Infusion site phlebitis
- Infusion site swelling
- Infusion site thrombosis
- Infusion site warmth
- Necrosis
- Pyrexia
- Swelling

IMMUNE SYSTEM DISORDER:

- Anaphylactic / anaphylactoid reactions, including skin, gastrointestinal and respiratory manifestations
- Hypersensitivity reaction

INJURY, POISONING AND PROCEDURAL COMPLICATIONS:

- Infusion related reaction
- Scar

INVESTIGATIONS:

- Blood bilirubin increased
- Hepatic enzyme increased

HEPATOBILIARY DISORDERS:

- Cholecystitis
- Cholelithiasis
- Cholestasis
- Hepatic cirrhosis
- Hepatic failure
- Hepatic fibrosis
- Hepatic steatosis

METABOLISM AND NUTRITION DISORDERS:

- Metabolic acidosis

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS:

- Arthralgia
- Myalgia

NERVOUS SYSTEM DISORDERS:

- Headache

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS:

- Pulmonary Vascular disorder

SKIN AND SUBCUTANEOUS TISSUE DISORDERS:

- Blister
- Erythema
- Pruritus
- Urticaria

VASCULAR DISORDER:

- Hypertension
- Hypotension
- Infusion site pain
- Shock
- Vein disorder

DRUG INTERACTIONS

Overview
No interaction studies have been performed by Baxter Healthcare Corporation with PRIMENE 10% (Amino Acid Injection 10% w/v).

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

Drug-Food Interactions
No drug-food interaction studies have been evaluated.

Drug-Laboratory Interactions
No drug-laboratory interaction studies have been evaluated.

Drug-Lifestyle Interactions
Interactions with lifestyle have not been evaluated.

DOSAGE AND ADMINISTRATION

PRIMENE 10% (Amino Acid Injection 10% w/v) is intended for intravenous use. The product

is in Pharmacy Bulk Package and not for direct infusion.

PRIMENE 10% (Amino Acid Injection 10% w/v) is not intended for fluid or volume replacement.

Dosing Considerations
The total daily dose of PRIMENE10% (Amino Acid Injection 10% w/v) 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.

When used in neonates and children below 2 years, the solution (in containers and administration sets) should be protected from light exposure after admixture through administration.

Any unused portion of PRIMENE 10% (Amino Acid Injection 10% w/v) should be discarded and should not be used for subsequent admixing.

Recommended Dose and Dosage Adjustment
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 10% (Amino Acid Injection 10% w/v),
- additional nutrition that may be provided parenterally and/or enterally.

The recommended dosage of PRIMENE 10% (Amino Acid Injection 10% w/v) is 1.5 to 3.5 grams of amino acids per kilogram of body weight per day.

Typically, PRIMENE10% (Amino Acid Injection 10% w/v) is admixed with 50% dextrose and supplemented with electrolytes and administered continuously over a 24 hour period.
The healthy new born child requires 2.2 g/kg of protein and 120 Kcal/kg/day. For premature infants, especially those in catabolic state, these requirements could be even higher.
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. Provision of additional nitrogen may not be possible due to fluid intake limits, nitrogen, or glucose intolerance. In addition, the provision of sufficient intracellular electrolytes, principally potassium, magnesium, and phosphate, is required for optimum utilization of amino acids, and sufficient quantities of the major extracellular electrolytes sodium, calcium, and chloride, must be given. Therefore, if oral feeding is not possible or advisable and TPN is necessary, the volume restrictions dictate how to administer Primene, dextrose and most electrolytes in the same hypertonic solution through intravenous lines. Even such hypertonic solutions will not provide the required daily calories. If prolonged TPN is required (5 days or more), intravenous lipid emulsions will also have to be administered. The following scenario can serve as an example.

Premature baby, weight 1 kg, requiring 2.5 g/kg of amino acid per day and 125 cc/kg/day fluid volume.

Product	mL	Grams of Nutrients per 100 mL	Calories	mOsmols
Primene 10%	25 mL	2.5 g	10	20
Dextrose 50%	42 mL	21 g	71	110
Water for Injection and electrolytes	33 mL	--	--	e.g. 15
Total	**100 mL**	**--**	**81**	**145**
Osmolarity (mOsm/Kg of H_2O)	--	--	--	1500
Lipid 20%	25 mL	--	50	--
Total	**125 mL**	**--**	**131**	--

When prolonged parenteral nutrition (more than 5 days) is required fat emulsion should also be considered 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.

In patients with hyperchloremic or other metabolic acidoses, sodium and potassium may be added as the acetate salts to provide bicarbonate precursor. Serum electrolytes, including magnesium and phosphorus, should be monitored frequently.

This product does not contain clinically significant amounts of electrolytes. Electrolyte supplementation may be indicated according to the clinical needs of the patient. Additional electrolytes and trace elements should be administered as required.

As indicated on an individual basis, vitamins and trace elements and other components (including dextrose and lipids) can be added to the parenteral nutrition regimen to prevent deficiencies and complications from developing (see **Additives** subsection below).

Administration

The flow rate should be increased gradually during the first hour. The flow rate must be adjusted taking into account the dose being administered, the daily volume intake, and the duration of the infusion.

Central Vein Administration: When enteral feeding is inadvisable, PRIMENE 10% (Amino Acid Injection 10% w/v) given by central venous infusion in combination with energy sources, vitamins, trace elements and electrolytes, will meet the requirements for weight maintenance or weight gain, depending upon the dose selected. The energy component in parenteral nutrition by central infusion may be derived solely from dextrose or may be provided by a combination of dextrose and intravenous fat emulsion. The addition of intravenous fat emulsion provides essential fatty acids and permits a dietary balance of fat and carbohydrate, at the same time offering the option of reducing the dextrose load and/or increasing the total caloric input. An adequate energy supply is essential for optimal utilization of amino acids.

Hypertonic mixtures of amino acids and dextrose may be administered safely by continuous infusion through a central vein catheter with the tip located in the vena cava. Initial infusion rates should be slow, and gradually increased to the recommended 60-125 mL per kilogram body weight per day. 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.

Peripheral Vein Administration: 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.

For patients requiring parenteral nutrition in whom the central vein route is not indicated, this injection can be mixed with low concentration dextrose solutions and administered by peripheral vein in conjunction with or without fat emulsions. Reduction of protein loss can be achieved by use of diluted PRIMENE 10% (Amino Acid Injection 10% w/v) in combination with dextrose or with dextrose and intravenous fat emulsion by peripheral infusion. Complete peripheral intravenous nutrition can be achieved in patients with low caloric requirements by a PRIMENE 10% (Amino Acid Injection 10% w/v)-dextrose-fat regimen.

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.

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.

Intravenous fat emulsions provide approximately 1.1kcal/mL (10%) or 2.0kcal/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.

Instructions for Use and Handling, and Disposal

PRIMENE 10% (Amino Acid Injection 10% w/v) in the Pharmacy Bulk Package is intended for use in the preparation of sterile, intravenous admixtures.

For compounding only, not for direct infusion.

When compounding admixtures, aseptic conditions must be observed. Mix thoroughly.

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. Remove outer seal and metal disc. Swab surface of stopper using approved technique.
3. Insert vented connector of solution transfer set and suspend unit. Refer to directions accompanying set.
4. Once container closure has been penetrated, withdrawal of contents should be completed without delay. After initial entry, maintain contents at room temperature (25°C) and dispense within 4 hours.

Inspect final solution for discoloration and particulate matter. Use only if the solution is clear, colorless or slightly yellow.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Use of a final filter is recommended during administration of all parenteral nutrition solutions.

Additives
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. Do not add other medicinal products or substances without first confirming their compatibility and the stability of the resulting preparation. Consult with pharmacist, if available.

Excessive addition of calcium and phosphate increases the risk of the formation of calcium phosphate precipitates (see WARNINGS AND PRECAUTIONS).

To minimize the risk of possible incompatibilities arising from mixing this injection 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.

OVERDOSAGE

For suspected cases of drug overdose, contact the regional Poison Control Centre.

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. See WARNINGS AND PRECAUTIONS**.**

There is no specific antidote for overdose. Emergency procedures should include appropriate corrective measures.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

PRIMENE 10% (Amino Acid Injection 10% w/v) provides a mixture of essential and nonessential amino acids as well as taurine and cysteine. This amino acid injection has been specifically formulated to provide a well tolerated nitrogen source for nutritional support for neonates, infants and young children. The amino acid profile corresponds qualitatively and quantitatively to the protein needs in this patient population. Of the total amino acids, essential amino acids comprise 47.5% and branched chain amino acids comprise 24%.

Clinical studies in infants and young children who required TPN therapy showed that infusion of PRIMENE 10% (Amino Acid Injection 10% w/v) 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, electrolytes, vitamins, and minerals, PRIMENE10% (Amino Acid Injection 10% w/v) provides total parenteral nutrition in infants and young children, with the exception of essential fatty acids.

The amounts of chloride present in PRIMENE 10% (Amino Acid Injection 10% w/v) are not of clinical significance.
The electrolyte content of any additives that are introduced should be carefully considered and included in total input computations.

Pharmacodynamics

There have been no pharmacodynamic studies performed by Baxter Healthcare Corporation.

Pharmacokinetics

There have been no pharmacokinetic studies performed by Baxter Healthcare Corporation.

Special Populations and Conditions

The product is specifically indicated for the pediatric population. There have been no studies conducted in special populations other than pediatrics.

STORAGE AND STABILITY

Exposure of pharmaceutical products to heat should be minimized. Protect from freezing. It is recommended the product be stored at temperatures between 15 and 25°C, protected from light.

Do not store any unused portion of PRIMENE10% (Amino Acid Injection 10% w/v). These solutions 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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

PRIMENE 10% (Amino Acid Injection 10% w/v) is a sterile, nonpyrogenic, hypertonic solution of essential and nonessential amino acids in a 250 mL glass 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.

Availability
PRIMENE 10% (Amino Acid Injection 10% w/v) is available in 250 mL glass Pharmacy Bulk Packages.

Composition:

Each 100 mL of PRIMENE 10% (Amino Acid Injection 10% w/v) contains:

Amino Acids	10.0 g
Total Nitrogen	1.5 g
pH	5.5 (pH adjusted with malic acid)

Component	**Quantity per 100mL**
L-Alanine	0.800 g
L-Arginine	0.840 g
L-Aspartic acid	0.600 g
L-Glutamic acid	1.000 g
Glycine	0.400 g
L-Histidine	0.380 g
L-Isoleucine	0.670 g
L-Leucine	1.000 g
L-Lysine[1]	1.10 g
L-Methionine	0.240 g
L-Ornithine hydrochloride	0.318 g
L-Phenylalanine	0.420 g
L-Proline	0.300 g
L-Serine	0.400 g
Taurine	0.060 g
L-Threonine	0.370 g
L-Tryptophan	0.200 g
L-Tyrosine	0.045 g
L-Valine	0.760 g
L-Cysteine	0.189 g
Anion Profiles per liter	
Chloride	19 mmol/l
L-Malic acid	Qs to pH 5.5
Osmolarity	780 mOsmol/L

[1]As 1.235 g of Lysine monohydrate.

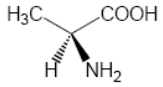
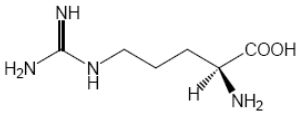
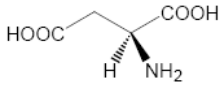
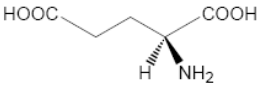
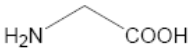
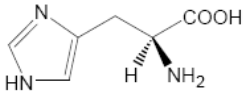
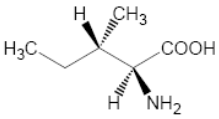
PART II: SCIENTIFIC INFORMATION

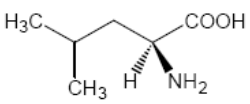
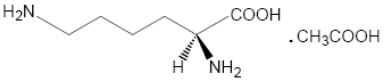
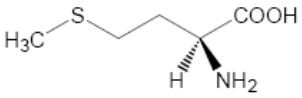
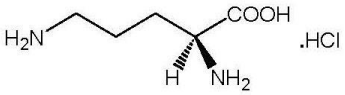
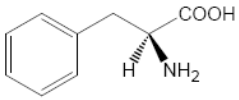
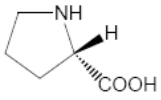
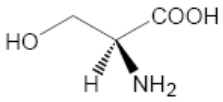
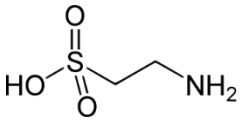
PHARMACEUTICAL INFORMATION

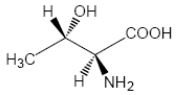
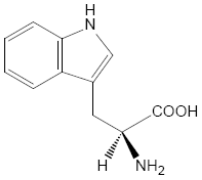
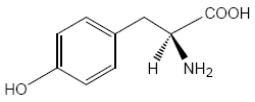
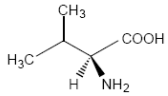
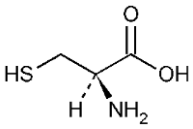
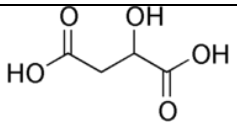
Drug Substance

Essential Amino Acids
L-Histidine, L-Isoleucine, L-Leucine, L-Lysine, L-Methionine, L Phenylalanine, L-Threonine, L-Tryptophan, L-Valine

Non-Essential Amino Acids
L-Alanine, L-Arginine, L-Aspartic Acid, L-Cysteine, L-Glutamic Acid, Glycine, L-Ornithine hydrochloride, L-Proline, Taurine, L-Tyrosine, L-Serine

Proper Name Chemical Name	Molecular Formula and Molecular Mass	Structural Formula	Physicochemical Properties
L-Alanine (S)-2-aminopropionic acid	$C_3H_7NO_2$ 89.09		White or almost white crystalline powder or colourless crystals, freely soluble in water, very slightly soluble in alcohol.
L-Arginine (2S)-2-amino-5-guanidinopentanoic acid	$C_6H_{14}N_4O_2$ 174.20		White or almost white crystalline powder or colourless crystals, freely soluble in water, very slightly soluble in alcohol.
L-Aspartic Acid (2S)-2-aminobutanedioic acid	$C_4H_7NO_4$ 133.10		White or almost white crystalline powder or colourless crystals, slightly soluble in water, practically insoluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.
L-Glutamic Acid (2S)-2-aminopentanedioic acid	$C_5H_9NO_4$ 147.13		White crystalline powder or colourless crystals, freely soluble in boiling water, slightly soluble in cold water, practically insoluble in acetic acid, in acetone and in alcohol.
Glycine Aminoacetic acid	$C_2H_5NO_2$ 75.07		White or almost white crystalline powder, freely soluble in water, very slightly soluble in alcohol.
L-Histidine (S)-2-amino-1H-imidazole-4-propionic acid	$C_6H_9N_3O_2$ 155.15		White or almost white crystalline powder or colourless crystals, soluble in water, very slightly soluble in ethanol (96%).
L-Isoleucine (2S, 3S)-2-amino-3-methylpentanoic acid	$C_6H_{13}NO_2$ 131.17		White or almost white crystalline powder or flakes, sparingly soluble in water, slightly soluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.

L-Leucine (2S)-2-amino-4-methylpentanoic acid	$C_6H_{13}NO_2$ 131.17		White or almost white crystalline powder or shiny flakes, sparingly soluble in water, practically insoluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.
L-Lysine (S)-2,6-diaminohexanoic acid monohydrate	$C_6H_{14}N_2O_2 \cdot H_2O$ 164.21		White or almost white crystalline powder or colourless crystals, freely soluble in water, very slightly soluble in ethanol (96%).
L-Methionine (2S)-2-amino-4-(methylsulfanyl) butanoic acid	$C_5H_{11}NO_2S$ 149.21		White or almost white crystalline powder or colourless crystals, soluble in water, very slightly soluble in ethanol.
L-Ornithine hydrochloride (S) 2,5-diaminopentanoic acid monohydrochloride	$C_5H_{12}N_2O_2.HCl$ 168.62		White crystalline powder. Soluble in water, practically insoluble in methanol.
L-Phenylalanine (2S)-2-amino-3-phenylpropanoic acid	$C_9H_{11}NO_2$ 165.19		White or almost white crystalline powder or shiny, white flakes, sparingly soluble in water, very slightly soluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.
L-Proline (S)-2-pyrrolidinecarboxylic acid	$C_5H_9NO_2$ 115.13		White or almost white crystalline powder or colourless crystals, very soluble in water, freely soluble in alcohol.
L-Serine (S)-2-amino-3-hydroxypropionic acid	$C_3H_7NO_3$ 105.09		White or almost white crystalline powder or colourless crystals, freely soluble in water, practically insoluble in alcohol.
Taurine 2-Aminoethanesulfonic acid	$C_2H_7NO_3S$ 125.15		White crystals or crystalline powder. Soluble in water and insoluble in abs. alcohol.

L-Threonine (2S, 3R)-2-amino-3-hydroxybutanoic acid	$C_4H_9NO_3$ 119.12		White crystalline powder or colourless crystals, soluble in water, practically insoluble in ethanol.
L-Tryptophan (2S)-2-amino-3-(indol-3-yl)propanoic acid	$C_{11}H_{12}N_2O_2$ 204.23		White or almost white crystalline or amorphous powder, sparingly soluble in water, slightly soluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.
L-Tyrosine (S)-2-amino-3-(4-hydroxyphenyl) propionic acid	$C_9H_{11}NO_3$ 181.19		White crystalline powder or colourless crystals, very slightly soluble in water, practically insoluble in alcohol. It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.
L-Valine (2S)-2-amino-3-methylbutanoic acid	$C_5H_{11}NO_2$ 117.15		White or almost white crystalline powder or colourless crystals, soluble in water, very slightly soluble in ethanol.
L-Cysteine (R)-2-amino-3-mercaptopropionic acid	$C_3H_7NO_2S$ 121.16		White crystals or crystalline powder. Soluble in water and alcohol.
L-Malic Acid 2-hydroxybutanedioic acid	$C_4H_6O_5$ 134.09		White to nearly white crystals or crystal powder.

CLINICAL TRIALS
Study demographics and trial design

There have been two pivotal studies on humans to assess the efficacy of the formulation when used on new born infants.
In a study designed as a comparative study between Primene and an adult amino acid formulation (Vamin glucose), the solutions were administered in a random double blind study using premature infants requiring parenteral nutrition at birth (Trial C3).

In Trial C6, a non-comparative safety study, 84 premature and dysmature newborn infants receiving parenteral nutrition during the first days of life.

Table 1 - Summary of patient demographics for clinical trials in specific indication

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Trial C3 (Investigator: N McIntosh)	Comparative, randomized double blind	Both PRIMENE 10% and Vamin glucose contained the same total density of nitrogen (2.79 g/L) and energy (1.59 MJ/L, 380 kcal/L); administered continuously over 24 hours usually by peripheral infsion	PRIMENE 10%: n=34 Vamin glucose: n=34; 20 babies excluded from analysis (n=11 on PRIMENE 10%; n=9 on Vamin glucose)	Premature infants	Data not available
Trial C6 (Investigator: Bernard Salle)	Non-comparative safety study	PRIMENE 10%: 1.2 -2.9 g/24 h; Duration: 4-33 days	n=84	Gestational age: 32.4 +/- 0.3 weeks	39 male, 45 female

Study results

In the comparative, randomized double blind study, the plasma amino acid levels after a minimum of 5 days infusion were normal for the infants on Primene but were abnormal (elevated levels of tyrosine, phenylalanine, serine, and proline) in the infants given the adult formulation.

In the non-comparative safety study, the dosages ranged from 1.2 and 2.9 g/24hr, and the duration of the feed was between 4 and 33 days. The purpose of the study was to evaluate the tolerance of Primene from a clinical and laboratory standpoint. The results showed excellent clinical tolerance with no reports of side effects linked to Primene. There was also no laboratory abnormalities found which were imputable to the preparation. As a rule, the blood electrolyte parameters were improved.

TOXICOLOGY

Study Type	Species	Duration of Observation	# of Animals	Dose	Description of Study	Results
Acute Toxicity	Mouse	14 days	20	50 mL/kg	Single dose, IV administered amino acid solution to male and female mice at a rate of 1 mL/min.	No signs of toxicity
Acute Toxicity	Rat	14 days	20	10 mL/kg	Single dose, IV administered amino acid solution to male and female rats at a rate of 2 mL/min.	No signs of toxicity
Acute Toxicity (LD50)	Mouse	14 days	20		IV administered at a rate of 1 mL/min.	LD50 female mouse= 109.7 mL/kg LD50 male mouse=98 mL/kg This is 1000 times greater than that suggested for human clinical use
Acute Toxicity (LD50)	Rat	14 days	20		IV administration at a rate of 2 mL/min.	LD50(M)= 91 mL/kg LD50(F)=84 mL/kg
Repeated dose Toxicity	Newborn Rat	32 days	66	35 mL/kg	3 way Comparative study using Primene, distilled water, and an adult amino acid solution. Administered subcutaneously.	Daily administration of Primene at a dose greater than the maximum indicated for human use did not cause any disturbance in growth or behavior of the newborn rat.
Repeated dose Toxicity	Beagle Dog	13 weeks	16	30 mL/kg per day	IV administered in a comparative trial with NaCl Solution at a rate of 1.5 mL/min.	Daily infusion of 30 mL/kg for 90 days did not lead to an notable change of a toxicological nature, despite a relative rate of infusion 3 greater than the human maximum dose.

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1. KEMPSON C., MCINTOSH N., VENTURA V., FORGET D., STEINBERG G., VARLAN E.The plasma aminograms of very low birthweight infants on supplementary intravenous amino acids in the first week of life. Pediatric Research, 1987, 22, abstract 93, p.232. ESPR, Padoue, June, 1987
2. KEMPSON C., MCINTOSH N., VENTURA V., FORGET D., STEINBERG G., VARLAN E. The metabolic tolerance of intravenous amino acids in preterm infants in the first week of life. Pediatric Research, 1987, 22, abstract 92, p.232. ESPR, Padoue, June, 1987
3. MCINTOSH N. Results of a randomised double blind comparative study of two parenteral nutritive solutions (Vamin-9-Glucose Kabivitrum / MB 233 G Cernep). British Pediatric Assessment Meeting, April 12, 1989, l, York, communication orale.
4. MCINTOSH N., VENTURA V. KEMPSON C. A new amino acid preparation for low birthweight infants. Int. Ther. Clin. Monit., 1990. 11. (5), 175-184.
5. MCINTOSH N, MITCHELL, V. A clinical trial of two parenteral nutrition solutions in neonates. Arch. Dis. Child., 1990, 65, 692-699.
6. RIGO J., SENTERRE J. Development of a new amino acid solution for parenteral nutrition in preterm and full-term neonates. ESPEN, 7ème Congrès, Munich, September 9-11 1985, poster 0.58, p.123
7. RIGO J., SENTERRE J., PUTET G., SALLE B. A new amino acid solution specially adapted to preterms infants. Clin. Nutr., 1987, 6, (2), 105-109.

PART III: CONSUMER INFORMATION

PRIMENE 10%
(Amino Acid Injection 10% w/v)

This leaflet is part III of a three-part "Product Monograph" published when PRIMENE 10% (Amino Acid Injection 10% w/v) was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PRIMENE 10% (Amino Acid Injection 10% w/v). Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
PRIMENE 10% (Amino Acid Injection 10% w/v) is a nutritive supplement used to provide nutrition to infants and young children, through a tube in a vein when normal feeding by mouth or enterally (directly to the stomach through a tube) is not possible or suitable.

PRIMENE product must be administered by a healthcare professional.

What it does:
The use of PRIMENE product is a way to ensure that patients (young children and infants) who are unable to eat, get an adequate intake of energy, nitrogen and other nutrients, and helps treat or prevent malnutrition.

When it should not be used:
PRIMENE 10% (Amino Acid Injection 10% w/v) should not be used if your child:

- is allergic to any ingredients (See **What the medicinal ingredients are** and **What the nonmedicinal ingredients are**.)
- has problems processing some amino acids and these amino acids are included in PRIMENE product
- has liver failure or coma from liver failure
- has decreased kidney function resulting in absence or defective urine output

What the medicinal ingredient is:
Each 100mL of solution contains:
L-Alanine 800mg, L-Arginine 840mg, L-Aspartic Acid 600mg, L-Cysteine 189mg, L-Glutamic Acid 1000mg, Glycine 400mg, L-Histidine 380mg, L-Isoleucine 670mg, L-Leucine 1000mg, L-Lysine 1100mg, L-Methionine 240mg, L-Ornithine Hydrochloride 318mg, L-Phenylalanine 420mg, L-Proline 300mg, L-Serine 400mg, Taurine 60mg, L-Threonine 370mg, L-Tryptophan 200mg, L-Tyrosine 45mg, L-Valine 760mg

What the important nonmedicinal ingredients are:
L-Malic acid (for pH adjustment), Water for injection

What dosage forms it comes in:
PRIMENE product is a 250 ml solution for infusion (into the vein). It is supplied in a glass bottle.

The 10% amino acid solution will be mixed with other solutions for infusion, by your child's healthcare professional who can tailor the infusion to your child's particular needs.

WARNINGS AND PRECAUTIONS

Your child's healthcare professional may run tests to determine the status of some conditions. BEFORE PRIMENE product is administered to your child, talk to your child's healthcare professional if your child:

- is allergic to any ingredients. (See **What the medicinal ingredients are** and **What the nonmedicinal ingredients are**).
- suffers from too much ammonia in the blood
- suffers from metabolic acidosis (when the blood is excessively acid)
- suffers from metabolic alkalosis (when the blood is excessively basic)
- suffers from low phosphate in the blood
- has kidney or liver problems
- is taking any other medicines on a regular basis
- has pulmonary edema (collection of fluid into the lung tissue)
- has heart failure
- has fluid overload (too much water in your body)

In all cases, your child's healthcare professional will base his/her decision to treat your child on factors such as age, weight and clinical condition, together with the results of any tests. Always be sure to check with your child's healthcare professional if anything about your child's condition changes.

In newborns and infants, your child's healthcare professional will measure blood ammonia frequently to check for the presence of a congenital abnormality of amino acid metabolism.

Your child's healthcare professional will need to monitor how your child is doing while you are on this intravenous nutritive supplement. This means that your child will need to have laboratory tests done on a routine basis.

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with PRIMENE 10% (Amino Acid Injection 10% w/v) include:

No drug interaction studies have been done with PRIMENE.

PRIMENE product must NOT be administered simultaneously with blood through the same infusion tubing.

Let your child's healthcare professional know if your child is receiving tetracycline.

PROPER USE OF THIS MEDICATION

Usual dose:
PRIMENE 10% (Amino Acid Injection 10% w/v) is in pharmacy bulk package and are not for direct infusion. Your child's pharmacist will mix the products so they can be administered safely by the healthcare professional based on your child's age, body weight and your child's clinical requirements.

Your child's healthcare professional will ensure that your child is getting sufficient calories so that the amino acids from PRIMENE product will be absorbed.

Overdose:
If a dose is too high or is infused too quickly, blood may become acidic or your child may suffer fluid overload.

To prevent this, the healthcare professional may monitor your child and test the blood and urine.

In case you feel your child has been administered too much PRIMENE product, contact your child's healthcare practitioner (e.g. healthcare professional), hospital emergency department or the regional poison control centre, even if there are no symptoms.

Missed Dose:
If you feel a dose has been missed contact your child's attending healthcare professional.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

If you notice any changes in the way your child feels during or after the treatment, tell your child's healthcare professional or another member of your child's medical team immediately.

The tests your child's healthcare professional will perform while your child is taking the intravenous nutritive supplement should reduce the risk of side effects.

If any symptoms of an allergic reaction develop, such as swelling of face or eyelid, skin rash contact your child's attending healthcare professional immediately.

If any side effect gets serious, or if you notice any side effect not listed in this leaflet, please tell your child's healthcare professional or a member of your child's medical team right away.

Occasional reddening and stinging may occur at the point where the tubing enters the body. If this occurs, tell your child's healthcare professional or nurse immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your healthcare professional		Stop the infusion and contact your doctor (or healthcare professional)
		Only if severe	In all cases	
Uncommon	**Allergic reactions with symptoms such as swelling (face, mouth, throat, or eyelid), skin rash, and difficulty breathing**			✓

This is not a complete list of side effects. For any unexpected effects while taking PRIMENE 10% (Amino Acid Injection), contact your healthcare professional.

HOW TO STORE IT

The heatlhcare professional will store the PRIMENE product at temperatures between 15°C and 25°C, protected from light and kept from freezing.

REPORTING SUSPECTED SIDE EFFECTS

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at: http://www.baxter.ca or by contacting the sponsor, Baxter Corporation, at: 1-888-719-9955.

This leaflet was prepared by Baxter Corporation, Mississauga, Ontario L5N 0C2, Canada.

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