SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

1. NAME OF THE MEDICINAL PRODUCT

OLIMEL N12E, emulsion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OLIMEL N12E 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			
	650 mL	1,000 mL	1,500 mL	2,000 mL
27.5% Glucose solution (corresponding to 27.5 g/100 mL)	173 mL	267 mL	400 mL	533 mL
14.2% Amino acid solution (corresponding to 14.2 g/100 mL)	347 mL	533 mL	800 mL	1,067 mL
17.5% Lipid emulsion (corresponding to 17.5 g/100 mL)	130 mL	200 mL	300 mL	400 mL

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

Active substances	**650 mL**	**1,000 mL**	**1,500 mL**	**2,000 mL**
Refined olive oil+ refined soya-bean oil[a]	22.75 g	35.00 g	52.50 g	70.00 g
Alanine	7.14 g	10.99 g	16.48 g	21.97 g
Arginine	4.84 g	7.44 g	11.16 g	14.88 g
Aspartic acid	1.43 g	2.20 g	3.30 g	4.39 g
Glutamic acid	2.46 g	3.79 g	5.69 g	7.58 g
Glycine	3.42 g	5.26 g	7.90 g	10.53 g
Histidine	2.94 g	4.53 g	6.79 g	9.06 g
Isoleucine	2.46 g	3.79 g	5.69 g	7.58 g
Leucine	3.42 g	5.26 g	7.90 g	10.53 g
Lysine (equivalent to lysine acetate)	3.88 g (5.48 g)	5.97 g (8.43 g)	8.96 g (12.64 g)	11.95 g (16.85 g)

Active substances	650 mL	1,000 mL	1,500 mL	2,000 mL
Methionine	2.46 g	3.79 g	5.69 g	7.58 g
Phenylalanine	3.42 g	5.26 g	7.90 g	10.53 g
Proline	2.94 g	4.53 g	6.79 g	9.06 g
Serine	1.95 g	3.00 g	4.50 g	5.99 g
Threonine	2.46 g	3.79 g	5.69 g	7.58 g
Tryptophan	0.82 g	1.26 g	1.90 g	2.53 g
Tyrosine	0.13 g	0.20 g	0.30 g	0.39 g
Valine	3.16 g	4.86 g	7.29 g	9.72 g
Sodium acetate, trihydrate	0.97 g	1.5 g	2.24 g	2.99 g
Sodium glycerophosphate, hydrated	2.39 g	3.67 g	5.51 g	7.34 g
Potassium chloride	1.45 g	2.24 g	3.35 g	4.47 g
Magnesium chloride, hexahydrate	0.53 g	0.81 g	1.22 g	1.62 g
Calcium chloride, dihydrate	0.34 g	0.52 g	0.77 g	1.03 g
Glucose (equivalent to glucose monohydrate)	47.67 g (52.43 g)	73.33 g (80.67 g)	110.00 g (121.00 g)	146.67 g (161.33 g)

[a] Mixture of refined olive oil (approximately 80%) and refined soya-bean oil (approximately 20%) corresponding to a ratio essential fatty acids / total fatty acids of 20%.

For the full list of excipients, see section 6.1.

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

	650 mL	1,000 mL	1,500 mL	2,000 mL
Lipids	22.8 g	35.0 g	52.5 g	70.0 g
Amino acids	49.4 g	75.9 g	113.9 g	151.9 g
Nitrogen	7.8 g	12.0 g	18.0 g	24.0 g
Glucose	47.7 g	73.3 g	110.0 g	146.7 g
Energy:				
Total calories approx.	620 kcal	950 kcal	1,420 kcal	1,900 kcal
Non-protein calories	420 kcal	640 kcal	960 kcal	1,280 kcal
Glucose calories	190 kcal	290 kcal	430 kcal	580 kcal
Lipid calories[a]	230 kcal	350 kcal	520 kcal	700 kcal
Non-protein calories / nitrogen ratio	53 kcal/g	53 kcal/g	53 kcal/g	53 kcal/g
Glucose / lipid calories ratio	45/55	45/55	45/55	45/55

	650 mL	**1,000 mL**	**1,500 mL**	**2,000 mL**
Lipid / total calories	37%	37%	37%	37%
Electrolytes:				
Sodium	22.8 mmol	35.0 mmol	52.5 mmol	70.0 mmol
Potassium	19.5 mmol	30.0 mmol	45.0 mmol	60.0 mmol
Magnesium	2.6 mmol	4.0 mmol	6.0 mmol	8.0 mmol
Calcium	2.3 mmol	3.5 mmol	5.3 mmol	7.0 mmol
Phosphate[b]	9.5 mmol	15.0 mmol	21.9 mmol	29.2 mmol
Acetate	46 mmol	70 mmol	105 mmol	140 mmol
Chloride	30 mmol	45 mmol	68 mmol	90 mmol
pH	6.4	6.4	6.4	6.4
Osmolarity approx..	1,270 mOsm/L	1,270 mOsm/L	1,270 mOsm/L	1,270 mOsm/L

[a] Includes calories from purified egg phospholipids

[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

OLIMEL N12E is indicated for parenteral nutrition for adults and children greater than 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.

4.2 Posology and method of administration

Posology

OLIMEL N12E 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 of the SmPC).

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 of nutrients varying from the composition of the static bag. In this situation, the impact of any volume (dose) adjustments must be taken into consideration and the resultant effect this will have on the dosing of all other nutrient components of OLIMEL N12E. In those situations, health care professionals may consider adjusting the volume (dose) of OLIMEL N12E in order to meet these increased requirements.

In adults

The dosage depends on the patient's energy expenditure, clinical status, body weight, and the ability to metabolise the constituents of OLIMEL N12E, 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. Special populations may require up to 0.4 g nitrogen/kg body weight (2.5 g of amino acids/kg).
- 20 to 40 kcal/kg,
- 20 to 40 mL fluid /kg, or 1 to 1.5 mL per expended kcal.

For OLIMEL N12E, the maximal daily dose is defined by amino acids intake, 26 mL/kg corresponding to 2.0 g/kg amino acids, 1.9 g/kg glucose, 0.9 g/kg lipids. For a 70 kg patient, this would be equivalent to 1,820 mL OLIMEL N12E per day, resulting in an intake of 138 g amino acids, 133 g glucose, and 64 g lipids (i.e., 1,171 non-protein kcal and 1,723 total kcal).

In Continuous Renal Replacement Therapy (CRRT): For OLIMEL N12E, the maximal daily dose is defined by amino acids intake, 33 mL/kg corresponding to 2.5 g/kg amino acids, 2.4 g/kg glucose, 1.2 g/kg lipids. For a 70 kg patient, this would be equivalent to 2,310 mL OLIMEL N12E per day, resulting in an intake of 175 g amino acids, 169 g glucose, and 81 g lipids (i.e., 1,486 non-protein kcal and 2,187 total kcal).

In patients with morbid obesity: The dosage should be calculated on basis of the ideal body weight (IBW). For OLIMEL N12E, the maximal daily dose is defined by amino acids intake, 33 mL/kg IBW corresponding to 2.5 g/kg amino acids, 2.4 g/kg glucose, 1.2 g/kg

lipids. For a 70 kg patient, this would be equivalent to 2,310 mL OLIMEL N12E per day, resulting in an intake of 175 g amino acids, 169 g glucose, and 81 g lipids (i.e., 1,486 non-protein kcal and 2,187 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 OLIMEL N12E, the maximal infusion rate is 1.3 mL/kg/hour, corresponding to 0.10 g/kg/hour amino acids, 0.10 g/kg/hour glucose, and 0.05 g/kg/hour lipids.

In children, greater than 2 years of age and adolescents

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 metabolise constituents of OLIMEL N12E, 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 OLIMEL N12E in the 2 to 11 year age group, amino acid and magnesium concentrations are the limiting factor for daily dose. In this age group, the amino acid concentration is the limiting factor for hourly rate. In the 12 to 18 year age group, amino acid and magnesium concentrations are the limiting factor for daily dose. In this age group, the amino acid concentration is the limiting factor for hourly rate. The resulting intakes are displayed below:

Constituent	2 to 11 years		12 to 18 years	
	Recommended[a]	OLIMEL N12E Max Vol	Recommended[a]	OLIMEL N12E Max Vol
Maximum Daily Dose				
Fluids (mL/kg/d)	60 – 120	33	50 – 80	26
Amino acids (g/kg/d)	1 – 2 (up to 2.5)	2.5	1 – 2	2
Glucose (g/kg/d)	1.4 – 8.6	2.4	0.7 – 5.8	1.9
Lipids (g/kg/d)	0.5 – 3	1.2	0.5 – 2 (up to 3)	0.9
Total energy (kcal/kg/d)	30 – 75	31.4	20 - 55	24.7
Maximum Hourly Rate				

OLIMEL N12E (mL/kg/h)		2.6		1.6
Amino acids (g/kg/h)	0.20	0.20	0.12	0.12
Glucose (g/kg/h)	0.36	0.19	0.24	0.12
Lipids (g/kg/h)	0.13	0.09	0.13	0.06

[a] Recommended values from 2018 ESPGHAN/ESPEN/ESPR 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 daily dose and gradually increase it up to the maximal dosage (see above).

Maximal infusion rate is 2.6 mL/kg/hour in children 2 to 11 years of age and 1.6 mL/kg/hour in children 12 to 18 years of age.

Method and duration 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.

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

Due to its high osmolarity, OLIMEL N12E must 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 OLIMEL N12E is contraindicated in the following situations:

- In premature neonates, infants, and children less than 2 years of age

- Hypersensitivity to egg, soya-bean, peanut proteins, or corn/corn products (see section 4.4) or to any of the active substances or excipients, listed in section 6.1
- Congenital abnormalities of amino acid metabolism
- Severe hyperlipidaemia or severe disorders of lipid metabolism characterised by hypertriglyceridaemia
- Severe hyperglycaemia
- 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 soya-bean oil, and egg phospholipids. Soya-bean and egg proteins may cause hypersensitivity reactions. Cross-allergic reactions between soya-bean and peanut proteins have been observed.

OLIMEL N12E contains glucose derived from corn, which may cause hypersensitivity reactions in patients with allergy to corn or corn products (see section 4.3).

Ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions even via different infusion lines or different infusion sites. Ceftriaxone and calcium-containing solutions may be administered sequentially one after another if infusion lines at different sites are used or if the infusion lines are replaced or thoroughly flushed between infusions with physiological salt-solution to avoid precipitation. In patients requiring continuous infusion with calcium-containing TPN solutions, healthcare professionals may wish to consider the use of alternative antibacterial treatments which do not carry a similar risk of precipitation. If use of ceftriaxone is considered necessary in patients requiring continuous nutrition, TPN solutions and ceftriaxone can be administered simultaneously, albeit via different infusion lines at different sites. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion, considering the advice to flush infusion lines between solutions (see sections 4.5 and 6.2).

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 (see section 6.2). 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 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). Formation of precipitates or destabilisation of the lipid emulsion could result in vascular occlusion (see sections 6.2 and 6.6).

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 hyperglycaemia can help recognise 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.

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

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

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.

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 OLIMEL N12E, 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.
The infusion should not be restarted in the same central vein.

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 hyperazotaemia 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.

Hepatobiliary disorders

Hepatobiliary disorders including cholestasis, hepatic steatosis, fibrosis and cirrhosis, possibly leading to hepatic failure, as well as cholecystitis and cholelithiasis are known to develop in some patients on parenteral nutrition. The etiology of these disorders is thought to be multifactorial and may differ between patients. Patients developing abnormal laboratory parameters or other signs of hepatobiliary disorders should be assessed early by a clinician knowledgeable in liver diseases in order to identify possible causative and contributory factors, and possible therapeutic and prophylactic interventions.

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. The reduced or limited ability to metabolise the lipids contained in OLIMEL N12E 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 hyperglycaemia, the infusion rate of OLIMEL N12E must be adjusted and/or insulin administered.

DO NOT ADMINISTER THROUGH 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. Trace elements and vitamins should be added in sufficient quantities to meet individual patient requirements and to prevent deficiencies from developing. See instructions for making additions to this product.

Caution should be exercised in administering OLIMEL N12E 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 gas contained in the primary bag.

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

OLIMEL N12E 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.

Interference with laboratory tests

The lipids contained in this emulsion may interfere with the results of certain laboratory tests (see section 4.5).

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.

OLIMEL N12E 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

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

Geriatric population

In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

OLIMEL N12E 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).

Precipitation of ceftriaxone-calcium can occur when ceftriaxone is mixed with calcium-containing solutions in the same intravenous administration line. Ceftriaxone must not be mixed or administered simultaneously with calcium-containing intravenous solutions, including OLIMEL N12E, through the same infusion line (e.g., via Y-site). However, ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between infusions with a compatible fluid (see sections 4.4 and 6.2).

OLIMEL N12E contains vitamin K, naturally present in lipid emulsions. The amount of vitamin K in recommended doses of OLIMEL N12E are not expected to influence effects of coumarin derivatives.

Due to the potassium content of OLIMEL N12E, special care should be taken in patients treated with potassium-sparing 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 hyperkalaemia.

Some medicinal products, like insulin, may interfere with the body's lipase system. This kind of interaction seems, however, to be of limited clinical importance.

Heparin given in clinical doses causes a transient release of lipoprotein lipase into the circulation. This may result initially in increased plasma lipolysis followed by a transient decrease in triglyceride clearance.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no clinical data from the use of OLIMEL N12E in pregnant women. No animal reproductive studies have been performed with OLIMEL N12E (see section 5.3). Taking into account the use and indications of OLIMEL N12E, the product may be considered during pregnancy, if necessary. OLIMEL N12E should only be given to pregnant women after careful consideration.

Breast-feeding

There is insufficient information on the excretion of OLIMEL N12E components/metabolites in human milk. Parenteral nutrition may become necessary during breast-feeding. OLIMEL N12E should only be given to breast-feeding women after careful consideration.

Fertility

No adequate data are available.

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 adverse drug reactions (ADRs) reported with OLIMEL N9-840 in a randomised, double-blind, active-controlled, efficacy and safety study, are listed in the table below. 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 OLIMEL group received drug product up to 40 mL/kg/d over 5 days.

The pooled data from clinical trials and the postmarketing experience indicate the following adverse drug reactions (ADRs) related to OLIMEL.

System Organ Class	**MedDRA Preferred Term**	**Frequency[a]**
Immune System Disorders	Hypersensitivity reactions including hyperhidrosis, pyrexia, chills, headache, skin rash (erythematous, papular, pustular, macular, generalised rash), pruritus, hot flush, dyspnoea	Not known[b]
Cardiac Disorders	Tachycardia	Common
Metabolism and Nutrition Disorders	Decreased appetite	Common
	Hypertriglyceridaemia	Common
Gastrointestinal Disorders	Abdominal pain	Common
	Diarrhoea	Common
	Nausea	Common
	Vomiting	Not known[b]
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/vesicles, inflammation, induration, skin tightness	Not known[b]

[a] Frequency is defined as very common (≥ 1/10); common (≥ 1/100 to < 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 OLIMEL

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: Cholestasis, Hepatomegaly, Jaundice
- Immune System Disorders: Hypersensitivity
- Injury, poisoning and procedural complications: Parenteral nutrition associated liver disease (see section 4.4)
- Investigations: Blood alkaline phosphatase increased, Transaminases increased, Blood bilirubin increased, Elevated liver enzymes
- Renal and Urinary Disorders: Azotemia
- Vascular disorders: Pulmonary vascular precipitates (pulmonary vascular embolism and respiratory distress) (see section 4.4).

Fat overload syndrome (very rare)

Fat overload syndrome has been reported with similar products. 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 product is administered according to instructions. The reduced or limited ability to metabolise the lipids contained in OLIMEL N12E 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 characterised by findings such as fever, anemia, leukopenia, thrombocytopenia, coagulation disorders, hyperlipidaemia, 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

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [to be completed nationally according to the national reporting system listed in Appendix V].

4.9 Overdose

In the event of inappropriate administration (overdose and/or infusion rate higher than recommended), nausea, vomiting, chills, headache, hot flush, hyperhidrosis and electrolyte disturbances and signs of hypervolemia or acidosis may occur and result in severe or fatal consequences. In such situations, the infusion must be stopped immediately. If medically appropriate, further intervention may be indicated.

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

The reduced or limited ability to metabolise lipids may result in a "fat overload syndrome", the results of which are usually reversible after the infusion of the lipid emulsion 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: B05BA10.

OLIMEL’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 OLIMEL N12E is an association of refined olive oil and refined soya-bean 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 OLIMEL N12E (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 OLIMEL N12E have been performed.

Preclinical toxicity studies performed using the lipid emulsion contained in OLIMEL N12E have identified the changes, which are conventionally found with a high intake of a lipid emulsion: fatty liver, thrombocytopenia and elevated cholesterol.

Preclinical studies performed using the solutions of amino acids and glucose contained in OLIMEL N12E 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 phospholipids

- Glycerol
- Sodium oleate
- Sodium hydroxide (for pH adjustment)
- Water for injections.

Compartment of amino-acid solution with electrolytes:

- Glacial acetic acid (for pH adjustment)
- Water for injections

Compartment of glucose solution with calcium:

- Hydrochloric acid (for pH adjustment)
- 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 destabilise the lipid emulsion.

As with any parenteral nutrition admixture, 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.

OLIMEL N12E contains calcium ions which pose additional risk of coagulation precipitated in citrate anticoagulated/preserved blood or components.

Ceftriaxone must not be mixed or administered simultaneously with intravenous calcium-containing solutions, including OLIMEL N12E, through the same infusion line (e.g., via Y-connector) because of the risk of precipitation of ceftriaxone-calcium salt (see sections 4.4 and 4.5).

Due to the risk of precipitation, OLIMEL N12E should not be administered through the same infusion line or admixed together with ampicillin or fosphenytoin.

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

2 years if the overwrap is not damaged.

After reconstitution

Chemical and physical in-use stability has been demonstrated for 7 days at 2°C- 8°C followed by 48 hours at temperature not exceeding 30°C.

From a microbiological point of view, the product 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 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

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

For specific admixtures, chemical and physical in-use stability has been demonstrated for 7 days at 2°C - 8°C followed by 48 hours at temperature not exceeding 30°C.

From a microbiological point of view, any admixture should be used immediately. If not used immediately, in-use 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 - 8°C, unless addition of supplements has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

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.

Pack sizes:

650 mL bag: 1 carton with 10 bags

1,000 mL bag: 1 carton with 6 bags

1,500 mL bag: 1 carton with 4 bags

2,000 mL bag: 1 carton with 4 bags

1 bag of 650 mL, 1,000 mL, 1,500 mL, 2,000 mL

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling.

To open

Remove the protective overpouch.

Discard the oxygen absorber 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).

Additions must be performed by qualified personnel under aseptic conditions.

OLIMEL N12E formulation may be supplemented with electrolytes, inorganic/organic phosphate and with commercially available preparations of multi-vitamin products (such as Cernevit) and multi-trace element products (such as Nutryelt). The maximal total levels for additions listed in the table below were demonstrated by stability data and should not be considered dosage recommendations. The supplementation should be dictated by the patient’s clinical needs and should not exceed nutritional guidelines. The electrolytes already present in the bag should be taken into account when reaching the maximal total level.

Compatibility may vary between products from different sources and health care professionals are advised to carry out appropriate checks when mixing OLIMEL N12E with other parenteral solutions.

Possible supplementations for 1000 mL Olimel N12E (for paediatrics)

	Included level	Maximal further addition	Maximal total level
Sodium	35 mmol	115 mmol	150 mmol
Potassium	30 mmol	120 mmol	150 mmol
Magnesium	4.0 mmol	1.6 mmol	5.6 mmol
Calcium	3.5 mmol	1.5 mmol	5.0 mmol
Inorganic Phosphate	0 mmol	10 mmol Pi or 10 mmol Po [b]	10 mmol Pi + 15 mmol Po or 25 mmol Po [a,b]
Organic Phosphate	15 mmol [a]		
Other supplementations (trace elements, vitamins, selenium and zinc) [c]			
Trace elements – Junyelt [d]	1 vial per bag (10mL concentrate solution)		
Vitamins [e]	1 vial (lyophilizate)		
Selenium	60 µg per bag		
Zinc	3 mg per bag		

[a] Including Phosphate provided by the lipid emulsion

[b] Pi - inorganic phosphate; Po - organic phosphate

[c] For all bag formats, the trace elements, vitamins, selenium and zinc supplementation could be the same as for 1L bag

[d] Junyelt (Composition per vial: Zinc 15.30 µmol; Copper 3.15 µmol; Manganese 0.091 µmol; Iodine 0.079 µmol; Selenium 0.253 µmol)

[e] Combination of 1 vial multi-vitamin product (Composition per vial: Vit. B1 (Thiamine) 2.5 mg, Vit. B2 (Riboflavin) 3.6 mg, Vit. B6 (Pyridoxine) 4.0 mg, Vit. B5 (Pantothenic acid) 15 mg, Vit. C (Ascorbic acid) 100 mg, Vit. B8 (Biotin) 0.06 mg, Vit. B9 (Folic acid) 0.4 mg, Vit. B12 (Cyanocobalamin) 0.005 mg, Vit. PP (Nicotinamide) 40 mg) and 1 vial multi-vitamin product (Composition per vial: Vit.A (as Retinol palmitate) 2300 IU, Vit.D (as ergocalciferol) 400 IU, Vit.E (Alpha-tocopherol) 6.4 mg, Vit. K (phytomenadione) 200 µg)

Possible supplementations for 1000 mL Olimel N12E (for adults)			
	Included level	Maximal further addition	Maximal total level
Sodium	35 mmol	115 mmol	150 mmol
Potassium	30 mmol	120 mmol	150 mmol
Magnesium	4.0 mmol	1.6 mmol	5.6 mmol
Calcium	3.5 mmol	1.5 mmol	5.0 mmol
Inorganic Phosphate	0 mmol	10 mmol Pi or 10 mmol Po[b]	10 mmol Pi + 15 mmol Po Or 25 mmol Po [a,b]
Organic Phosphate	15 mmol [a]		
Other supplementations (trace elements, vitamins, selenium and zinc) [c]			

Trace elements – Nutryelt [d]	2 vials per bag (10mL concentrate solution)
Vitamins – Cernevit [e]	1 vial (5 mL lyophilizate)
Selenium	500 µg per bag
Zinc	20 mg per bag

[a] Including Phosphate provided by the lipid emulsion

[b] Pi - inorganic phosphate; Po - organic phosphate

[c] For all bag formats, the trace elements, selenium and zinc supplementation could be the same as for 1L bag; vitamin supplementation is per L of emulsion

[d] Nutryelt (Composition per vial: Zinc 153 µmol; Copper 4.7 µmol; Manganese 1.0 µmol; Fluorine 50 µmol; Iodine 1.0 µmol; Selenium 0.9 µmol; Molybdenum 0.21 µmol; Chromium 0.19 µmol; Iron 18 µmol)

[e] Cernevit (Composition per vial: Vit. A (as Retinol palmitate) 3500 IU, Vit. D3 (Cholecalciferol) 220 IU, Vit. E (Alpha-tocopherol) 11.2 IU, Vit. C (Ascorbic acid) 125 mg, Vit. B1 (Thiamine) 3.51 mg, Vit. B2 (Riboflavin) 4.14 mg, Vit. B6 (Pyridoxine) 4.53 mg, Vit. B12 (Cyanocobalamin) 6 µg, Vit. B9 (Folic acid) 414 µg, Vit. B5 (Pantothenic acid) 17.25 mg, Vit. B8 (Biotin) 69 µg, Vit. PP (Nicotinamide) 46mg)

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 gas contained in the primary bag.

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

{DD/MM/YYYY}

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

{12/2019}