SUMMARY OF PRODUCT CHARACTERISTICS

Primene 10% Solution for Infusion

1. NAME OF THE MEDICINAL PRODUCT

Primene 10%

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each liter of the infusion solution contains:

L-Isoleucine	6.70 g
L-Leucine	10.0 g
L-Valine	7.60 g
L-Lysine	11.00 g
L-Methionine	2.40 g
L-Phenylalanine	4.20 g
L-Threonine	3.70 g
L-Tryptophan	2.00 g
L-Arginine	8.40 g
L-Histidine	3.80 g
L-Alanine	8.00 g
L-Aspartic Acid	6.00 g
L-Cysteine	1.89 g
L-Glutamic Acid	10.00 g
Glycine	4.00 g
L-Proline	3.00 g
L-Serine	4.00 g
L-Tyrosine	0.45 g
L-Ornithine Hydrochloride	3.18 g
Taurine	0.6 g

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
A clear, colourless solution.
Primene 10% has a pH of 5.5 and an osmolarity of 780 mOsmol/L.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Primene 10% is indicated in 1) children and infants 2) neonates, at term or premature, of normal or low birth weight when oral or enteral nutrition is impossible, insufficient or contraindicated.

4.2 Posology and method of administration

Posology

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%,
- additional nutrition that may be provided parenterally and/or enterally.

The usual range is:

Posology		Maximal administration rate
g/kg/day (24 hours)	ml/kg/day (24 hours)	ml/kg/min
1.5 to 3.5 g of amino acids or 0.23 to 0.53 g of nitrogen	15 to 35	0.05

The administration rate should never exceed 0.05 ml/kg/min.

Recommended flow rates

Neonates and infants: continuous infusion (over 24 hours).

Children up to 12 years: - continuous infusion over 24 hours;
- cyclic infusion (over about 12 hours in 24)

The flow rate should be adjusted according to the dosage, the characteristics of the infusion solution, the total volume intake per 24 hours and the infusion duration.

The flow rate should be increased gradually during the first hour.

Method of administration

Primene 10% is intended for intravenous use.

Primene 10% is not intended for fluid or volume replacement.

When used in neonates and children below 2 years of age, the solution (in bottles and administration sets) should be protected from light exposure until administration is completed (see sections 4.4, 6.3 and 6.6).

Primene 10% is usually administered with a source of energy that is adjusted to the child's needs, by co-administration or as a mixture.

Primene 10% may be included in the composition of nutritive mixtures combining carbohydrates, lipids, electrolytes, trace elements and vitamins to meet nutrient needs and prevent deficiencies and complications from developing, when compatibility and stability are known (see section 6.2).

Primene 10% alone should be administered in a central vein.

Primene 10% in co-administration or as a mixture should be administered according to the final osmolarity of the solution infused, in a peripheral or central vein.

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

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

If deemed appropriate by the healthcare professional, parenteral nutrition solution may be administered peripherally in patients of all ages if the osmolarity of the formulation is ≤ 900 mOsm/L.

4.3 Contraindications

Primene 10% is contraindicated in patients with:
- hypersensitivity to any of the active substances or to any of the excipients listed in section 6.1.
- congenital abnormality of amino acid metabolism.

4.4 Special warnings and precautions for use

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.

Precipitates in Patients Receiving Parenteral Nutrition
Pulmonary vascular precipitates have been reported in patients receiving parenteral nutrition. In some cases, fatal outcomes have occurred. Excessive addition of calcium and phosphate increases the risk of the formation of calcium phosphate precipitates. Precipitates have been reported even in the absence of phosphate salt in the solution. Precipitation distal to the in line filter and suspected in vivo precipitate formation has also been reported.
If signs of pulmonary distress occur, the infusion should be stopped and medical evaluation initiated.
In addition to inspection of the solution, the infusion set and catheter should also periodically be checked for precipitates.

Infectious complications
Infection and sepsis may occur as a result of intravenous catheters used to administer parenteral formulations, poor maintenance of catheters or contaminated solutions.
Immunosuppression and other factors such as hyperglycaemia, malnutrition and/or their underlying disease state may predispose patients to infectious complications.
Careful symptomatic and laboratory monitoring for fever/chills, leukocytosis, technical complications with the access device, and hyperglycaemia can help recognize early infections.
The occurrence of septic complications can be decreased with heightened emphasis on aseptic technique in catheter placement, maintenance, as well as aseptic technique in nutritional formula preparation.

Refeeding Syndrome in Patients Receiving Parenteral Nutrition
Refeeding severely undernourished patients may result in the refeeding syndrome that is characterized by the shift of potassium, phosphorus, and magnesium intracellularly as the patient becomes anabolic. Thiamine deficiency and fluid retention may also develop. Careful monitoring and slowly increasing nutrient intakes while avoiding overfeeding can prevent these complications.

Hypertonic solutions
Hypertonic infusion solutions may cause irritation of the vein, vein damage, and thrombosis when administered into a peripheral vein (see section 4.8).
In view of its osmolality, Primene 10% should not be infused alone into a peripheral vein.

General Monitoring
Monitoring should be appropriate to the patient's clinical situation and condition, and should include determinations of water and electrolyte balance, serum osmolarity, acid/base balance, blood glucose levels, blood ammonia levels, and liver and kidney function.

Metabolic Effects
Metabolic complications may occur if the nutrient intake is not adapted to the patient's requirements, or the metabolic capacity of any given dietary component is not accurately assessed. Adverse metabolic effects may arise from administration of inadequate or excessive nutrients or from inappropriate composition of an admixture for a particular patient's needs.

Hepatic function
Patients on parenteral nutrition may experience hepatic complications (including cholestasis, hepatic steatosis, fibrosis and cirrhosis, possibly leading to hepatic failure, as well as cholecystitis and cholelithiasis) and should be monitored accordingly.
The etiology of these disorders is thought to be multifactorial and may differ between patients. Patients developing abnormal laboratory parameters or other signs of hepatobiliary disorders should be assessed by a clinician knowledgeable in liver diseases in order to identify possible causative and contributory factors, and possible therapeutic and prophylactic interventions.
Amino acid solutions should be used with caution in patients with pre-existing liver disease or liver insufficiency.
Liver function parameters should be closely monitored in these patients, and they should be monitored for possible symptoms of hyperammonaemia.
Increase in blood ammonia levels and hyperammonaemia may occur in patients receiving amino acid solutions. In some patients this may indicate the presence of a congenital disorder of amino acid metabolism (see section 4.3) or hepatic insufficiency.
Blood ammonia should be measured frequently in newborns and infants to detect hyperammonaemia.
Depending on extent and etiology, hyperammonaemia may require immediate intervention.

Renal effects
Azotaemia has been reported with parenteral administration of solutions containing amino acids, and may occur in particular in the presence of renal impairment.
Use with caution in patients with renal insufficiency (with e.g., uraemia). Nitrogen tolerance may be altered and dosage may have to be adjusted. Fluid and electrolyte status should be closely monitored in these patients.

Additional precautions
- Light exposure of solutions for intravenous parenteral nutrition, especially after admixture with trace elements and/or vitamins, may have adverse effects on clinical outcomes in neonates, due to the generation of peroxides and other degradation products. When used in neonates and children below 2 years of age, Primene 10% should be protected from ambient light until administration is completed (see sections 4.2, 6.3, and 6.6).
- 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 section 4.8. Patients should be monitored accordingly.

- Severe water and electrolyte disorders, severe fluid overload states, and severe metabolic disorders should be corrected before starting the infusion.
- Use with caution in patients with pulmonary oedema or heart failure. Fluid status should be closely monitored.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
The compatibility and stability of nutritive mixtures should be confirmed before administration.

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of Primene 10% in pregnant or lactating women. Healthcare Professionals should carefully consider the potential risks and benefits for each specific patient before administering Primene 10%.

4.7 Effects on ability to drive and use machines

There is no information of the effects of Primene 10% on the ability to drive or operate other heavy machinery.

4.8 Undesirable effects

The adverse reactions listed below have been identified from post-marketing reports of Primene 10% administered as a component of parenteral nutrition. The frequency of the adverse drug reactions listed in this section cannot be estimated from the available data.

Tabulated summary of adverse reactions		
System Organ Class (SOC)	**Preferred MedDRA Term**	**frequency**
IMMUNE SYSTEM DISORDERS	Hypersensitivity reaction manifested by: • Face oedema, • Eyelid oedema, • Rash	Not known

Adverse reactions reported with parenteral amino acid products include:
- Azotaemia, Hyperammonaemia.

Adverse reactions reported with parenteral nutrition to which the amino acid component may play a causal or contributory role include:
- Anaphylactic/anaphylactoid reactions, including skin, gastrointestinal, and severe circulatory (shock) and respiratory manifestations as well as other hypersensitivity/ infusion reactions, including pyrexia, chills, hypotension, hypertension, arthralgia, myalgia, urticaria, pruritus, erythema, and headache.
- Hepatic failure, Hepatic cirrhosis, Hepatic fibrosis, Cholestasis, Hepatic steatosis, Blood bilirubin increased, Hepatic enzyme increased; Cholecystitis, Cholelithiasis.
- Raised blood urea nitrogen in children with renal insufficiency.
- Metabolic acidosis.
- Pulmonary vascular precipitates.
- Necrosis, blistering, swelling, scarring, skin discoloration at the infusion site associated with extravasation (See also infusion site reaction statement in section 4.4).
- Infusion site thrombophlebitis; Venous irritation (infusion site phlebitis, pain, erythema, warmth, swelling, induration).

Amino acid solutions may precipitate acute folic acid deficiency which should be corrected by supplements.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Solutions for parenteral nutrition - amino acids

ATC Code: B05BA01

Primene 10% is a solution of 20 L-Amino Acids, intended to correspond qualitatively and quantitatively to the protein needs of the child:
- contains all essential or semi-essential amino acids for the child;
- contains relatively high lysine content;
- contains Taurine;
- contains relatively low Methionine content;
- contains reduced Phenylalanine and Proline content.

$$\frac{\text{8 Essential Amino Acids}}{\text{Total Amino Acids}} = 47.5 \text{ per cent}$$

$$\frac{\text{Branched Chain Amino Acids}}{\text{Total Amino Acids}} = 24 \text{ per cent}$$

Clinical Trials have shown that in combination with a balanced energy supply Primene 10% allows for satisfactory growth in terms of height and weight as well as satisfactory psychomotor development in the child.

Primene 10% is deliberately formulated without electrolytes in order not to interfere with specific electrolyte therapy.

5.2 Pharmacokinetic Properties

Primene 10% is administered intravenously and is therefore immediately available in the blood stream.

5.3 Preclinical Safety Data

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Malic Acid (for pH adjustment)
Water for Injections

6.2 Incompatibilities

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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).

The addition of trace elements may cause formation of visible particulate matter (see section 6.6).

6.3. Shelf Life

The expiry date of the product is indicated on the packaging materials.

When used in neonates and children below 2 years of age, the solution (in bottles and administration sets) should be protected from light exposure until administration is completed (see sections, 4.2, 4.4 and 6.6).

6.4 Special precautions for storage

Do not store above 25°C. Protect from light.

6.5. Nature and Contents of Container

Type II Glass Bottles with an elastomeric stopper containing 100ml, 250ml of solution. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Visually inspect the container. Only use if the container is undamaged and the solution is clear.

Discard if the container is leaking or if the solution is discoloured, cloudy or contains a precipitate.

Aseptic conditions must be observed throughout the preparation and use of Primene 10%.

For single use only.

If additions are made to the container:
Ensure stability and compatibility of additives. Consult with pharmacist.
Prepare the injection site of the container as appropriate.
Puncture the injection site and inject the additives using an injection needle or a reconstitution device/transfer set, as appropriate.
Mix content of the container and the additives thoroughly.
Inspect final solution for discoloration and particulate matter.
Confirm the integrity of the container. Only use if the container is undamaged and the solution is clear.
Any unused portion of Primene 10% should be discarded and should not be used for subsequent admixing.
Ensure proper storage requirements of additives are followed.

Administration of the infusion:

When used in neonates and children below 2 years of age, protect from light exposure until administration is completed. Exposure of Primene 10% to ambient light, especially after admixture with trace elements and/ or vitamins, generates peroxides and other degradation products that can be reduced by protection from light exposure (see sections, 4.2, 4.4 and 6.3).

Allow the solution to reach room temperature before use.
The use of a final filter is required during administration of all formulations containing Primene 10% and trace elements (including copper, iron, or zinc) for removal of visible particulate matter which has been observed in the infusion line for some formulations.
For 2 in 1 (amino acid and carbohydrate) parenteral nutrition solutions, use a <1.2 micron filter for removal of particulate matter that may be formed with the use of trace elements (e.g. copper). For 3 in 1 (lipid, amino acid, and carbohydrate) parenteral nutrition solutions, use a 1.2 micron filter for particulate matter removal.
Perform visual inspections for cloudiness or precipitation of the TPN solution, infusion set, catheter and in-line filter after compounding, prior to administration and periodically during administration. If discolouration or precipitation is noted in the filter, perform blood levels of copper (or other trace elements) where medically relevant.
Discard any unused contents. Do not reconnect any partially used container.
Do not connect containers in series in order to avoid air embolism due to possible residual air in the primary container.
Primene 10% must not be infused through the same tubing with blood or blood components unless there is documentation that it is safe.
Attach administration set. Refer to 'Instructions for Use' accompanying the set.

7. LICENSE HOLDER AND MANUFACTURER

License Holder
Remedix Care Ltd., 8 Haorgim St., Ashdod.

Manufacturer
Baxter S.A, Lessines, Belgium.

8. REGISTRATION NUMBER

123.47.30286

Revised in January 2021