1 PRIMENE (10% solution for infusion)

Primene 10% solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Primene 10% amino acids intravenous (IV) solution for infusion contains essential and non-essential L-amino acids. The composition and quantity of the L-amino acids in Primene 10% are shown in the following table:

Each 1000mL of Primene 10% (w/v) solution for infusion contains	
Active constituents:	**(g)**
Lysine	11.00
Glutamic acid	10.00
Leucine	10.00
Arginine	8.40
Alanine	8.00
Valine	7.60
Isoleucine	6.70
Aspartic acid	6.00
Phenylalanine	4.20
Glycine	4.00
Serine	4.00
Histidine	3.80
Threonine	3.70
Ornithine monohydrochloride	3.18 (2.49)*
Proline	3.00
Methionine	2.40
Tryptophan	2.00
Cysteine	1.89
Taurine	0.60
Tyrosine	0.45
Note: Those amino acids are L-isomer form * equivalent to ornithine base 2.49g.	

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

Appearance

Primene 10% amino acids IV solution for infusion is a sterile, nonpyrogenic, hypertonic, clear, colourless solution of amino acids.

It is intended for nutritional support in infants administered as an intravenous infusion.

Primene 10% contains 100.24g/litre of amino acids, which supplies 15.15g/litre of nitrogen. It does not contain electrolytes.

Osmolality/Osmolarity

Primene 10% is a hypertonic solution having osmolality of 840mOsmol/kg (10% solution) and Osmolarity of 780mOsmol/L. Under dilute conditions, osmolarity (mOsmol/L) is similar to osmolality (mOsmol/kg).

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Primene 10% amino acids IV solution for infusion is indicated in infants and neonates at term or premature for short-term use, of normal or low birth-weight, when oral or enteral nutrition is impossible, insufficient or contraindicated. It is used as an amino acid component in a composite admixture of total parenteral nutrition.

4.2 Dose and method of administration

Primene 10% amino acid IV solution for infusion is intended for intravenous use in a single patient on a single occasion.

When used in infants and neonates, the solution (in containers and administration sets) should be protected from light exposure after admixture through administration (see section 4.4). Discard any unused portion and should not be used for subsequent admixing.

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 metabolise the constituents of Primene 10% amino acids IV solution for infusion,
- additional nutrition that may be provided parenterally and/or enterally.

Primene solution for infusion is not intended for fluid or volume replacement.

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 meet nutrient needs and prevent deficiencies and complications from developing (see section 6.2).

The osmolarity of a specific infusion solution must be taken into account when peripheral administration is considered.

Strongly hypertonic parenteral nutrition solutions (> 900mOsm/L) should be administered through a central venous catheter with the tip located in a large central vein.

The flow rate must be adjusted taking into account the dose being administered, the daily volume intake, and the duration of the infusion.

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

The use of a final filter is required during administration of 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.

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.

Parenteral protein requirements for pre-term (2.5 - 3.0g/kg/day), neonates (2.0 - 2.5g/kg/day) and infants (1.5 - 2.0g/kg/day) are greater than those of older children and adults.

Dosage

The recommended dosage of Primene 10% amino acids IV solution for infusion, in neonates and infants, is 1.5 to 3.5 grams of amino acids per kilogram of body weight per day, which corresponds to 15 to 35mL of Primene 10%. This dosage will provide an amount of 0.23 to 0.53 grams of nitrogen per kilogram per day.

Routes of administration

Central or peripheral venous catheter:

- *Primene 10% alone:* administered by central venous catheter with a maximum infusion rate of 0.05mL/kg/minute.
- *Primene in co-administration or mixed with another product:* administered by central or peripheral venous catheter depending on the final Osmolarity of the infused solution.

Duration of the infusion

Primene 10% solution: in order to deliver the maximum recommended daily dose of Primene 10%, it should be given as 24 hours continuous infusion at a rate of 0.024mL/kg/min, or as 12 hours continuous infusion at a rate of 0.05mL/kg/min.

Neonates and infants: 24-hours continuous infusion but the duration is not to exceed 24 hours from opening of the bottle.

The flow rate must be adjusted taking into account the dose being administered, the daily volume intake, and the duration of the infusion.

Notes on the dosage and administration: Strongly hypertonic nutrient solutions should be administered through an indwelling intravenous catheter with the tip located in the superior vena cava (see section 4.2/Compatibility). Administration of amino acid solutions and other nutrients via central venous catheter may be associated with complications, which may be prevented or minimised by careful attention to all aspects of the procedure. This includes attention to the preparation of the solution, administration and patient monitoring. It is essential that a carefully prepared protocol, based on current medical practices, be followed, preferably by an experienced team. The following summary lists complications based on current literature.

Hepatic impairment

Administration of parenteral amino acids to a patient with hepatic insufficiency may result in serum amino acid imbalances; hyperammonemia, stupor and coma (see section 4.4).

Renal impairment

Care should be taken to avoid circulatory overload in patients with renal impairment (see section 4.4).

Sepsis

A risk of sepsis is present during administration of parenteral nutrition solutions. Since contaminated solutions and infusion catheter are potential sources of infection, it is imperative that the preparation of the solution and the placement and care of the catheters be accomplished under controlled aseptic conditions. If fever develops, the solution, its delivery system and the site of indwelling catheter should be changed. Solutions ideally should be prepared in the hospital pharmacy under a laminar

flow hood. The key factor in their preparation is careful aseptic technique to avoid inadvertent touch contamination during mixing of solutions and addition of other nutrients. These solutions should be used promptly after mixing, within 24 hours of preparation. Discard any portion of Primene 10% remaining in the bottle (see section 4.2/Compatibility).

Technical

Insertion 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, haemothorax, artery puncture and transection, injury to the brachial plexus, malposition of catheter, formation of arteriovenous fistula, phlebitis, thrombosis, cardiac arrhythmia and catheter embolus.

The total daily dose of Primene 10% 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 nitrogen requirements. Dosage should also be guided by the patient's fluid intake limits and glucose, and nitrogen tolerances, as well as metabolic and clinical response.

Total daily fluid intake should be appropriate for the patient's age and size. A fluid dose of 125mL per kilogram body weight per day is appropriate for most infants on total parenteral nutrition (TPN). Therefore, if oral feeding is not possible or advisable and TPN is necessary, the volume restrictions dictate how to administer Primene 10%, glucose, lipids and most electrolytes in the same hypertonic solution through intravenous line.

Central vein administration

Strongly hypertonic (> 900mOsm/L) mixtures of amino acids and glucose 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, 0.04mL/kg/min., gradually increasing to the recommended 60 - 120mL 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 glucose. Daily intake of amino acids and glucose should be increased gradually to the maximum of required dose, as indicated by frequent determinations of urine and blood sugar levels.

Peripheral vein administration

For patients requiring parenteral nutrition, in which the central vein route is not indicated, this injection can be mixed with low concentration glucose solutions and administered by peripheral vein in conjunction with or without fat emulsions. Reduction of protein loss can be achieved by the use of diluted Primene 10% in combination with glucose or with glucose and intravenous fat emulsion by peripheral infusion. Complete peripheral intravenous nutrition can be achieved in patients with low caloric requirements by a Primene infusion-glucose-fat regimen.

Compatibility

The complex chemical and physical properties of intravenous lipid emulsions may lead to instability of the emulsion when it is incorporated in a matrix of admixture of 3-in-1 TPN. Instability may result in cracking or oiling out of the emulsion. Thus, caution should be exercised regarding compatibility of Primene 10% solution for infusion with IV glucose solution and IV fat emulsion in admixture of 3-in-1 TPN. The order of the mixing should be firstly to mix Primene 10% having a buffer capacity with glucose component (pH ranges 3.2 to 6.5), then to add intravenous fat emulsion into the obtained Primene 10% and glucose admixture. The final admixture is a light, milky-white, homogenous

solution. The mixture should remain free from any separated oil and should not have any cream layer.

It is expected that a 3-in-1 TPN admixture compounded from solutions of amino acid (hypertonic), glucose (10% and higher are hypertonic) and lipid emulsion (isotonic) would result in a hypertonic solution. The osmolarity of the final admixture will depend on the proportions of these components with or without electrolytes addition. A typical admixture of 3-in-1 TPN compounded from Primene 10% (100mL), Glucose solution (40g/L), lipid emulsion 20% (100mL) and electrolytes (sodium 35mmol, potassium 35mmol, magnesium 2.5mmol, calcium gluconate 10mmol, phosphate 10mmol, of the final admixture) had been shown to have an osmolality of 490mOsmol/kg. The administration of such hypertonic admixture should be by central venous catheter.

The hyperosmolar solutions used in TPN lead readily to phlebitis and dermal and subcutaneous extravasation from peripheral cannulae. It is strongly advised that the peripheral cannulae sites are inspected frequently (one to two hourly) and that cannulae are resited once a day as the conditions of the infants permit.

4.3 Contraindications

Primene 10% amino acids IV solution for infusion solution is contraindicated in children with a congenital abnormality in the metabolism of one or more amino acids, irreversible hepatic damage, untreated uraemia, or known hypersensitivity to any of the active substances or excipients, or to components of the container.

4.4 Special warnings and precautions for use

Administrations of Primene 10% amino acids IV solutions for infusion require knowledge of fluid-electrolyte balance and nutrition as well as clinical expertise in recognition and treatment of the complications, which may occur. Frequent clinical evaluation and laboratory determinations are necessary during the treatment with Primene 10% amino acids IV solution for infusion. Monitoring should be appropriate to the patient's clinical situation and condition, and should include determinations of water and electrolyte balance, acid/base balance, blood and urine dextrose, serum proteins, kidney and liver function tests, serum and urine osmolarity, and the level of ammonia in the plasma.

It is essential to provide adequate energy from other sources concurrently if the amino acids administered parenterally are to be retained by the body and utilised for protein synthesis. Concentrated glucose solutions and lipid emulsions are an effective source of such energy. Electrolytes may be added with this injection as dictated by the patient's electrolyte profile.

Care should be taken to avoid circulatory overload, particularly in patients with cardiac insufficiency and/or renal failure.

Jaundice in children has been reported in association with administration of some parenteral nutrients containing amino acids. The jaundice appeared to be cholestatic in type, and was reversible after reduction of parenteral nutrition intake. This reaction appears to be related to product origin or deficiency of the enzymes required in the urea cycle of the amino acid metabolism, such as carbamoyl phosphate synthetase (cysthathionase deficiency), which is under genetic control. It is essential that blood ammonia be measured frequently in infants. The normal ammonia plasma level in neonates is (20 – 100µmol/L) which is about twice the adult values (10 – 50µmol/L).

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 (see section 4.8). The infusion must be stopped immediately if any signs or symptoms of a reaction develop.

The solution can give rise to allergic-type reactions in susceptible individuals, particularly those with a history of asthma.

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 recognise 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 characterised 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 (see section 4.8).

Metabolic effects
The following metabolic complications have also been reported: metabolic acidosis, hypophosphataemia, alkalosis, hyperglycaemia and glycosuria, osmotic diuresis and dehydration, rebound hypoglycaemia, elevated liver enzyme, hypo- and hypervitaminosis, electrolyte imbalances. Frequent clinical evaluation and laboratory determinations are necessary, especially during the first few days of therapy, to prevent or minimise these complications.

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 (see section 4.4/Use in hepatic impairment).

Risk of air embolism

Do not connect containers in series in order to avoid air embolism due to possible residual air in the primary container.

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 (e.g. with necrosis and blistering) when associated with extravasation (see section 4.8/Other Reactions). Patients should be monitored accordingly.

Primene amino acids IV infusion must not be infused through the same tubing with blood or blood components unless there is documentation that it is safe.

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.

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 infants and neonates, Primene 10% amino acids intravenous solution for infusion should be protected from ambient light after admixture until administration is complete (see section 4.2).

Use in hepatic impairment

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 (see below).

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 (see section 4.3) or hepatic insufficiency.

Administration of parenteral amino acid solutions to a patient with hepatic insufficiency may result in serum amino acid imbalances, hyperammonaemia, stupor and coma. Hyperammonaemia is of special significance in infants.

Blood ammonia should be measured frequently in newborns and infants to detect hyperammonaemia.

Depending on extent and aetiology, hyperammonaemia may require immediate intervention.

Use in renal impairment
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 (e.g. with uraemia). Nitrogen tolerance may be altered and dosage may have to be adjusted. Fluid and electrolyte status should be closely monitored in these patients.

Use in the elderly
No data available.

Paediatric use
Please refer to precautions above.

Effects on laboratory tests
No data available.

4.5 Interaction with other medicines and other forms of interaction
No interaction studies have been performed by Baxter Healthcare Corporation with Primene 10% amino acids IV solution for infusion.

4.6 Fertility, pregnancy and lactation
Fertility
No animal studies were conducted to investigate impairment of fertility potential of Primene 10% amino acids IV solution for infusion.

Use in pregnancy
There are no adequate data from the use of Primene 10% amino acids IV solution for infusion in pregnant women. The prescriber should carefully consider the potential risks and benefits for each specific patient before administering Primene 10% amino acids IV solution for infusion.

Breast-feeding
There are no adequate data from the use of Primene 10% amino acids IV solution for infusion in lactating women. The prescriber should carefully consider the potential risks and benefits for each specific patient before administering Primene 10% amino acids IV solution for infusion.

4.7 Effects on ability to drive and use machines
There is no information of the effects of Primene 10% amino acids IV solution for infusion on the ability to operate an automobile or other heavy machinery.

4.8 Undesirable effects
The subjects treated in the clinical trial were premature infants, thus, the adverse events classified by body system are restricted to respiratory system and laboratory data. The following table lists adverse events occurring in the 5-day comparative clinical trial, between Primene 10% and Vamin/glucose.

Adverse events in a 5-day comparative clinical study between Primene 10% *vs*. Vamin/glucose (total infants included, n = 48, and located in one hospital)		
Adverse events by body system	Primene 10% (n = 23)	Vamin/glucose (n = 25)
Respiratory system:		
Respiratory distress: day 1	18 (78%)	23 (92%)
day 5	11 (48%)	16 (64%)
Laboratory data:		
Plasma electrolytes	within reference ranges	within reference ranges
Blood urea nitrogen (BUN)	within reference ranges	within reference ranges
Liver function*:	mean (± sd) in Unit/L	mean (± sd) in Unit/L
- alanine aminotransferase, ALT		
day 1	6.9 (6.1)	4.9 (2.9)
day 5	3.7 (1.1)	11.3 (9.6)
- aspartate aminotransferase, AST		
day 1	30.8 (23.8)	47.5 (30.6)
day 5	16.4 (10.3)	33.0 (18.4)
- γ glutamyltransferase, γGT		
day 1	79 (49)	62.0 (33)
day 5	63 (66)	60.0 (28)
* Note: normal range for premature infants: alanine aminotransferase (ALT, 20.0 – 132.0U/L); aspartate aminotransferase (AST, 19.0 – 138.0U/L); [γ-glutamyl transferase, γGT, 65.0U/L for male and 45U/L for female adult, the Merck Manual (1999), 17th Ed, p.2535; the value for infants is about twice that of adult].		

Both groups of infants included were acidotic in conventional terms throughout the clinical study, but they were within the values of the neonatal unit's reference for infants with severe respiratory problems on ventilators.

As described under the Pharmacology/Clinical trial section, four infants died, three in the Primene 10% group and one in the amino acids 7% with glucose 10% IV infusion group, at the stage of allocation to the five-day first-week of life clinical trial. These deaths were not attributed to either of the amino acids parenteral treatments but were thought due to their extreme prematurity. No death was reported during the five-day clinical study.

However, during the treatment for a gradual adjustment to the oral feeding, eight deaths occurred in the amino acids 7% with 10% glucose IV infusion group. Four infants who had birth weight of < 1kg died at days 6, 10, 17 and 28, whilst those having birth weight of > 1kg died at days 10, 11, 20 and 28. The cause of the deaths was mainly due to respiratory distress syndrome. Deaths in all cases were related to complications of prematurity, including sepsis, intra-abdominal haemorrhage and sepsis, intraventricular haemorrhage, chronic lung dysplasia and hyaline membrane disease.

Adverse events in a 5-day open and non-randomised clinical study with Primene 10% (total infants included (n = 51), completed (n = 42), and located in one hospital)			
Adverse events by body system		Primene (n = 42, completed)	Normal range in the centre (hospital)
Respiratory system:			
Respiratory distress:	day 0	37 (37/42 = 88%)	
	day 5	29 (29/42 = 69%)	
Laboratory data:			
Plasma electrolytes: mmol/L		mean (± sd; n)	
Sodium	day 0	138.359 (1.076; n = 39)	136 - 148mmol/L
	day 5	138.351 (0.927; n = 37)	
Potassium	day 0	4.417 (0.151; n = 40)	4.3 - 7.6mmol/L
	day 5	4.631 (0.145; n = 36)	
Calcium	day 0	2.168 (0.064; n = 40)	2.00 - 2.80mmol/L
	day 5	2.538 (0.044; n = 37)	2.20 - 2.70mmol/L
Phosphorous	day 0	1.622 (0.078; n = 39)	1.87 - 2.90mmol/L
	day 5	0.955 (0.069; n = 33)	1.58 - 2.87mmol/L
Blood urea nitrogen (BUN)			
	day 0	5.656 (0.454; n = 41)	2.5 - 6.5mmol/L
	day 5	5.105 (0.615; n = 38)	
Plasma ammonia (NH_3): µmol/L		mean (n = 14)	20 - 100µmol/L
	day 5	132.72µmol/L	(not in the hospital list)
Liver function:		mean (± sd) in IU/L	
alkaline phosphatase	day 0	208.967 (16.145; n = 30)	< 300U/L
	day 5	270.00 (19.696; n = 34)	(normal:50.0 - 675.0U/L)
Bilirubin		mean (± sd) in µmol/L	
	day 0	99.673 (9.248; n = 32)	< 25 hrs (< 100µmol/L)
	day 5	104.010 (9.852; n = 33)	48 hrs (< 130µmol/L)
			3 – 5 days (< 200µmol/L)

The adverse events listed in the table above were compiled from a 5-day non-randomised clinical trial with Primene 10%. As in the case of the randomised comparative clinical trial between Primene 10% and amino acids 7% with glucose 10% IV infusion, the adverse events profile is similar. The electrolytes and BUN levels were within the normal ranges of that hospital. In this clinical study, 14/51 infants had serum ammonia performed at day 6 of the trial with an average of 132.72µmol/L level, ranging from 52.8 – 232.3µmol/L. This average is slightly higher than the normal range for infant in full term (20 – 100µmol/L), in particular one of the infants had a level of 232.3µmol/L.

Fourteen of the 51 infants included in the trial died. All 14 infants were < 1200g at birth (range 700 to 1190g) and gestational age varied from 23 to 32 weeks. Six of the infants died during or just after the trial, i.e. from 2 - 9 days and the causes of the death are sepsis (n = 1), cardiogenic shock or cardiac arrest (n = 2), pneumothorax (n = 2), pneumothorax and sepsis (n = 1). The other 8 infants died long after the clinical trial was completed with similar causes of death. The mortality rate in that hospital was 50% and 20% for premature infants of < 1000g birth weight and of > 1000g birth weight, respectively. Thus, the mortality rate of 27% (14/51) for these critically ill infants was in keeping with the unit's usual mortality rate.

Post-marketing adverse reactions

The adverse reactions listed below have been identified from post-marketing reports of Primene 10% amino acids IV solution for infusion administered as a component of parenteral nutrition.

IMMUNE SYSTEM DISORDERS: Hypersensitivity reaction manifested by face oedema, eyelid oedema, rash.

Other reactions

Adverse reactions reported with parenteral amino acid products include:

- Azotemia, hyperammonemia

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.
- Metabolic acidosis.
- Pulmonary vascular precipitates.
- Necrosis, blistering, swelling, scarring, skin discoloration at the infusion site associated with extravasation (see section 4.4/Infusion Site Reaction statement).
- Infusion site thrombophlebitis; venous irritation (infusion site phlebitis, pain, erythema, warmth, swelling, induration).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continuing monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphv.otago.ac.nz/reporting/

4.9 Overdose

In the event of inappropriate administration (overdose, and/or infusion rate higher than recommended), hypervolaemia, 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.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group

Solutions for parenteral nutrition - amino acids

ATC code

B05BA01.

Mechanism of action

The composition of the amino acids formulated in Primene 10% amino acids IV solution for infusion was designed to mimic that of amino acids in the umbilical cord of the last trimester of pregnancy. When Primene 10% is mixed with hypertonic glucose in a TPN admixture, it provides essential and nonessential amino acids for protein synthesis, while the glucose component provides energy. It contains relatively low methionine and reduced amounts of phenylalanine and proline in order to match a limited capacity of the neonate's immature enzyme system.

Primene 10% amino acids IV solution for infusion also contains taurine. Taurine plays a role in the development and function of the brain and retina. The intracellular level of taurine is normally high in mature retina, muscle and in developing brain tissue. In neonates, the activity of cystathionase, the enzyme that converts methionine to cysteine, is low. Cysteine is a substrate for taurine synthesis.

Clinical trials

A five-day comparative study between Primene 10% and Vamin/glucose, designed as a double blind and randomised trial in neonates, using a total parenteral nutrition (TPN) admixture delivery system, was conducted at a single centre in London, UK. The TPN solutions were infused by constant intravenous infusion over 24 hours through peripheral cannulae. [*N. McIntosh, V Mitchell, "A clinical trial of two parenteral nutrition solutions in neonates", Arch. Dis Child*, (1990), 65, 692 – 699].

The inclusion criteria were neonates who were unable to tolerate enteral feeds (oral feeding) and thus requiring TPN for at least five consecutive days in the first week of life. Sixty-eight neonates were randomly allocated to either Primene 10% (n = 34) or comparator IV infusion, amino acids 7% with glucose 10% (n = 34) in a double-blind fashion. Comparability of the groups was stratified to infants above and below 1000g birth-weights. As premature infants, they were critically ill, 41 were ventilated (85%) at the time of the entry to the study and 27 (52%) were still ventilated on the sixth day, the end of the trial.

Forty-eight of the infants completed the five-day study protocol, Primene 10% group (n = 23) and amino acids 7% with glucose 10% IV infusion group (n = 25). Four infants died at the stage of allocation to this five-day first-week of life clinical trial. These deaths were not related to either of the amino acids parenteral nutrition supplement compounded in the TPN admixtures. These infants died due to their extreme prematurity and all had birth-weight of less than 1000g. Death frequency for these critically ill patients was in accordance with the mortality rate of these types of patients treated at that hospital. The other 16 infants (eight in each group), who dropped out did not require the full five days parenteral amino acids infusion, thus, were excluded from the analysis.

Efficacy was evaluated clinically on the basis of head circumference, and plasma amino acid levels. The body weight was also measured. Plasma amino acids levels and liver function tests were analysed on Days 1 and 5. When interpreting the results, it should be borne in mind that these infants were unstable, both from clinical and biochemical parameter perspectives.

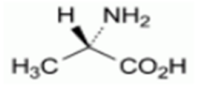
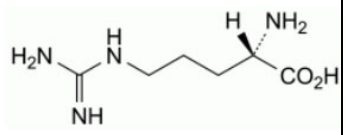
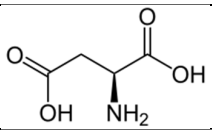
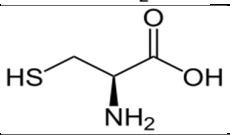
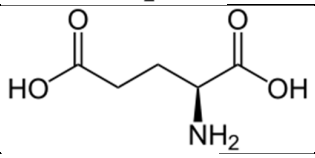
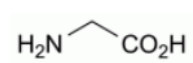
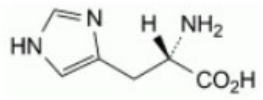
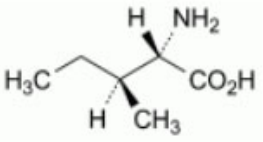
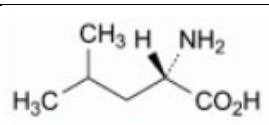
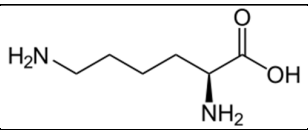
The body weight losses in both groups were similar, which were comparable to body weight decreases of infants borne at full term. No significant differences were detected on the head circumference-decreases in both groups.

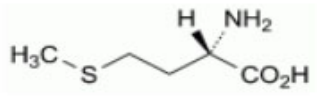
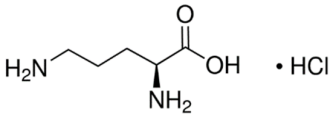
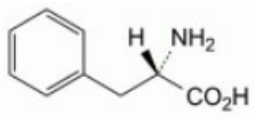
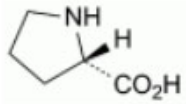
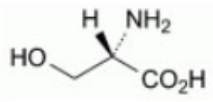
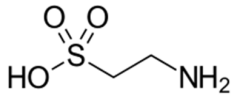
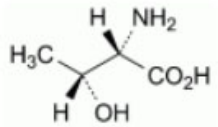
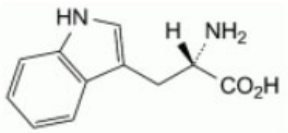
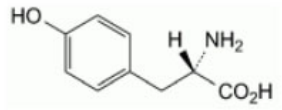
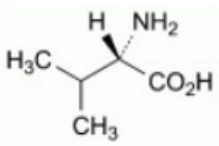
On Day 5 of the trial, blood plasma of infants treated with Primene 10% (n = 14) and those treated with amino acids 7% with glucose 10% IV infusion (n = 16) were taken for assay of amino acid levels. Eighteen (9 in each group) were not assayed due to insufficient amount of plasma samples. The results are shown in the following table. For a discussion on the other results, see section 4.8.

Plasma aminograms (µmol/L) on Day 5 in infants on Primene 10% and Vamin/glucose, according to birth weight, in comparison with range of values in cord blood from full terms infants.				
	Birth weight (kg)	Primene 10%	Vamin	Normal Range
Leu	< 1	97.6 (47.8)	142.9 (67.8)	82.7 - 187.3
	> 1	140.7 (65.2)	134.5 (50.6)	
IsoL	< 1	37.2 (27.6)	79.6 (47.6)	36.4 - 107.6
	> 1	71.2 (39.3)	85.6 (30.6)	
Val	< 1	175.1 (67.2)	244.5 (76.1)	171.8 - 314.2
	> 1	240.3 (99.5)	272.5 (75.9)	
Meth	< 1	30.5 (15.5)	46.8 (15.6)	20.4 - 49.7
	> 1	39.4 (15.8)	54.6 (15.3)[a]	
Cyst	< 1	15.4 (5.8)[b]	32.8 (18.8)	32.4 - 57.6
	> 1	34.5 (8.4)	49.6 (24.2)	
Tau	< 1	90.8 (34.7)[b]	110 (96.4)[b]	115.1 - 378.9
	> 1	142.6 (69.4)	194.6 (115.1)	
Phe	< 1	86.4 (15.8)	206.1 (73)[a]	48.9 - 99.1
	> 1	89.4 (33)	198.5 (68.7)[a]	
Tyr	< 1	91.4 (100)[a]	368.7 (309.7)[a]	35.8 - 90.2
	> 1	61.3 (51.6)	386.1 (372.7)[a]	
Lys	< 1	195.9 (93.5)[b]	198.2 (88.7)[b]	216.4 - 467.6
	> 1	322.1 (151.7)	201.1 (84.4)[b]	
Thr	< 1	144.2 (40.2)[b]	281.1 (125.6)	161.3 - 374.7
	> 1	182.7 (74.1)	299.1 (133.8)	
Hist	< 1	88.8 (26.8)	121.1 (44.1)	63.4 - 180.6
	> 1	119 (45.7)	117.8 (29.2)	
Arg	< 1	46.7 (33.8)[b]	54.3 (44.5)	47.5 - 114.5
	> 1	90.3 (52.3)	49 (23.5)	
Asp. Acid	< 1	16.8 (10.4)	61.5 (70.3)[a]	6.4 - 35.7
	> 1	40.1 (50.9)[a]	51.7 (32.9)[a]	
Ser	< 1	131.9 (36)[b]	315.1 (167.7)[a]	143.4 - 214.6
	> 1	197 (66.2)	344.1 (183.1)[a]	
Asn (Asparagin)	< 1	22.8 (13.4)[b]	24.4 (12.3)[b]	28.4 - 53.6
	> 1	31.3 (18.9)	28.9 (25.7)	
Glu	< 1	55.2 (15.4)[b]	204.7 (156.5)	58.3 - 313.7
	> 1	110 (130.6)	192.4 (150.5)	
Gln	< 1	328.1 (111.2)	321.3 (131.4)	219.3 - 834.7
	> 1	710.3 (680.5)	432.5 (130.6)	
Pro	< 1	126.6 (88.2)	411.5 (169.4)[a]	101.7 - 252.4
	> 1	200.9 (72.2)	478.3 (211.1)[a]	
Gly	< 1	216.8 (54.1)	358.6 (101.8)[a]	199.9 - 338.1
	> 1	335.7 (108.8)	417.2 (177.6)[a]	
Ala	< 1	224.8 (114.8)[b]	285.5 (136.8)	281 - 595
	> 1	306.3 (176)	379.7 (228)	
Cit	< 1	7.2 (3.6)	14.6 (4.7)	2.55
	> 1	8.8 (4.2)	15.0 (11.1)	
Orn	< 1	80 (49.4)	78.4 (54.3)	45.4 - 162.6
	> 1	137.3 (71.6)	98 (75)	

Notes : Birth weight < 1kg # = 5; > 1kg # = 9 on **Primene** 10%
Birth weight < 1kg # = 8; > 1kg # = 8 on Vamin/glucose
a = above normal range; b = below normal range.
*) = Rigo J. Thesis University of Liege, Belgium (1980) see, *N.McIntosh, V. Mitchell, "A clinical trial of two parenteral nutrition solutions in neonates", Arch. Dis. Child., (1990), **65**, 695*)

Chemical structure and CAS numbers

Chemical Name	Molecular Formula and Molecular Mass	Structural Formula	Physiochemical properties	CAS Number
Alanine	$C_3H_7NO_2$ 89.1		White or almost white, crystalline powder or colourless crystals. Freely soluble in water, very slightly soluble in ethanol (96%).	56-41-7
Arginine	$C_6H_{14}N_4O_2$ 174.2		White or almost white, crystalline powder or colourless crystals, hygroscopic. Freely soluble in water, very slightly soluble in ethanol (96%).	74-79-3
Aspartic acid	$C_4H_7NO_4$ 133.1		Colourless crystals. Solubility in water: 4.5g/L. Insoluble in ethanol, ethyl ether, benzene; soluble in dilute HCl, pyridine.	6899-03-2
Cysteine	$C_3H_7NO_2S$ 121.15		White crystals or powder. Soluble in water; soluble 1.5g/100g ethanol (19°C).	52-90-4
Glutamic acid	$C_5H_9NO_4$ 147.1		White crystals or crystalline powder. Sparingly soluble in water; practically insoluble in ethanol or ether.	56-86-0
Glycine	$C_2H_5NO_2$ 75.1		White or almost white, crystalline powder. Freely soluble in water, very slightly soluble in ethanol (96%).	56-40-6
Histidine	$C_6H_9N_3O_2$ 155.2		White or almost white, crystalline powder or colourless crystals. Soluble in water, very slightly soluble in ethanol (96%).	71-00-1
Isoleucine	$C_6H_{13}NO_2$ 131.2		White or almost white, crystalline powder or flakes. Sparingly soluble in water, slightly soluble in ethanol (96%). It dissolves in dilute mineral acids and in dilute solutions or alkali hydroxides.	73-32-5
Leucine	$C_6H_{13}NO_2$ 131.2		White or almost white, crystalline powder or shiny flakes. Sparingly soluble in water, practically insoluble in ethanol (96%). It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.	61-90-5
Lysine	$C_6H_{14}N_2O_2$ 146.2		Colourless crystalline powder. Freely soluble in water, Insoluble in ethanol, ethyl ether, acetone, benzene.	56-87-1

Chemical Name	Molecular Formula and Molecular Mass	Structural Formula	Physiochemical properties	CAS Number
Methionine	$C_5H_{11}NO_2S$ 149.2		White or almost white, crytalline powder or colourless crystals. Soluble in water, very slightly soluble in ethanol (96%).	63-68-3
Ornithine mono-hydrochloride	$C_5H_{12}N_2O_2 \cdot HCl$ 168.62		White and odourless powder. Soluble in water.	3184-13-2
Phenylalanine	$C_9H_{11}NO_2$ 165.2		White or almost white, crystalline powder, or shiny, white flakes. Sparingly soluble in water, very slightly soluble in ethanol (96%). It dissolves in dilute mineral acids and in dilute solutions of alkali hydroxides.	63-91-2
Proline	$C_5H_9NO_2$ 115.1		White or almost white, crystalline powder or colourless crystals. Very soluble in water, freely soluble in ethanol (96%).	147-85-3
Serine	$C_3H_7NO_3$ 105.1		White or almost white, crystalline powder or colourless crystals. Freely soluble in water, practically insoluble in ethanol (96%).	56-45-1
Taurine	$C_2H_7NO_3S$ 125.1		Colourless crystals. Solubility in water: 62.5mg/mL at 20°C, water (65mg/mL at 12°C), and DMSO (< 1 mg/mL, 25°C). Insoluble in ethanol, and diethyl ether.	107-35-7
Threonine	$C_4H_9NO_3$ 119.1		White or almost white, crystalline powder or colourless crystals. Soluble in water, practically insoluble in ethanol (96%).	72-19-5
Tryptophan	$C_{11}H_{12}N_2O_2$ 204.2		White or almost white, crystalline or amorphous powder. Sparingly soluble in water, slightly soluble in ethanol (96%). It dissolves in dilute solutions of mineral acids and alkali hydroxides.	73-22-3
Tyrosine	$C_9H_{11}NO_3$ 181.2		White or almost white, crystalline powder or colourless crystals. Very slightly soluble in water, practically insoluble in ethanol (96%). It dissolves in dilute mineral acids in dilute solutions of alkali hydroxides.	60-18-4
Valine	$C_5H_{11}NO_2$ 117.1		White or almost white, crystalline powder or colourless crystals. Soluble in water, very soluble in ethanol (96%).	72-18-4

5.2 Pharmacokinetic properties

As the administration of **Primene** 10% is by the intravenous route, bioavailability of the active ingredients is complete. No other data are available.

Metabolism

Ammonia is one of the deamination products of amino acids metabolism, that is, the amino group is converted to either ammonia or it is transferred via the enzyme aminotransferase to form another amino acid. Ammonia is metabolised to urea. The first step in the urea biosynthesis is the reaction of ammonia and carbon dioxide catalysed by carbamoyl phosphate synthetase (CPS) to form carbamoyl phosphate. Then, carbamoyl phosphate enters the Krebs Cycle urea synthesis.

5.3 Preclinical safety data

Genotoxicity

No animal studies were conducted to investigate genotoxic potential of **Primene** 10% amino acids IV solution for infusion.

Carcinogenicity

No animal studies were conducted to investigate carcinogenic potential of **Primene** 10% amino acids IV solution for infusion.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Primene contains the following excipients:

Each 1000mL of Primene 10% (w/v) solution for infusion contains	
Other Constituents	
Malic acid q.s. to make pH 5.5 (range 5 – 6.5)	≤ 3.2g
Water for Injection q.s. for	1000mL

6.2 Incompatibilities

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 (see section 4.4).

6.3 Shelf life

24 months from date of manufacture. The expiry date can be found on the packaging.

Open shelf life

When compounding use aseptic technique: see section 4.2. Any admixture should be used as soon as possible after compounding; otherwise it should be stored under refrigeration and used within 24 hours from the time of compounding of the admixture. Discard any unused portion (including any admixtures) after 24 hours from opening the bottle.

6.4 Special precautions for storage

Store product at or below 25°C. Protect from light.

6.5 Nature and contents of container

Primene 10% amino acids IV solution for infusion is presented in glass bottles (clear, colourless to slightly yellow solution): 100mL and 250mL.

Note: Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused product or waste material should be disposed of in accordance with local requirements.

Instructions for use and handling, and disposal

- Visually inspect the container for cracks. If the port protector is damaged, detached, or not present, discard container as solution path sterility may be impaired.
- Aseptic conditions must be observed.
- Inspect final solution for discoloration and particulate matter. Use only if the solution is clear.

If additions to the container are made

- Aseptic conditions must be observed.
- 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.
- When used in infants and neonates, protect from light exposure when admixtures include trace elements and/or vitamins, after admixture through administration. Exposure of Primene 10% amino acids IV infusion to ambient light after admixture generates peroxides and other degradation products that can be reduced by photoprotection (see section 4.4).
- Inspect final solution for discoloration and particulate matter.
- Confirm the integrity of the container. Use only if the container is not damaged and the solution is clear.
- Ensure proper storage requirements of additives are followed.

Administration of the infusion

- Allow the solution to reach room temperature before use.
- Aseptic conditions must be observed.
- For single use only.
- Confirm the integrity of the container. Use only if the container is not damaged and the solution is clear.
- Do not reconnect any partially used container.
- Inspect final solution for discoloration and particulate matter.
- Do not connect containers in series in order to avoid air embolism due to possible residual air contained in the primary container.

7 MEDICINE SCHEDULE

General Sale Medicine.

8 SPONSOR

Primene is distributed in New Zealand by:

Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

Primene is distributed in Australia by:
Baxter Healthcare Pty Ltd
1 Baxter Drive
Old Toongabbie, NSW 2146.

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
4 April 2002.

10 DATE OF REVISION OF THE TEXT

19 November 2019.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All sections	Formatting, spelling, grammar corrected throughout.
4.2, 4.4, 6.6	Safety related changes - Information added regarding protect from light exposure.
6.5	Appearance included.

Based on Australian PI most recent amendment 7 November 2019; and CCSI433 2019 2308.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.

Primene and Baxter are trademarks of Baxter International Inc.