תעשיות פרמצבטיות בע"מ

יוני 2013

רופא/ה, רוקח/ת נכבד/ה
חברת טבע שמחה לבשר שמשרד הבריאות אישר את רישומם של התכשירים:

TRIOMEL 9 g/l nitrogen 1070 kcal/l,
TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes

Emulsion for infusion
FOR TOTAL PARENTERAL NUTRITION (TPN)

Emulsions for infusion containing mixture of aminoacids, Nitrogen in L-series amino acids And energy (glucose and triglycerides)
TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes: with electrolytes
TRIOMEL 9 g/l nitrogen 1070 kcal/l without electrolytes

תכשירים חדשים

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

Parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.

העלון לרופא נשלח לפרסום במאגר התרופות שבאתר האינטרנט של משרד הבריאות http://www.health.gov.il, וניתן לקבלו מודפס ע"י פניה לחברת טבע.

טבע תעשיות פרמצבטיות בע"מ.
רחוב התאנה 1 פארק תעשיה חמ"ן, ת.ד. 975 , שוהם 60850 טל: 03-6864645 , פקס 03-6864944 www.tevapharm.com

"פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר".
עלון מאושר: מרץ 2013

"This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved." Date of approval: March 2013

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, is presented in the form of a 3-compartment bag.

Each bag contains a glucose solution, a lipid emulsion and an amino acid solution.

	1500 ml	2000 ml
27.5% Glucose solution (corresponding to 27.5 g/100 ml)	600 ml	800 ml
14.2% Amino acid solution (corresponding to 14.2 g/100 ml)	600 ml	800 ml
20% Lipid emulsion (corresponding to 20 g/100 ml)	300 ml	400 ml

Composition of the reconstituted emulsion after mixing the contents of the 3 compartments:

Active substances	1500 ml	2000 ml
Refined olive oil + refined soybean oil[a]	60.00 g	80.00 g
Alanine	12.36 g	16.48 g
Arginine	8.37 g	11.16 g
Aspartic acid	2.47 g	3.30 g
Glutamic acid	4.27 g	5.69 g
Glycine	5.92 g	7.90 g
Histidine	5.09 g	6.79 g
Isoleucine	4.27 g	5.69 g
Leucine	5.92 g	7.90 g
Lysine (equivalent to lysine acetate)	6.72 g (9.48 g)	8.96 g (12.64 g)
Methionine	4.27 g	5.69 g
Phenylalanine	5.92 g	7.90 g
Proline	5.09 g	6.79 g
Serine	3.37 g	4.50 g
Threonine	4.27 g	5.69 g
Tryptophan	1.42 g	1.90 g
Tyrosine	0.22 g	0.30 g
Valine	5.47 g	7.29 g
Glucose anhydrous (equivalent to glucose monohydrate)	165.00 g (181.50 g)	220.00 g (242.00 g)

a: Mixture of refined olive oil (approximately 80%) and refined soybean oil (approximately 20%) corresponding to a ratio essential fatty acids/total fatty acids of 20%.

For a full list of excipients, see section 6.1.

Nutritional intakes of reconstituted emulsion for each of the bag sizes:

	1500 ml	2000 ml
Lipids	60 g	80 g
Amino acids	85.4 g	113.9 g
Nitrogen	13.5 g	18.0 g
Glucose	165.0 g	220.0 g
Energy:		
Total calories approx.	1600 kcal	2140 kcal
Non-protein calories	1260 kcal	1680 kcal
Glucose calories	660 kcal	880 kcal
Lipid calories[a]	600 kcal	800 kcal
Non-protein calories/nitrogen ratio	93 kcal/g	93 kcal/g
Glucose/lipid calories ratio	52/48	52/48
Lipid/total calories	37%	37%
Electrolytes:		
Phosphate[b]	4.5 mmol	6.0 mmol
Acetate	60 mmol	80 mmol
pH	6.4	6.4
Osmolarity	1170 mosm/l	1170 mosm/l

a: Includes calories from purified egg phosphatide
b: Includes phosphate provided by the lipid emulsion

3. PHARMACEUTICAL FORM

After reconstitution:

Emulsion for infusion.

Appearance prior to reconstitution:

- The amino acids and glucose solutions are clear, colourless or slightly yellow,
- The lipid emulsion is homogenous with a milky appearance.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, is indicated for parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.

4.2 Posology and method of administration

Posology

TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion is not recommended for use in children less than 2 years of age due to inadequate composition and volume (see sections 4.4, 5.1 and 5.2).

In adults

The dosage depends on the patient's energy expenditure, clinical status, body weight, and the ability to metabolise the constituents of TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, as well as additional energy or proteins provided orally/enterally; therefore, the bag size should be chosen accordingly.

The average daily requirements are:

- 0.16 to 0.35 g nitrogen/kg body weight (1 to 2 g of amino acids/kg), depending on the patient's nutritional status and degree of catabolic stress,
- 20 to 40 kcal/kg,
- 20 to 40 ml fluid/kg, or 1 to 1.5 ml per expended kcal.

For TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, the maximal daily dose defined by amino acids intake, 35 ml/kg corresponding to 2.0 g/kg amino acids, 3.9 g/kg glucose, and 1.4 g/kg lipids. For a 70 kg patient, this would be equivalent to 2450 ml TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, per day, resulting in an intake of 140 g amino acids, 270 g glucose, and 98 g lipids (i.e., 2058 non-protein kcal and 2622 total kcal).

Normally, the flow rate must be increased gradually during the first hour and then be adjusted to take into account the dose being administered, the daily volume intake, and the duration of the infusion.

For TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, the maximal infusion rate is 1.8 ml/kg/hour, corresponding to 0.10 g/kg/hour amino acids, 0.19 g/kg/hour glucose, and 0.07 g/kg/hour lipids.

In children greater than 2 years of age

There have been no studies performed in the pediatric population.

The dosage depends on the patient's energy expenditure, clinical status, body weight, and the ability to metabolise constituents of TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, as well as additional energy or proteins given orally/enterally; therefore, the bag size should be chosen accordingly.

In addition, daily fluid, nitrogen, and energy requirements continuously decrease with age. Two groups, ages 2 to 11 years and 12 to 18 years, are considered.

For TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, the limiting factors for the above-mentioned paediatric age groups are the amino acid concentration for both daily dose and hourly rate, resulting in the following intakes:

	2 to 11 years		12 to 18 years	
Constituent	Recommended[a]	TRIOMEL 9 g/l nitrogen 1070 kcal/l Max Vol	Recommended[a]	TRIOMEL 9 g/l nitrogen 1070 kcal/l Max Vol
Maximum Daily Dose				
Fluids (ml/kg/d)	60–120	53	50–80	35
Amino acids (g/kg/d)	1–2 (up to 3)	3	1–2	2
Glucose (g/kg/d)	12–14 (up to 18)	5.8	3–10 (up to 14)	3.9
Lipids (g/kg/d)	0.5–3	2.1	0.5–2 (up to 3)	1.4
Total energy (kcal/kg/d)	75–90	56	30–75	37
Maximum Hourly Rate				
TRIOMEL 9 g/l nitrogen 1070 kcal/l (ml/kg/h)		3.5		2.1
Amino acids (g/kg/h)	0.20	0.20	0.12	0.12
Glucose (g/kg/h)	1.2	0.39	1.2	0.23
Lipids (g/kg/h)	0.17	0.14	0.13	0.08

a: Recommended values from ESPEN-ESPGHAN Guidelines

Normally, the flow rate must be increased gradually during the first hour and then be adjusted to take into account the dose being administered, the daily volume intake, and the duration of the infusion.

In general, it is recommended to start the infusion for small children with low dose (i.e., 12.5 to 25 ml/kg) and gradually increase it up to the maximal dosage (see above).

Method and duration of administration

For single use only.

It is recommended that, after opening the bag, the contents are used immediately and are not stored for a subsequent infusion.

After reconstitution, the mixture is homogenous with a milky appearance.

For instructions for preparation and handling of the emulsion for infusion, see section 6.6.

Due to its high osmolarity, TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion can only be administered through a central vein.

The recommended duration of infusion for a parenteral nutrition bag is between 12 and 24 hours.

Treatment with parenteral nutrition may be continued for as long as required by the patient's clinical conditions.

4.3 Contraindications

The use of TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion is contraindicated in the following situations:

- In premature neonates, infants, and children less than 2 years of age,
- Hypersensitivity to egg, soybean, or peanut proteins, or to any of the active substances or excipients,
- Congenital abnormalities of amino acid metabolism,
- Severe hyperlipidaemia or severe disorders of lipid metabolism characterized by hypertriglyceridemia,
- Severe hyperglycemia,

4.4 Special warnings and precautions for use

An excessively fast administration of total parenteral nutrition (TPN) solutions may result in severe or fatal consequences.

The infusion must be stopped immediately if any signs or symptoms of an allergic reaction (such as sweating, fever, chills, headache, skin rashes, or dyspnea) develop. This medicinal product contains soybean oil, and egg phosphatide. Soybean and egg proteins may cause hypersensitivity reactions. Cross-allergic reactions between soybean and peanut proteins have been observed.

Do not add other medicinal products or substances to any components of the bag or to the reconstituted emulsion without first confirming their compatibility and the stability of the resulting preparation (in particular, the stability of the lipid emulsion).

Excess addition of calcium and phosphorus may result in the formation of calcium phosphate precipitates. Formation of such precipitates or destabilization of the lipid emulsion could result in vascular occlusion (see section 6.2 and 6.6).

Severe water and electrolyte equilibration disorders, severe fluid overload states, and severe metabolic disorders must be corrected before starting the infusion.

Specific clinical monitoring is required when an intravenous infusion is started.

Vascular-access infection and sepsis are complications that may occur in patients receiving parenteral nutrition, particularly in case of poor maintenance of catheters, immunosuppressive effects of illness or drugs. Careful monitoring of signs, symptoms, and laboratory test results for fever/chills, leukocytosis, technical complications with the access device, and hyperglycemia can help recognize early infections. Patients who require parenteral nutrition are often predisposed to infectious complications due to malnutrition and/or their underlying disease state. The occurrence of septic complications can be decreased with heightened emphasis on aseptic techniques in catheter placement and maintenance, as well as aseptic techniques in the preparation of the nutritional formula.

Monitor water and electrolyte balance, serum osmolarity, serum triglycerides, acid/base balance, blood glucose, liver and kidney function tests, coagulation tests, and blood count, including platelets, throughout treatment.

Elevated liver enzymes and cholestasis have been reported with similar products. Monitoring of serum ammonia should be considered if hepatic insufficiency is suspected.

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.

Administration of amino acid solutions may precipitate acute folate deficiency; folic acid is, therefore, recommended to be given daily.

Hepatic insufficiency

Use with caution in patients with hepatic insufficiency because of the risk of developing or worsening neurological disorders associated with hyperammonaemia. Regular clinical and laboratory tests are required, particularly blood glucose, electrolytes and triglycerides.

Renal insufficiency

Use with caution in patients with renal insufficiency, particularly if hyperkalaemia is present, because of the risk of developing or worsening metabolic acidosis and hyperazotemia if extra-renal waste removal is not being performed. Fluid, triglycerides and electrolyte status should be closely monitored in these patients.

Hematologic

Use with caution in patients with coagulation disorders and anaemia. Blood count and coagulation parameters should be closely monitored.

Endocrine and metabolism

Use with caution in patients with:

- Metabolic acidosis. Administration of carbohydrates is not recommended in the presence of lactic acidosis. Regular clinical and laboratory tests are required.
- Diabetes mellitus. Monitor glucose concentrations, glucosuria, ketonuria and, where applicable adjust insulin dosages.
- Hyperlipidaemia due to the presence of lipids in the emulsion for infusion. Regular clinical and laboratory tests are required.
- Amino acid metabolism disorders.

Serum triglyceride concentrations and the ability of the body to remove lipids must be checked regularly.

Serum triglyceride concentrations must not exceed 3 mmol/L during the infusion.

If a lipid metabolism abnormality is suspected, it is recommended to measure daily serum triglyceride levels after a period of 5 to 6 hours without administering lipids. In adults, the serum must be clear in less than 6 hours after stopping the infusion containing the lipid emulsion. The next infusion must only be administered when the serum triglyceride concentrations have returned to baseline values.

Fat overload syndrome has been reported with similar products. Reduced ability to remove the lipids contained in TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion may result in a "fat overload syndrome" which may be caused by overdose; however, the signs and symptoms of this syndrome may also occur when the product is administered according to instructions (see also section 4.8).

In the event of hyperglycemia, the infusion rate of TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, must be adjusted and/or insulin administered.

DO NOT ADMINISTER THROUGH A PERIPHERAL VEIN.

When making additions, the final osmolarity of the mixture must be measured before administration. The mixture obtained must be administered through a central or peripheral venous line depending on its final osmolarity. If the final mixture administered is hypertonic, it may cause irritation of the vein when administered into a peripheral vein.

Although there is a natural content of trace elements and vitamins in the product, the levels are insufficient to meet body requirements, and these should be added to prevent deficiencies from developing. See instructions for making additions to this product.

Caution should be exercised in administering TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, to patients with increased osmolarity, adrenal insufficiency, heart failure or pulmonary dysfunction.

In malnourished patients, initiation of parenteral nutrition can precipitate fluid shifts resulting in pulmonary oedema and congestive heart failure, as well as a decrease in the serum concentration of potassium, phosphorus, magnesium, or water-soluble vitamins. These changes can occur within 24 to 48 hours; therefore, careful and slow initiation of parenteral nutrition is recommended together with close monitoring and appropriate adjustments of fluid, electrolytes, trace elements, and vitamins.

Do not connect bags in series in order to avoid the possibility of air embolism due to residual air contained in the primary bag.

Special precautions in paediatrics

When administered to children greater than 2 years of age, it is essential to use a bag that has a volume corresponding to the daily dosage.

TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, is not suitable for the use in children less than 2 years of age because:

- The glucose intake is too low, leading to a low glucose/lipid ratio,
- The absence of cysteine makes the amino acid profile inadequate,
- Phosphates are too low and other electrolytes are not included,
- The bag volumes are not appropriate.

In children greater than 2 years of age, additional glucose should be infused to reach the above-mentioned recommended daily dose. Phosphates and calcium should be supplemented to reach the recommended amounts in children (approximately 0.2 mmol/kg/d).

Vitamin and trace elements supplementation is always required. Paediatric formulations must be used.

To avoid risks associated with excessively rapid infusion rates, it is recommended to use a continuous and controlled infusion.

Intravenous infusion of amino acids is accompanied by increased urinary excretion of trace elements, in particular copper and zinc. This should be taken into account in the dosing of trace elements, especially during long-term intravenous nutrition.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion must not be administered simultaneously with blood through the same infusion tubing because of the possibility of pseudoagglutination.

The lipids contained in this emulsion may interfere with the results of certain laboratory tests (for example, bilirubin, lactate dehydrogenase, oxygen saturation, blood haemoglobin) if the blood sample is taken before the lipids are eliminated (these are generally eliminated after a period of 5 to 6 hours without receiving lipids).

TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, contains vitamin K, naturally present in lipid emulsions. The amount of vitamin K in recommended doses of TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, is not expected to influence effects of coumarin derivatives.

4.6 Fertility, pregnancy and lactation

There are no clinical data from the use of TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, in pregnant or lactating women. Taking into account the use and indications of TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, the product may be considered during pregnancy and breastfeeding, if necessary.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Potential undesirable effects may occur as a result of inappropriate use (for example: overdose, excessively fast infusion rate) (see sections 4.4 and 4.9).

At the beginning of the infusion, any of the following abnormal signs (sweating, fever, shivering, headache, skin rashes, dyspnoea) should be cause for immediate discontinuation of the infusion:

The following adverse drug reactions (ADRs) were reported with TRIOMEL 9g/l nitrogen 1070 kcal/l in a randomized, double-blind, active-controlled, efficacy and safety study. Twenty-eight patients with various medical conditions (i.e., postsurgical fasting, severe malnutrition, enteral intake insufficient or forbidden) were included and treated; patients in the TRIOMEL 9g/l nitrogen 1070 kcal/l group received drug product up to 40 mL/kg/d over 5 days.

System Organ Class	MedDRA Preferred Term	Frequency[a]
Cardiac Disorders	Tachycardia	Common
Metabolism and Nutrition Disorders	Anorexia	Common
	Hypertriglyceridemia	Common
Gastrointestinal Disorders	Abdominal pain	Common
	Diarrhea	Common
	Nausea	Common
Vascular Disorders	Hypertension	Common

a: Frequency is defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); or not known (cannot be estimated from the available data).

The following class-like-adverse drug reactions (ADRs) have been described in other sources in relation to similar parenteral nutrition products; the frequency of these events is not known.

Blood and lymphatic system disorders: thrombocytopenia

Hepatobiliary disorders: hepatomegaly, jaundice

Immune system disorders: hypersensitivity

Investigations: blood alkaline phosphatase increased, transaminases increased, blood bilirubin increased

Renal and urinary disorders: azotemia

Fat overload syndrome (very rare)

Fat overload syndrome has been reported with similar products. Reduced ability to remove the lipids contained in TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, may result in a "fat overload syndrome" which may be caused by overdose; however, the signs and symptoms of this syndrome may also occur at the start of an infusion when the product is administered according to instructions. This syndrome is associated with a sudden deterioration in the patient's clinical condition and is characterized by hyperlipidemia, fever, liver fatty infiltration, hepatomegaly, anemia, leukopenia, thrombocytopenia, coagulation disorders, and coma, requiring hospitalization. These symptoms are usually reversible when the lipid emulsion infusion is stopped.

4.9 Overdose

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

An excessively fast infusion or administration of an inappropriately large volume of the product may cause nausea, vomiting, chills and electrolyte disturbances. In such situations the infusion must be stopped immediately.

Hyperglycaemia, glucosuria, and a hyperosmolar syndrome may develop if glucose infusion rate exceeds clearance.

A reduced ability to remove lipids may result in a "fat overload syndrome", the effects of which are usually reversible after the lipid infusion is stopped (see also section 4.8).

In some serious cases, haemodialysis, haemofiltration or haemodiafiltration may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Solutions for parenteral nutrition/combinations

ATC code: B05 BA10.

TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion's content in nitrogen (L series amino acids) and energy (glucose and triglycerides) enables maintaining an adequate nitrogen/energy balance.

This formulation without electrolytes allows individual electrolyte intake to be adapted to meet specific requirements.

The lipid emulsion included in TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, is an association of refined olive oil and refined soybean oil (ratio 80/20), with the following approximate distribution of fatty acids:

- 15% saturated fatty acids (SFA)
- 65% monounsaturated fatty acids (MUFA)
- 20% polyunsaturated essential fatty acids (PUFA)

The phospholipid/triglyceride ratio is 0.06.

Olive oil contains significant amounts of alpha-tocopherol which, combined with a moderate PUFA intake, contribute to improved vitamin E status and the reduction of lipid peroxidation.

The amino acid solution contains 17 L series amino acids (including 8 essential amino acids), which are required for protein synthesis.

Amino acids also represent an energy source. Their oxidation results in excretion of nitrogen in the form of urea.

The amino acid profile is as follows:

- Essential amino acids/total amino acids: 44.8%
- Essential amino acids (g)/total nitrogen (g): 2.8%
- Branched-chain amino acids/total amino acids: 18.3%

The carbohydrate source is glucose.

5.2 Pharmacokinetic properties

The ingredients of TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion (amino acids, glucose and lipids) are distributed, metabolised and removed in the same way as if they had been administered individually.

5.3 Preclinical safety data

No preclinical studies with TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion have been performed.

Preclinical toxicity studies performed using the lipid emulsion contained in TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, have identified the changes, which are conventionally found with a high intake of a lipid emulsion: fatty liver, thrombocytopaenia and elevated cholesterol.

Preclinical studies performed using the solutions of amino acids and glucose contained in TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion, of different qualitative compositions and concentrations have not, however, revealed any specific toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lipid emulsion compartment:

Purified egg phosphatide, Glycerol, Sodium oleate, Sodium hydroxide (for pH adjustment), Nitrogen, Water for injections.

Amino acid solution compartment:

Glacial acetic acid (for pH adjustment), Nitrogen, Water for injections.

Glucose solution compartment:

Hydrochloric acid (for pH adjustment), Nitrogen, Water for injections.

6.2 Incompatibilities

Do not add other medicinal products or substances to any components of the bag or to the reconstituted emulsion without first confirming their compatibility and the stability of the resulting preparation (in particular, the stability of the lipid emulsion).

Incompatibilities may be produced, for example, by excessive acidity (low pH) or inappropriate content of divalent cations (Ca^{2+} and Mg^{2+}), which may destabilize the lipid emulsion.

Check compatibility with solutions administered simultaneously through the same administration set, catheter, or cannula.

Do not administer before, simultaneously with, or after blood through the same equipment because of the risk of pseudoagglutination.

6.3 Shelf life after reconstitution

After reconstitution

It is recommended that the product be used immediately after the nonpermanent seals between the 3 compartments have been reconstituted. However, the stability of the reconstituted emulsion has been demonstrated for 7 days (between 2°C and 8°C) and maximum 48 hours at temperature not exceeding 25°C.

After addition of supplements (electrolytes, trace elements and vitamins; see section 6.6)

For specific admixtures, in-use stability has been demonstrated for 7 days (between 2°C and 8°C) followed by 48 hours at temperature not exceeding 25°C.

From a microbiological point of view, any admixture should be used immediately. If not used immediately, storage times and conditions, after mixing and prior to use, are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless addition of supplements has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 25°C.

Do not freeze.

Store in the overpouch.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

The 3-compartment bag is a multilayer plastic bag. The inner (contact) layer of the bag material is made of a blend of polyolefinic copolymers and is compatible with amino acid solutions, glucose solutions, and lipid emulsions. Other layers are made of polyethylene vinyl acetate (EVA), and of copolyester.

The glucose compartment is fitted with an injection site to be used for addition of supplements.

The amino acid compartment is fitted with an administration site for insertion of the spike of the infusion set.

The bag is packaged in an oxygen barrier overpouch with an oxygen absorber sachet and may include an oxygen indicator (OXYDETECT™).

Pack sizes:

1500 ml bag: 1 carton with 4 bags

2000 ml bag: 1 carton with 4 bags

6.6 Special precautions for disposal and other handling

Check the colour of the oxygen indicator, if present, before opening the overpouch. Compare it to the reference colour printed next to the OK symbol and depicted in the printed area of the indicator label. Do not use the product if the colour of the oxygen indicator does not correspond to the reference colour printed next to OK symbol.

To open

Remove the protective overpouch.

Discard the oxygen absorber/oxygen indicator sachet.

Confirm the integrity of the bag and of the nonpermanent seals. Use only if the bag is not damaged; if the nonpermanent seals are intact (i.e., no mixture of the contents of the 3 compartments); if the amino acid solution and the glucose solution are clear, colourless, or slightly yellow, and practically free of visible particles; and if the lipid emulsion is a homogeneous liquid with a milky appearance.

Mixing the solutions and the emulsion

Ensure that the product is at room temperature when breaking the nonpermanent seals.

Manually roll the bag onto itself, starting at the top of the bag (hanger end). The nonpermanent seals will disappear from the side near the inlets. Continue to roll the bag until the seals are open along approximately half of their length.

Mix by inverting the bag at least 3 times.

After reconstitution, the mixture is a homogeneous emulsion with a milky appearance.

Additions

The capacity of the bag is sufficient to enable additions such as vitamins, electrolytes, and trace elements.

Any additions (including vitamins) may be made into the reconstituted mixture (after the nonpermanent seals have been opened and after the contents of the 3 compartments have been mixed).

Vitamins may also be added into the glucose compartment before the mixture is reconstituted (before opening the nonpermanent seals and before mixing the 3 compartments).

When making additions to formulations containing electrolytes, the amount of electrolytes already present in the bag should be taken into account.

Additions must be performed by qualified personnel under aseptic conditions.

TRIOMEL 9 g/l nitrogen 1070 kcal/l, emulsion for infusion may be supplemented with electrolytes according to the table below:

	Per 1000 ml		
	Included level	**Maximal further addition**	**Maximal total level**
Sodium	0 mmol	150 mmol	150 mmol
Potassium	0 mmol	80 mmol	80 mmol (except for patients that are in Intensive Care Unit)
Magnesium	0 mmol	5.6 mmol	5.6 mmol
Calcium	0 mmol	5.0 (3.5[a]) mmol	5.0 (3.5[a]) mmol
Inorganic Phosphate	0 mmol	8.0 mmol	8.0 mmol
Organic Phosphate	3 mmol[b]	22 mmol	25 mmol[b]

a: Value corresponding to the addition of inorganic phosphate.
b: Including phosphate provided by the lipid emulsion.

Trace elements and vitamins:

Stability has been demonstrated with commercially-available preparations of vitamins and trace elements (containing up to 1 mg of iron).

Compatibility for other additives is available upon request.

When making additions, the final osmolarity of the mixture must be measured before administration via a peripheral vein.

To perform an addition:

- Aseptic conditions must be observed.
- Prepare the injection site of the bag.
- Puncture the injection site and inject the additives using an injection needle or a reconstitution device.
- Mix content of the bag and the additives.

Preparation of the infusion

Aseptic conditions must be observed.

Suspend the bag.

Remove the plastic protector from the administration outlet.

Firmly insert the spike of the infusion set into the administration outlet.

Administration

For single use only.

Only administer the product after the nonpermanent seals between the 3 compartments have been broken and the contents of the 3 compartments have been mixed.

Ensure that the final emulsion for infusion does not show any evidence of phase separation.

After opening the bag, the contents must be used immediately. The opened bag must never be stored for a subsequent infusion. Do not reconnect any partially used-bag.

Do not connect bags in series in order to avoid the possibility of air embolism due to air contained in the primary bag.

Any unused product or waste material and all necessary devices must be discarded.

7. REGISTRATION NUMBER

149 52 33420 00

8. MANUFACTURER

Baxter Healthcare Limited,
Thetford, Norfolk,
United Kingdom.

9. LICENCE HOLDER

Teva Medical Marketing Ltd.,
Haorgim St. 8, Ashdod 77100.

"פורמט עלון זה נקבע ע"י משרד הבריאות ותוכנו נבדק ואושר."
עלון מאושר: מרץ 2013
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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion is presented in the form of a 3-compartment bag.

Each bag contains a glucose solution with calcium, a lipid emulsion and an amino acid solution with other electrolytes.

	Contents per bag		
	1000 ml	**1500 ml**	**2000 ml**
27.5% Glucose solution (corresponding to 27.5 g/100 ml)	400 ml	600 ml	800 ml
14.2% Amino acid solution (corresponding to 14.2 g/100 ml)	400 ml	600 ml	800 ml
20% Lipid emulsion (corresponding to 20 g/100 ml)	200 ml	300 ml	400 ml

Composition of the reconstituted emulsion after mixing the contents of the 3 compartments:

Active substances	**1000 ml**	**1500 ml**	**2000 ml**
Refined olive oil+ refined soybean oil[a]	40.00 g	60.00 g	80.00 g
Alanine	8.24 g	12.36 g	16.48 g
Arginine	5.58 g	8.37 g	11.16 g
Aspartic acid	1.65 g	2.47 g	3.30 g
Glutamic acid	2.84 g	4.27 g	5.69 g
Glycine	3.95 g	5.92 g	7.90 g
Histidine	3.40 g	5.09 g	6.79 g
Isoleucine	2.84 g	4.27 g	5.69 g
Leucine	3.95 g	5.92 g	7.90 g
Lysine (equivalent to lysine acetate)	4.48 g (6.32 g)	6.72 g (9.48 g)	8.96 g (12.64 g)
Methionine	2.84 g	4.27 g	5.69 g
Phenylalanine	3.95 g	5.92 g	7.90 g
Proline	3.40 g	5.09 g	6.79 g
Serine	2.25 g	3.37 g	4.50 g
Threonine	2.84 g	4.27 g	5.69 g
Tryptophan	0.95 g	1.42 g	1.90 g
Tyrosine	0.15 g	0.22 g	0.30 g
Valine	3.64 g	5.47 g	7.29 g
Sodium acetate, trihydrate	1.50 g	2.24 g	2.99 g
Sodium glycerophosphate, hydrated	3.67 g	5.51 g	7.34 g
Potassium chloride	2.24 g	3.35 g	4.47 g
Magnesium chloride, hexahydrate	0.81 g	1.22 g	1.62 g
Calcium chloride, dihydrate	0.52 g	0.77 g	1.03 g
Glucose anhydrous (equivalent to glucose monohydrate)	110.00 g (121.00 g)	165.00 g (181.50 g)	220.00 g (242.00 g)

a: Mixture of refined olive oil (approximately 80%) and refined soybean oil (approximately 20%) corresponding to a ratio essential fatty acids/total fatty acids of 20%.

For a full list of excipients, see section 6.1.

Nutritional intakes of reconstituted emulsion for each of the bag sizes:

	1000 ml	**1500 ml**	**2000 ml**
Lipids	40 g	60 g	80 g
Amino acids	56.9 g	85.4 g	113.9 g
Nitrogen	9.0 g	13.5 g	18.0 g
Glucose	110.0 g	165.0 g	220.0 g
Energy:			
Total calories approx.	1070 kcal	1600 kcal	2140 kcal
Non-protein calories	840 kcal	1260 kcal	1680 kcal
Glucose calories	440 kcal	660 kcal	880 kcal
Lipid calories[a]	400 kcal	600 kcal	800 kcal
Non-protein calories/ nitrogen ratio	93 kcal/g	93 kcal/g	93 kcal/g
Glucose/ lipid calories ratio	52/48	52/48	52/48
Lipid/total calories	37%	37%	37%
Electrolytes:			
Sodium	35.0 mmol	52.5 mmol	70.0 mmol
Potassium	30.0 mmol	45.0 mmol	60.0 mmol
Magnesium	4.0 mmol	6.0 mmol	8.0 mmol
Calcium	3.5 mmol	5.3 mmol	7.0 mmol
Phosphate[b]	15.0 mmol	22.5 mmol	30.0 mmol
Acetate	54 mmol	80 mmol	107 mmol
Chloride	45 mmol	68 mmol	90 mmol
pH	6.4	6.4	6.4
Osmolarity	1310 mosm/l	1310 mosm/l	1310 mosm/l

a: Includes calories from purified egg phosphatide
b: Includes phosphate provided by the lipid emulsion

3. PHARMACEUTICAL FORM

After reconstitution:

Emulsion for infusion.

Appearance prior to reconstitution:

- The amino acids and glucose solutions are clear, colourless or slightly yellow,
- The lipid emulsion is homogenous with a milky appearance.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion is indicated for parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.

4.2 Posology and method of administration

Posology

TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion is not recommended for use in children less than 2 years of age due to inadequate composition and volume (see sections 4.4, 5.1 and 5.2).

In adults

The dosage depends on the patient's energy expenditure, clinical status, body weight, and the ability to metabolise the constituents of TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, as well as additional energy or proteins provided orally/enterally; therefore, the bag size should be chosen accordingly.

The average daily requirements are:

- 0.16 to 0.35 g nitrogen/kg body weight (1 to 2 g of amino acids/kg), depending on the patient's nutritional status and degree of catabolic stress,
- 20 to 40 kcal/kg,
- 20 to 40 ml fluid/kg, or 1 to 1.5 ml per expended kcal.

For TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion the maximal daily dose is defined by amino acids intake, 35 ml/kg corresponding to 2.0 g/kg amino acids, 3.9 g/kg glucose, 1.4 g/kg lipids, 1.2 mmol/kg sodium, and 1.1 mmol/kg potassium. For a 70 kg patient, this would be equivalent to 2450 ml TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, per day, resulting in an intake of 140 g amino acids, 270 g glucose, and 98 g lipids (i.e., 2058 non-protein kcal and 2622 total kcal).

Normally, the flow rate must be increased gradually during the first hour and then be adjusted to take into account the dose being administered, the daily volume intake, and the duration of the infusion.

For TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, the maximal infusion rate is 1.8 ml/kg/hour, corresponding to 0.10 g/kg/hour amino acids, 0.19 g/kg/hour glucose, and 0.07 g/kg/hour lipids.

In children greater than 2 years of age

There have been no studies performed in the pediatric population.

The dosage depends on the patient's energy expenditure, clinical status, body weight, and the ability to metabolise constituents of 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, as well as additional energy or proteins given orally/enterally; therefore, the bag size should be chosen accordingly.

In addition, daily fluid, nitrogen, and energy requirements continuously decrease with age. Two groups, ages 2 to 11 years and 12 to 18 years, are considered.

For TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, the limiting factors for the above-mentioned paediatric age groups are phosphate concentration for daily dose and amino acid concentration for the hourly rate, resulting in the following intakes:

	2 to 11 years		**12 to 18 years**	
Constituent	Recommended[a]	TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes Max Vol	Recommended[a]	TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes Max Vol
Maximum Daily Dose				
Fluids (ml/kg/d)	60–120	13	50–80	13
Amino acids (g/kg/d)	1–2 (up to 3)	0.8	1–2	0.8
Glucose (g/kg/d)	12–14 (up to 18)	1.5	3–10 (up to 14)	1.5
Lipids (g/kg/d)	0.5–3	0.5	0.5–2 (up to 3)	0.5
Total energy (kcal/kg/d)	75–90	14	30–75	14
Maximum Hourly Rate				
TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes (ml/kg/h)		3.5		2.1
Amino acids (g/kg/h)	0.20	0.20	0.12	0.12
Glucose (g/kg/h)	1.2	0.39	1.2	0.23
Lipids (g/kg/h)	0.17	0.14	0.13	0.08

a: Recommended values from ESPEN-ESPGHAN Guidelines

Normally, the flow rate must be increased gradually during the first hour and then be adjusted to take into account the dose being administered, the daily volume intake, and the duration of the infusion.

In general, it is recommended to start the infusion for small children with low dose (i.e., 12.5 to 25 ml/kg) and gradually increase it up to the maximal dosage (see above).

Method and duration of administration

For single use only.

It is recommended that, after opening the bag, the contents are used immediately and are not stored for a subsequent infusion.

After reconstitution, the mixture is homogenous with a milky appearance.

For instructions for preparation and handling of the emulsion for infusion, see section 6.6.

Due to its high osmolarity, TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, can only be administered through a central vein.

The recommended duration of infusion for a parenteral nutrition bag is between 12 and 24 hours.

Treatment with parenteral nutrition may be continued for as long as required by the patient's clinical conditions.

4.3 Contraindications

The use of TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, is contraindicated in the following situations:

- In premature neonates, infants, and children less than 2 years of age,
- Hypersensitivity to egg, soybean, or peanut proteins, or to any of the active substances or excipients,
- Congenital abnormalities of amino acid metabolism,
- Severe hyperlipidaemia or severe disorders of lipid metabolism characterized by hypertriglyceridemia,
- Severe hyperglycemia,
- Pathologically-elevated plasma concentrations of sodium, potassium, magnesium, calcium, and/or phosphorus.

4.4 Special warnings and precautions for use

An excessively fast administration of total parenteral nutrition (TPN) solutions may result in severe or fatal consequences.

The infusion must be stopped immediately if any signs or symptoms of an allergic reaction (such as sweating, fever, chills, headache, skin rashes, or dyspnea) develop. This medicinal product contains soybean oil, and egg phosphatide. Soybean and egg proteins may cause hypersensitivity reactions. Cross-allergic reactions between soybean and peanut proteins have been observed.

Do not add other medicinal products or substances to any components of the bag or to the reconstituted emulsion without first confirming their compatibility and the stability of the resulting preparation (in particular, the stability of the lipid emulsion).

Excess addition of calcium and phosphorus may result in the formation of calcium phosphate precipitates. Formation of such precipitates or destabilization of the lipid emulsion could result in vascular occlusion (see section 6.2 and 6.6).

Severe water and electrolyte equilibration disorders, severe fluid overload states, and severe metabolic disorders must be corrected before starting the infusion.

Specific clinical monitoring is required when an intravenous infusion is started.

Vascular-access infection and sepsis are complications that may occur in patients receiving parenteral nutrition, particularly in case of poor maintenance of catheters, immunosuppressive effects of illness or drugs. Careful monitoring of signs, symptoms, and laboratory test results for fever/chills, leukocytosis, technical complications with the access device, and hyperglycemia can help recognize early infections. Patients who require parenteral nutrition are often predisposed to infectious complications due to malnutrition and/or their underlying disease state. The occurrence of septic complications can be decreased with heightened emphasis on aseptic techniques in catheter placement and maintenance, as well as aseptic techniques in the preparation of the nutritional formula.

Monitor water and electrolyte balance, serum osmolarity, serum triglycerides, acid/base balance, blood glucose, liver and kidney function tests, coagulation tests, and blood count, including platelets, throughout treatment.

Elevated liver enzymes and cholestasis have been reported with similar products. Monitoring of serum ammonia should be considered if hepatic insufficiency is suspected.

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.

Administration of amino acid solutions may precipitate acute folate deficiency; folic acid is, therefore, recommended to be given daily.

Hepatic insufficiency

Use with caution in patients with hepatic insufficiency because of the risk of developing or worsening neurological disorders associated with hyperammonaemia. Regular clinical and laboratory tests are required, particularly blood glucose, electrolytes and triglycerides.

Renal insufficiency

Use with caution in patients with renal insufficiency, particularly if hyperkalaemia is present, because of the risk of developing or worsening metabolic acidosis and hyperazotemia if extra-renal waste removal is not being performed. Fluid, triglycerides and electrolyte status should be closely monitored in these patients.

Hematologic

Use with caution in patients with coagulation disorders and anaemia. Blood count and coagulation parameters should be closely monitored.

Endocrine and metabolism

Use with caution in patients with:

- Metabolic acidosis. Administration of carbohydrates is not recommended in the presence of lactic acidosis. Regular clinical and laboratory tests are required.
- Diabetes mellitus. Monitor glucose concentrations, glucosuria, ketonuria and, where applicable adjust insulin dosages.
- Hyperlipidaemia due to the presence of lipids in the emulsion for infusion. Regular clinical and laboratory tests are required.
- Amino acid metabolism disorders.

Serum triglyceride concentrations and the ability of the body to remove lipids must be checked regularly.

Serum triglyceride concentrations must not exceed 3 mmol/L during the infusion.

If a lipid metabolism abnormality is suspected, it is recommended to measure daily serum triglyceride levels after a period of 5 to 6 hours without administering lipids. In adults, the serum must be clear in less than 6 hours after stopping the infusion containing the lipid emulsion. The next infusion must only be administered when the serum triglyceride concentrations have returned to baseline values.

Fat overload syndrome has been reported with similar products. Reduced ability to remove the lipids contained in TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, may result in a "fat overload syndrome" which may be caused by overdose; however, the signs and symptoms of this syndrome may also occur when the product is administered according to instructions (see also section 4.8).

In the event of hyperglycemia, the infusion rate of TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, must be adjusted and/or insulin administered.

DO NOT ADMINISTER THROUGH A PERIPHERAL VEIN.

When making additions, the final osmolarity of the mixture must be measured before administration. The mixture obtained must be administered through a central or peripheral venous line depending on its final osmolarity. If the final mixture administered is hypertonic, it may cause irritation of the vein when administered into a peripheral vein.

Although there is a natural content of trace elements and vitamins in the product, the levels are insufficient to meet body requirements, and these should be added to prevent deficiencies from developing. See instructions for making additions to this product.

Caution should be exercised in administering TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, to patients with increased osmolarity, adrenal insufficiency, heart failure or pulmonary dysfunction.

In malnourished patients, initiation of parenteral nutrition can precipitate fluid shifts resulting in pulmonary oedema and congestive heart failure, as well as a decrease in the serum concentration of potassium, phosphorus, magnesium, or water-soluble vitamins. These changes can occur within 24 to 48 hours; therefore, careful and slow initiation of parenteral nutrition is recommended together with close monitoring and appropriate adjustments of fluid, electrolytes, trace elements, and vitamins.

Do not connect bags in series in order to avoid the possibility of air embolism due to residual air contained in the primary bag.

Special precautions in paediatrics

When administered to children greater than 2 years of age, it is essential to use a bag that has a volume corresponding to the daily dosage.

TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, is not suitable for use in children less than 2 years of age because:

- The glucose intake is too low, leading to a low glucose/lipid ratio,
- The absence of cysteine makes the amino acid profile inadequate,
- Calcium is too low,
- The bag volumes are not appropriate.

In children greater than 2 years of age, the amount of phosphate limits the daily intakes; therefore, all macronutrients and calcium should be supplemented.

Maximal infusion rate is 3.5 ml/kg/hour in children 2 to 11 years of age and 2.1 ml/kg/hour in children 12 to 18 years of age.

Vitamin and trace elements supplementation is always required. Paediatric formulations must be used.

To avoid risks associated with excessively rapid infusion rates, it is recommended to use a continuous and controlled infusion.

TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, must be administered with caution to patients with a tendency towards electrolyte retention.

Intravenous infusion of amino acids is accompanied by increased urinary excretion of trace elements, in particular copper and zinc. This should be taken into account in the dosing of trace elements, especially during long-term intravenous nutrition.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, must not be administered simultaneously with blood through the same infusion tubing because of the possibility of pseudoagglutination.

The lipids contained in this emulsion may interfere with the results of certain laboratory tests (for example, bilirubin, lactate dehydrogenase, oxygen saturation, blood haemoglobin) if the blood sample is taken before the lipids are eliminated (these are generally eliminated after a period of 5 to 6 hours without receiving lipids).

Ceftriaxone must not be co-administered with calcium-containing IV solutions because of the risk of precipitation of ceftriaxone-calcium salt.

TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, contains vitamin K, naturally present in lipid emulsions. The amount of vitamin K in recommended doses of TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, is not expected to influence effects of coumarin derivatives.

Due to the potassium content of TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, special care should be taken in patients treated with potassium-saving diuretics (e.g., amiloride, spironolactone, triamterene), angiotensin converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists, or the immunosuppressants tacrolimus or cyclosporine in view of the risk of hyperkalemia.

4.6 Fertility, pregnancy and lactation

There are no clinical data from the use of TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, in pregnant or lactating women. Taking into account the use and indications of TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, the product may be considered during pregnancy and breastfeeding, if necessary.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Potential undesirable effects may occur as a result of inappropriate use (for example: overdose, excessively fast infusion rate) (see sections 4.4 and 4.9).

At the beginning of the infusion, any of the following abnormal signs (sweating, fever, shivering, headache, skin rashes, dyspnoea) should be cause for immediate discontinuation of the infusion:

The following adverse drug reactions (ADRs) were reported with TRIOMEL 9 g/l nitrogen 1070 kcal/l in a randomized, double-blind, active-controlled, efficacy and safety study. Twenty-eight patients with various medical conditions (i.e., postsurgical fasting, severe malnutrition, enteral intake insufficient or forbidden) were included and treated; patients in the TRIOMEL 9 g/l nitrogen 1070 kcal/l group received drug product up to 40 mL/kg/d over 5 days.

System Organ Class	MedDRA Preferred Term	Frequency[a]
Cardiac Disorders	Tachycardia	Common
Metabolism and Nutrition Disorders	Anorexia	Common
	Hypertriglyceridemia	Common
Gastrointestinal Disorders	Abdominal pain	Common
	Diarrhea	Common
	Nausea	Common
Vascular Disorders	Hypertension	Common

a: Frequency is defined as very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to <1/100); rare (≥1/10,000 to <1/1000); very rare (<1/10,000); or not known (cannot be estimated from the available data).

The following class-like-adverse drug reactions (ADRs) have been described in other sources in relation to similar parenteral nutrition products; the frequency of these events is not known.

Blood and lymphatic system disorders: thrombocytopenia

Hepatobiliary disorders: hepatomegaly, jaundice

Immune system disorders: hypersensitivity

Investigations: blood alkaline phosphatase increased, transaminases increased, blood bilirubin increased

Renal and urinary disorders: azotemia

Fat overload syndrome (very rare)

Fat overload syndrome has been reported with similar products. Reduced ability to remove the lipids contained in TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, may result in a "fat overload syndrome" which may be caused by overdose; however, the signs and symptoms of this syndrome may also occur at the start of an infusion when the product is administered according to instructions. This syndrome is associated with a sudden deterioration in the patient's clinical condition and is characterized by hyperlipidemia, fever, liver fatty infiltration, hepatomegaly, anemia, leukopenia, thrombocytopenia, coagulation disorders, and coma, requiring hospitalization. These symptoms are usually reversible when the lipid emulsion infusion is stopped.

4.9 Overdose

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

An excessively fast infusion or administration of an inappropriately large volume of the product may cause nausea, vomiting, chills and electrolyte disturbances. In such situations the infusion must be stopped immediately.

Hyperglycaemia, glucosuria, and a hyperosmolar syndrome may develop if glucose infusion rate exceeds clearance.

A reduced ability to remove lipids may result in a "fat overload syndrome", the effects of which are usually reversible after the lipid infusion is stopped (see also section 4.8).

In some serious cases, haemodialysis, haemofiltration or haemodiafiltration may be necessary.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Solutions for parenteral nutrition/combinations

ATC code: B05 BA10.

TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion's content in nitrogen (L series amino acids) and energy (glucose and triglycerides) enables maintaining an adequate nitrogen/energy balance.

This formulation also contains electrolytes.

The lipid emulsion included in TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, is an association of refined olive oil and refined soybean oil (ratio 80/20), with the following approximate distribution of fatty acids:

- 15% saturated fatty acids (SFA)
- 65% monounsaturated fatty acids (MUFA)
- 20% polyunsaturated essential fatty acids (PUFA)

The phospholipid/triglyceride ratio is 0.06.

Olive oil contains significant amounts of alpha-tocopherol which, combined with a moderate PUFA intake, contribute to improved vitamin E status and the reduction of lipid peroxidation.

The amino acid solution contains 17 L series amino acids (including 8 essential amino acids), which are required for protein synthesis.

Amino acids also represent an energy source. Their oxidation results in excretion of nitrogen in the form of urea.

The amino acid profile is as follows:

- Essential amino acids/total amino acids: 44.8%
- Essential amino acids (g)/total nitrogen (g): 2.8%
- Branched-chain amino acids/total amino acids: 18.3%

The carbohydrate source is glucose.

5.2 Pharmacokinetic properties

The ingredients of TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion (amino acids, electrolytes, glucose and lipids) are distributed, metabolised and removed in the same way as if they had been administered individually.

5.3 Preclinical safety data

No preclinical studies with TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, have been performed.

Preclinical toxicity studies performed using the lipid emulsion contained in TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, have identified the changes, which are conventionally found with a high intake of a lipid emulsion: fatty liver, thrombocytopaenia and elevated cholesterol.

Preclinical studies performed using the solutions of amino acids and glucose contained in TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, of different qualitative compositions and concentrations have not, however, revealed any specific toxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lipid emulsion compartment:

Purified egg phosphatide, Glycerol, Sodium oleate, Sodium hydroxide (for pH adjustment), Nitrogen, Water for injections.

Compartment of amino-acid solution with electrolytes:

Glacial acetic acid (for pH adjustment), Nitrogen, Water for injections.

Compartment of glucose solution with calcium:

Hydrochloric acid (for pH adjustment), Nitrogen, Water for injections.

6.2 Incompatibilities

Do not add other medicinal products or substances to any components of the bag or to the reconstituted emulsion without first confirming their compatibility and the stability of the resulting preparation (in particular, the stability of the lipid emulsion).

Incompatibilities may be produced, for example, by excessive acidity (low pH) or inappropriate content of divalent cations (Ca^{2+} and Mg^{2+}), which may destabilize the lipid emulsion.

Calcium-containing IV solutions such as TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, must not be co-administered with ceftriaxone (see section 4.5).

Check compatibility with solutions administered simultaneously through the same administration set, catheter, or cannula.

Do not administer before, simultaneously with, or after blood through the same equipment because of the risk of pseudoagglutination.

6.3 Shelf life after reconstitution

After reconstitution

It is recommended that the product be used immediately after the nonpermanent seals between the 3 compartments have been reconstituted. However, the stability of the reconstituted emulsion has been demonstrated for 7 days (between 2°C and 8°C) and maximum 48 hours at temperature not exceeding 25°C.

After addition of supplements (electrolytes, trace elements and vitamins; see section 6.6)

For specific admixtures, in-use stability has been demonstrated for 7 days (between 2°C and 8°C) followed by 48 hours at temperature not exceeding 25°C.

From a microbiological point of view, any admixture should be used immediately. If not used immediately, storage times and conditions, after mixing and prior to use, are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless addition of supplements has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 25ºC.

Do not freeze.

Store in the overpouch.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

The 3-compartment bag is a multilayer plastic bag. The inner (contact) layer of the bag material is made of a blend of polyolefinic copolymers and is compatible with amino acid solutions, glucose solutions, and lipid emulsions. Other layers are made of polyethylene vinyl acetate (EVA), and of copolyester.

The glucose compartment is fitted with an injection site to be used for addition of supplements.

The amino acid compartment is fitted with an administration site for insertion of the spike of the infusion set.

The bag is packaged in an oxygen barrier overpouch with an oxygen absorber sachet and may include an oxygen indicator (OXYDETECT™).

Pack sizes:

1000 ml bag: 1 carton with 6 bags

1500 ml bag: 1 carton with 4 bags

2000 ml bag: 1 carton with 4 bags

6.6 Special precautions for disposal and other handling

Check the colour of the oxygen indicator, if present, before opening the overpouch. Compare it to the reference colour printed next to the OK symbol and depicted in the printed area of the indicator label. Do not use the product if the colour of the oxygen indicator does not correspond to the reference colour printed next to OK symbol.

To open

Remove the protective overpouch.

Discard the oxygen absorber/oxygen indicator sachet.

Confirm the integrity of the bag and of the nonpermanent seals. Use only if the bag is not damaged; if the nonpermanent seals are intact (i.e., no mixture of the contents of the 3 compartments); if the amino acid solution and the glucose solution are clear, colourless, or slightly yellow, and practically free of visible particles; and if the lipid emulsion is a homogeneous liquid with a milky appearance.

Mixing the solutions and the emulsion

Ensure that the product is at room temperature when breaking the nonpermanent seals.

Manually roll the bag onto itself, starting at the top of the bag (hanger end). The nonpermanent seals will disappear from the side near the inlets. Continue to roll the bag until the seals are open along approximately half of their length.

Mix by inverting the bag at least 3 times.

After reconstitution, the mixture is a homogeneous emulsion with a milky appearance.

Additions

The capacity of the bag is sufficient to enable additions such as vitamins, electrolytes, and trace elements.

Any additions (including vitamins) may be made into the reconstituted mixture (after the nonpermanent seals have been opened and after the contents of the 3 compartments have been mixed).

Vitamins may also be added into the glucose compartment before the mixture is reconstituted (before opening the nonpermanent seals and before mixing the 3 compartments).

When making additions to formulations containing electrolytes, the amount of electrolytes already present in the bag should be taken into account.

Additions must be performed by qualified personnel under aseptic conditions.

TRIOMEL 9 g/l nitrogen 1070 kcal/l with electrolytes, emulsion for infusion, may be supplemented with electrolytes according to the table below:

	Per 1000 ml		
	Included level	**Maximal further addition**	**Maximal total level**
Sodium	35 mmol	115 mmol	150 mmol
Potassium	30 mmol	50 mmol	80 mmol (except for patients that are in Intensive Care Unit)
Magnesium	4.0 mmol	1.6 mmol	5.6 mmol
Calcium	3.5 mmol	1.5 (0.0[a]) mmol	5.0 (3.5[a])mmol
Inorganic Phosphate	0 mmol	3.0 mmol	3.0 mmol
Organic Phosphate	15 mmol[b]	10 mmol	25 mmol[b]

a: Value corresponding to the addition of inorganic phosphate.
b: Including phosphate provided by the lipid emulsion.

Trace elements and vitamins:

Stability has been demonstrated with commercially-available preparations of vitamins and trace elements (containing up to 1 mg of iron).

Compatibility for other additives is available upon request.

When making additions, the final osmolarity of the mixture must be measured before administration via a peripheral vein.

To perform an addition:

- Aseptic conditions must be observed.
- Prepare the injection site of the bag.
- Puncture the injection site and inject the additives using an injection needle or a reconstitution device.
- Mix content of the bag and the additives.

Preparation of the infusion

Aseptic conditions must be observed.

Suspend the bag.

Remove the plastic protector from the administration outlet.

Firmly insert the spike of the infusion set into the administration outlet.

Administration

For single use only.

Only administer the product after the nonpermanent seals between the 3 compartments have been broken and the contents of the 3 compartments have been mixed.

Ensure that the final emulsion for infusion does not show any evidence of phase separation.

After opening the bag, the contents must be used immediately. The opened bag must never be stored for a subsequent infusion. Do not reconnect any partially used-bag.

Do not connect bags in series in order to avoid the possibility of air embolism due to air contained in the primary bag.

Any unused product or waste material and all necessary devices must be discarded.

7. REGISTRATION NUMBER

149 51 33419 00

8. MANUFACTURER

Baxter Healthcare Limited,
Thetford, Norfolk,
United Kingdom.

9. LICENCE HOLDER

Teva Medical Marketing Ltd.,
Haorgim St. 8, Ashdod 77100.

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