תאריך: אוקטובר 2019

רופא/ה, רוקח/ת נכבד/ה

חברת טבע מודיעה על העדכונים הבאים בעלון לרופא של התכשיר

פרימן® 10 %

PRIMENE® 10% Solution for Infusion

Contains:

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

עדכונים בעלון לרופא

<u>התוויה כפי שאושרה בתעודת הרישום:</u>

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.

ברצוננו להודיע שהעלונים עודכנו, בפירוט שלהלן כלולים העדכונים העיקריים בלבד (תוספות מסומנות באדום):

עדכונים בעלון לרופא:

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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
• 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 in pregnant or lactating women.
Healthcare Professionals should carefully consider the potential risks and benefits for each specific patient before administering Primene.

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4.8 Undesirable effects

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

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

Adverse reactions reported with parenteral amino acid products include:

- Azotaemia, Hyperammonaemia.

Adverse reactions reported with parenteral nutrition to which the amino acid component may play a causal or contributory role include:

- Anaphylactic/anaphylactoid reactions, including skin, gastrointestinal, and severe circulatory (shock) and respiratory manifestations as well as other hypersensitivity/infusion reactions, including pyrexia, chills, hypotension, hypertension, arthralgia, myalgia, urticaria, pruritus, erythema, and headache.
- Hepatic failure, Hepatic cirrhosis, Hepatic fibrosis, Cholestasis, Hepatic steatosis, Blood bilirubin increased, Hepatic enzyme increased; Cholecystitis, Cholelithiasis.
- Raised blood urea nitrogen in children with renal insufficiency.
- Metabolic acidosis.

- Pulmonary vascular precipitates.
- Necrosis, blistering, swelling, scarring, skin discoloration at the infusion site associated with extravasation (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.

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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.

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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).

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

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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 should be discarded and should not be used for subsequent admixing.
Ensure proper storage requirements of additives are followed.

Administration of the infusion:
Allow the solution to reach room temperature before use.
The use of a final filter is required during administration of all formulations containing Primene and trace elements (including copper, iron, or zinc) for removal of visible particulate matter which has been observed in the infusion line for some formulations.
For 2 in 1 (amino acid and carbohydrate) parenteral nutrition solutions, use a <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 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.