SCHEDULING STATUS: S3

1. NAME OF THE MEDICINE: TRIOMEL N7-960, TRIOMEL N9-840 (Emulsion for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Per 1 litre Bag of solution

Active Substances	**Lipid emulsion compartment (200 ml)**		**Amino Acid solution compartment (400 ml)**		**Glucose solution compartment (400 ml)**	
	N7-960	**N9-840**	**N7-960**	**N9-840**	**N7-960**	**N9-840**
Refined Olive Oil + Refined Soya-bean Oil*	40 g	40 g				
Alanine			6,41 g	8,24 g		
Arginine			4,34 g	5,58 g		
Aspartic acid			1,28 g	1,65 g		
Glutamic acid			2,21 g	2,84 g		
Glycine			3,07 g	3,95 g		
Histidine			2,64 g	3,40 g		
Isoleucine			2,21 g	2,84 g		
Leucine			3,07 g	3,95 g		

TdeBeaubourg

Lysine acetate *(equiv to Lysine)*			4,88 g *3,48 g*	6,32 g *4,48 g*		
Methionine			2,21 g	2,84 g		
Phenylalanine			3,07 g	3,95 g		
Proline			2,64 g	3,40 g		
Serine			1,75 g	2,25 g		
Threonine			2,21 g	2,84 g		
Tryptophan			0,74 g	0,95 g		
Tyrosine			0,11 g	0,15 g		
Valine			2,83 g	3,64 g		
Glucose Monohydrate *(equiv to glucose anhydrous)*					154 g *140 g*	121,0 g *110,0 g*

* A mixture of refined olive oil (approximately 80 % m/v) and refined soya-bean oil (approximately 20 % m/v), is calculated to reach an essential fatty acids content of 20 % of total fatty acids.

TdeBrabandere

After the contents of the three compartments have been mixed, the ternary mixture for each of the bag presentations provides the following:-

Per bag	**1 litre**		**1,5 litre**		**2 litre**	
	N7-960	**N9-840**	**N7-960**	**N9-840**	**N7-960**	**N9-840**
Nitrogen (g)	7,0	9,0	10,5	13,5	14,0	18,0
Amino Acids (g)	44,3	56,9	66,4	85,4	88,6	113,9
Glucose (g)	140	110	210	165	280	220
Lipids (g)	40	40	60	60	80	80
Energy:						
Total calories (Kcal)	1140	1070	1710	1600	2270	2140
Non-protein calories (Kcal)	960	840	1440	1260	1920	1680
Glucose calories (Kcal)	560	440	840	660	1120	880
Lipid calories (Kcal)**	400	400	600	600	800	800

TdeBeaubourg

Non-protein calories/nitrogen ratio (Kcal/g)	137	93	137	93	137	93
Glucose/lipid calories ratio	58 / 42	52 / 48	58 / 42	52 / 48	58 / 42	52 / 48
Lipid/total calories (%)	35	37	35	37	35	37
Electrolytes:						
Phosphate (mmol)***	3,0	3,0	4,5	4,5	6,0	6,0
Acetate (mmol)	31	40	46	60	62	80
pH	6,4	6,4	6,4	6,4	6,4	6,4
Osmolarity (mosm/l)	1220	1170	1220	1170	1220	1170

**Includes calories from purified egg phosphatides

*** Includes phosphate provided by the lipid emulsion

TdeBeaubourg

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Emulsion for infusion

Identification prior to reconstitution:

The lipid compartment contains the lipid emulsion which is a homogenous liquid with a milky appearance.

The amino acids and glucose compartments consist of solutions which are clear and colourless or slightly yellow and practically free from particles.

Identification after reconstitution:

Homogenous liquid, with a milky appearance.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Parenteral nutrition for adults and children greater than 2 years of age, when oral and/or enteral feeding/nutrition is impossible, insufficient or contra-indicated.

4.2 Posology and method of administration

Posology

TRIOMEL should be individualised and used in collaboration with a dietician.

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

The maximum daily dose mentioned below should not be exceeded. Due to the static composition of the multi-chamber bag, the ability to simultaneously meet all nutrient needs of the patient may not be possible. Clinical situations may exist where patients require amounts

TdeBeaubourg

of nutrients varying from the composition of the static bag. In this situation any volume (dose) adjustments must take into consideration the resultant effect this will have on the dosing of all other nutrient components of TRIOMEL.

In Adults

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

The administration may be continued for as long as is required by the patient's clinical conditions.

Requirements

Average daily nitrogen requirements are 0,16 to 0,35 g/kg body weight (approximately 1 to 2 g of amino acids/kg/day)**,** depending on the patient's nutritional state 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.

The maximum daily dose should be individualised and administered in accordance with approved guidelines.

Maximum daily dose

N7-960: The maximal daily dose is defined by total calorie intake, 40 kcal/kg provided in a volume of 35 ml/kg corresponding to 1,5 g/kg of amino acids, 4,9 g/kg of glucose and 1,4 g/kg of lipids. For a 70 kg patient, this would be equivalent to 2 450 ml TRIOMEL N7-960 per

TdeBeaubourg

day, resulting in an intake of 108 g of amino acids, 343 g of glucose and 98 g of lipids (i.e. 2 352 non-protein kcal and 2 793 total kcal).

N9-840: The maximal daily dose is defined by amino acid intake, 35 ml/kg corresponding to 2,0 g/kg of amino acids, 3,9 g/kg of glucose, 1,4 g/kg of lipids. For a 70 kg patient, this would be equivalent to 2 450 ml TRIOMEL N9-840 per day, resulting in an intake of 140 g of amino acids, 270 g of glucose and 98 g of lipids (i.e. 2 058 non-protein kcal and 2 622 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.

Maximum Infusion Rate

The maximum infusion rate should be individualised and administered in accordance with approved guidelines.

N7-960: The maximal infusion rate is 1,7 ml/kg/hour, corresponding to 0,08 g/kg/hour for amino acids, 0,24 g/kg/hour for glucose, 0,07 g/kg/hour for lipids

N9-840: The maximal infusion rate is 1,8 ml/kg/hour (except for Intradialytic parenteral nutrition [IDPN], see below), corresponding to 0,10 g/kg/hour for amino acids, 0,19 g/kg/hour for glucose, 0,07 g/kg/hour for lipids

Patients on intradialytic parenteral nutrition (IDPN): Intradialytic parenteral nutrition is intended for non-acutely ill malnourished patients. The selection of the appropriate TRIOMEL formulation and volume to be used for IDPN should be guided by the gap between spontaneous intakes as estimated e.g. by dietary interview and the recommended intakes.

TdeBeaubourg

Additionally, metabolic tolerance needs to be taken into consideration. For **TRIOMEL N9-840**, in patients on IDPN, the maximum hourly infusion rate is 3,6 ml/kg/hour, corresponding to 0,2 g/kg/hour amino acids, 0,40 g/kg/hour glucose, and 0,14 g/kg/hour lipids administered over 4 hours.

In children greater than two years of age

Requirements, Maximum daily dosage and Maximum infusion rate.

The maximum daily dose and infusion rate should be individualised and administered in accordance with approved international guidelines**.**

There have been no studies performed in the paediatric population.

The dosage depends on the patient's energy expenditure, clinical status, body weight, and the ability to metabolize constituents of TRIOMEL, 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.

TRIOMEL N7-960

Maximum Daily Dose

	2 to 11 years		**12 to 18 years**	
Constituent	Recommended Max Daily Dose[a]	**N7-960**	Recommended Max Daily Dose[a]	**N7-960**

TdeBeaubourg

		Max Daily Dose[b].		**Max Daily Dose[c]**
Fluids (ml/kg/d)	60 – 120	56	50 – 80	41
Amino acids (g/kg/d)	1 – 2 (up to 2,5)	2,5	1 – 2	1,8
Glucose (g/kg/d)	1,4 – 8,6	7,8	0,7 – 5,8	5,7
Lipids (g/kg/d)	0,5 – 3	2,2	0,5 – 2 (up to 3)	1,6
Total energy (kcal/kg/d)	30 - 75	63,8	20 - 55	46,7

a: Recommended values from 2018 ESPGHAN/ESPEN/ESPR Guidelines

b: Amino acid concentration is the limiting factor for maximum daily dose in 2-11 years' age group

c: Glucose concentration is the limiting factor for maximum daily dose in 12-18 years' age group

Maximum Hourly Rate

Constituent	**2 to 11 years**		**12 to 18 years**	
	Recommended Max Hourly Rate[a]	**N7-960 Max Hourly Rate[b]**	Recommended Max Hourly Rate[a]	**N7-960 Max Hourly Rate[b]**
Fluids (ml/kg/h)	N/A	2,6	N/A	1,7
Amino acids (g/kg/h)	0,20	0,11	0,12	0,08
Glucose (g/kg/h)	0,36	0,36	0,24	0,24
Lipids (g/kg/h)	0,13	0,10	0,13	0,07

TdeBeaubourg

a: Recommended values from 2018 ESPGHAN/ESPEN/ESPR Guidelines

b: Glucose concentration is the limiting factor for maximum hourly rate in both age groups.

TRIOMEL N9-840

Maximum Daily Dose

	2 to 11 years		**12 to 18 years**	
Constituent	Recommended Max Daily Dose[a]	**N9-840 Max Daily Dose[b].**	Recommended Max Daily Dose[a]	**N9-840 Max Daily Dose[b]**
Fluids (ml/kg/d)	60 – 120	44	50 – 80	35
Amino acids (g/kg/d)	1 – 2 (up to 2,5)	2,5	1 – 2	2,0
Glucose (g/kg/d)	1,4 – 8,6	4,8	0,7 – 5,8	3,9
Lipids (g/kg/d)	0,5 – 3	1,8	0,5 – 2 (up to 3)	1,4
Total energy (kcal/kg/d)	30 - 75	47,1	20 - 55	37,5

a: Recommended values from 2018 ESPGHAN/ESPEN/ESPR Guidelines

b: Amino acid concentration is the limiting factor for maximum daily dose in both age groups

Maximum Hourly Rate

	2 to 11 years		**12 to 18 years**	
Constituent	Recommended Max Hourly Rate[a]	**N9-840 Max Hourly Rate[b]**	Recommended Max Hourly Rate[a]	**N9-840 Max Hourly Rate[c]**

TdeBeaubourg

Fluids (ml/kg/h)	N/A	3,3	N/A	2,1
Amino acids (g/kg/h)	0,20	0,19	0,12	0,12
Glucose (g/kg/h)	0,36	0,36	0,24	0,23
Lipids (g/kg/h)	0,13	0,13	0,13	0,08

a: Recommended values from 2018 ESPGHAN/ESPEN/ESPR Guidelines

b: Glucose concentration is the limiting factor for maximum hourly rate in 2-11 years' age group

c: Amino acid concentration is the limiting factor for maximum hourly rate in 12-18 years' age group

Usually, 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 daily dose and gradually increase it up to the maximal dosage.

Paediatric population

TRIOMEL is not recommended for use in children less than 2 years of age due to inadequate composition and volume.

Method of administration

For single use only.

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

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

TdeBeaubourg

Due to their high osmolarity, **TRIOMEL N7-960** and **N9-840** can only be administered through a central vein.

The recommended duration of the parenteral nutrition infusion is between 12 – 24 hours.

For precaution to be taken before manipulating or administering the product, see section 6.6

4.3 Contraindications

Use of TRIOMEL is contraindicated in the following situations:

- in premature neonates, infants and children less than 2 years old, as the calorie-nitrogen ratio and energy supply are inappropriate.
- Hypersensitivity to egg, soybean, or peanut proteins, or to any other ingredients.
- severe renal insufficiency without the possibility of hemofiltration or dialysis
- congenital abnormalities of amino acid metabolism
- severe hyperlipidaemia or severe disorders of lipid metabolism characterised by hypertriglyceridaemia
- severe hyperglycaemia

General contraindications for administering an intravenous infusion are as follows: -

- acute pulmonary oedema, hyperhydration, uncompensated cardiac insufficiency and hypotonic dehydration.
- unstable conditions (e.g., following severe post-traumatic conditions, uncompensated diabetes mellitus, acute phase of circulatory shock, acute myocardial infarction, severe metabolic acidosis, severe sepsis and hyperosmolar coma).

TdeBeaubourg

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 dyspnoea) develop. This medicine 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.

Pulmonary vascular precipitates causing pulmonary vascular embolism and respiratory distress 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 formation of calcium phosphate precipitates.

Precipitates of various natures have been reported even in the absence of phosphate salt in the solution.

Suspected precipitate formation in the blood stream has also been reported.

In addition to inspection of the solution, the infusion set and catheter should also periodically be checked for precipitates. If signs of respiratory distress occur, the infusion should be stopped and medical evaluation initiated.

Do not add other medicines 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). Formation of precipitates or destabilization of the lipid emulsion could result in vascular occlusion

TdeBeaubourg

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.

Extravasation

Catheter site should be monitored regularly to identify signs of extravasation.

If extravasation occurs the administration should be stopped immediately, keeping the inserted catheter or cannula in place for immediate management of the patient. If possible, aspiration should be performed through the inserted catheter/ cannula in order to reduce the amount of fluid present in the tissues before removing the catheter/ cannula.

Depending on the extravasated product (including the product(s) being mixed with if applicable) and the stage/extent of any injury, appropriate specific measures should be taken. Options for management may include non-pharmacologic, pharmacologic and/or surgical intervention. In case of large extravasation, plastic surgeon advice should be sought within the first 72 hours. The extravasation site should be monitored at least every 4 hours during the first 24 hours, then once daily

TdeBeaubourg

The infusion should not be restarted in the same central vein.

When making additions, the final osmolarity of the mixture must be measured before administration. The mixture obtained must be administered through a central venous line. If the final mixture, which is administered, is hypertonic, it may cause irritation of the vein if 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 medicine.

Caution should be exercised in administering TRIOMEL to patients with increased serum 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 concentrations of potassium, phosphorus, magnesium and 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.

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.

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.

TdeBeaubourg

These concentrations should not be determined before a minimum of a 3 hour period of continuous infusion.

If a lipid metabolism abnormality is suspected, it is recommended that tests be performed daily by measuring serum triglycerides 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 should only be administered when the serum triglyceride concentrations have returned to pre-existing values.

Fat overload syndrome has been reported with similar products. The reduced or limited ability to metabolise the lipids contained in TRIOMEL 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 section 4.8)

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 liver function parameters, 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.

TRIOMEL is contraindicated in severe renal insufficiency where hemofiltration or dialysis is not possible (see section 4.3).

TdeBeaubourg

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.

The blood count and coagulation factors must be monitored more frequently during long term administration (several weeks).

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.

TdeBeaubourg

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

In the event of hyperglycemia, the infusion rate of TRIOMEL must be adjusted and/or insulin administered.

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

Special precautions in paediatrics

Dosage should be adapted according to age, nutritional status, disease and when necessary, additional energy or protein should be given orally/enterally.

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

TRIOMEL 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 acids profile inadequate,
- Phosphates are too low and other electrolytes are not included,
- And 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 (about 0,2 mmol/kg/day).

TdeBeaubourg

For **TRIOMEL N7-960**: Maximal infusion rate is 3,3 ml/kg/hour in children 2 to 11 years of age and 2,7 ml/kg/hour in children 12 to 18 years of age.
For **TRIOMEL N9-840**: Maximal infusion rate is 3,3 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.

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.

TRIOMEL N7-960 and N9-840 must only be administered through a central vein. **DO NOT ADMINSTER THROUGH A PERIPHERAL VEIN.**

4.5 Interactions with other medicines and other forms of interaction

This emulsion for infusion must not be administered simultaneously with blood through the same infusion tubing due to the possibility of pseudoagglutination.

The lipids contained in this emulsion may interfere with the results of certain laboratory tests (e.g. bilirubin, lactate dehydrogenase, oxygen saturation, blood haemoglobin) if the blood

TdeBeaubourg

sample is taken before the lipids have been eliminated (these are generally eliminated after a period of 5 to 6 hours without receiving lipids).

TRIOMEL contains vitamin K, naturally present in lipid emulsions. The amount of vitamin K in recommended doses of TRIOMEL are not expected to influence effects of coumarin derivatives.

4.6 Fertility, pregnancy and lactation

Safety in pregnancy and lactation has not been established.

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

a. Summary of the safety profile

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.

b. Tabulated summary of adverse reactions

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:

b. Tabulated summary of adverse reactions

TdeBeaubourg

1) The following adverse drug reactions (ADRs) were reported with TRIOMEL N9-840 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 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
General disorders and administration site conditions	Extravasation which may result at infusion site level in: pain, irritation, swelling/oedema, erythema/warmth, skin necrosis, blisters	Not known[b]

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

b: ADRs reported during post-marketing experience with TRIOMEL

TdeBeaubourg

2) The following adverse reactions have been reported in the Post-marketing experience, listed by MedDRA System Organ Class (SOC), then by Preferred Term in order of severity.

System Organ Class	**MedDRA Preferred Term**	**Frequency**
Gastrointestinal Disorders	Vomiting	Unknown
Skin and Subcutaneous skin disorders	Rash	Unknown
General disorders and administration site conditions	Injection site extravasation Pyrexia Chills	Unknown

3) The following class-like-adverse medicine 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
Immune system disorders	Hypersensitivity
Hepatobiliary disorders	- Hepatomegaly - Jaundice - Cholestasis

TdeBeaubourg

Investigations	- Increased blood alkaline phosphatase - Increased transaminases - Increased blood bilirubin - Elevated liver enzymes
Renal and Urinary Disorders	Azotemia
Vascular disorders:	Pulmonary vascular precipitates (pulmonary vascular embolism and respiratory distress)

c. Description of selected adverse reactions

Fat overload syndrome

Fat overload syndrome has been reported with similar medicines. This may be caused by inappropriate administration (e.g. overdose and/or infusion rate higher than recommended, see section 4.9); however, the signs and symptoms of this syndrome may also occur at the start of an infusion when the medicine is administered according to instructions. The reduced or limited ability to metabolize the lipids contained in TRIOMEL accompanied by prolonged plasma clearance may result in a “fat overload syndrome”. This syndrome is associated with a sudden deterioration in the patient’s clinical condition and is characterized by findings such as fever, anemia, leukopenia, thrombocytopenia, coagulation disorders, hyperlipidemia, liver fatty infiltration (hepatomegaly), deteriorating liver function, and central nervous system manifestations (e.g. coma). The syndrome is usually reversible when infusion of the lipid emulsion is stopped.

Reporting of suspected adverse reactions

TdeBeaubourg

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

For reporting of side effects directly to the HCR, contact +27 11 635 0134 or email Adcock.aereports@adcock.com

4.9 Overdose

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

Hyperglycaemia, glucosuria and hyperosmolar syndrome may develop if excessive glucose is administered.

An excessively fast infusion or administration of too large a volume may cause nausea, vomiting, shivering and electrolyte disturbances. In such situations the infusion should be stopped immediately.

Reduced ability to remove lipids may result in a "fat overload syndrome", the effects of which are reversible after the lipid infusion is stopped. See section 4.8.

In some serious cases, haemodialysis, hemofiltration or haemo-dia-filtration may be necessary.

TdeBeaubourg

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group and ATC code: Solutions for parenteral nutrition/combinations, ATC code: B05 BA10.

TRIOMEL is a ternary mixture enabling the nitrogen/energy balance to be maintained from the nitrogen source (L-series amino acids) as well as energy in the form of glucose and essential fatty acids. These formulations without electrolytes allows individual electrolyte intake to be adapted to meet specific requirements.

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 acids 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:

- N7-960 = 140,0 g/l of ternary emulsion
- N9-840 **=** 110,0 g/l of ternary emulsion

The lipid emulsion is an association of refined olive oil and refined soybean oil (ratio 80/20). The following is the approximate distribution of fatty acids:

- 15 % saturated fatty acids (SFA)

TdeBeaubourg

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

The phospholipid/ triglyceride ratio is 0,06.

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

5.2 Pharmacokinetic properties

The ingredients of the emulsion for infusion (amino acids, glucose and lipids) are distributed, metabolised and removed in the same way as if they had been administered individually. The pharmacokinetic properties of the amino acids administered intravenously are principally the same as those of amino acids supplied by oral feeding. However amino acids from food proteins, first pass through the gastro-intestinal tract (vena porta) before absorption into the systemic circulation.

The elimination rate of lipid emulsions depends on particle size. Small lipid particles appear to delay clearance whereas they increase lipolysis by lipoprotein lipase. The size of the lipid particles in the emulsion contained in TRIOMEL are close to that of chylomicrons. This emulsion therefore has a similar elimination rate.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

TdeBeaubourg

List of excipients: Purified egg phosphatide, glycerol, sodium oleate, water for injection, glacial acetic acid (for pH adjustment), hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

6.2 Incompatibilities

Do not add other medicinal products or substances to one of the three components of the bag or to the reconstituted emulsion without firstly confirming their compatibility and the stability of the resulting preparation (in particular 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 de-stabili**s**e the lipid emulsion.
Calcium and phosphate ratios must be considered. Excess addition of calcium and phosphate, especially in the form of mineral salts, may result in the formation of calcium phosphate precipitates.

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

Not Applicable

6.4 Special precautions for storage

Before Reconstitution:

TdeBeaubourg

Store at or below 30 °C. Do not freeze. Store in the overpouch. Keep container in the outer carton.

After Reconstitution:

It is recommended that the product be used immediately after the peel seals have been broken and any unused portion of the reconstituted product must be discarded in accordance with local requirements.

The reconstituted emulsion, is stable for a maximum of 7 days at between 2 °C to 8 °C followed by a maximum of 48 hours at temperatures not exceeding 25 °C.

After addition of supplements (electrolytes, organic phosphates, trace elements, vitamins):

For specific admixtures, chemical and physical in-use stability has been demonstrated for 7 days at 2 °C to 8 °C followed by 48 hours at or below 25 °C. From a microbiological point of view, any admixture should be used immediately. If not used immediately, in-use storage times and conditions 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.

6.5 Nature and contents of container

TRIOMEL is packed into a three-compartment bag. The triple-compartment bag is a multi-layer, clear and colourless plastic container packaged into an overpouch (silver, aluminium foil, or clear, colourless laminated plastic). The inner (contact) layer of the bag material is made up of blend of ployolefinic 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. One compartment contains a lipid emulsion, the second compartment contains an amino acid solution and the third compartment contains a glucose solution.

TdeBeaubourg

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

The amino acids 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.

TRIOMEL is available in pack sizes of 1 l, 1,5 l and 2 l.

6.6 Special precautions for disposal and other handling

Method

Before opening the overpouch and if present, check the colour of the oxygen indicator. 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 non-permanent seals. Use only if the bag is not damaged, if the non-permanent seals are intact (i.e. no mixture of the contents of the three compartments), if the amino acids solution and the glucose solution are clear, colourless or slightly yellow, 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 non-permanent seals.

TdeBeaubourg

Manually roll the bag onto itself, starting at the top of the bag (hanger end). The non-permanent seals will disappear from the side near the inlets. Continue to roll 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 addition (including vitamins) may be made into the reconstituted mixture (after the non-permanent seals have been opened and after the contents of the three compartments have been mixed). Vitamins may also be added into the glucose compartment before the mixture is reconstituted (before opening the non-permanent seals and before mixing the 3 compartments).

Additions must be performed by qualified personnel under aseptic conditions.

TRIOMEL may be supplemented with electrolytes according to the table below:

Per 1 000 ml			
	Included level	**Maximal further addition**	**Maximal total level**
Sodium	0 mmol	150 mmol	150 mmol
Potassium	0 mmol	150 mmol	150 mmol
Magnesium	0 mmol	5,6 mmol	5,6 mmol
Calcium	0 mmol	5,0 (3,5**) mmol	5,0 (3,5**) mmol

TdeBeaubourg

Inorganic Phosphate	0 mmol	8,0 mmol	8,0 mmol
Organic Phosphate	3 mmol*	22 mmol	25 mmol*

*Including phosphate provided by the lipid emulsion

** Value corresponding to the addition of inorganic phosphate

Trace elements and vitamins:

Stability has been demonstrated with 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 (see section 4.4)

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.

TdeBeaubourg

Administration

For single use only

Only administer the product after the non-permanent seals between the three compartments have been broken and the contents of the three compartments have been mixed.

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

After opening the bag the content 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 first bag.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Adcock Ingram Critical Care (Pty) Ltd

1 Sabax Road

Aeroton

Johannesburg

2013

Tel: +27 11 494 8000

8. REGISTRATION NUMBER(S)

TRIOMEL N7-960: 46/25.2/0424

TRIOMEL N9-840: 46/25.2/0425

TdeBeaubourg

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date Approved: 23 March 2015

10. DATE OF REVISION OF THE TEXT

Date of amendment: 10 June 2022

TdeBeaubourg