SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

OLEUNOR N7E, emulsion for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

OLEUNOR N7E, emulsion for infusionis 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**
35% Glucose solution (corresponding to 35 g/100 mL)	400 mL	600 mL	800 mL
11.1% Amino acid solution (corresponding to 11.1 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	**Contents per bag**		
	1000 mL	**1500 mL**	**2000 mL**
Refined olive oil+ refined soybean oil[a]	40.00 g	60.00 g	80.00 g
L-Alanine	6.41 g	9.61 g	12.82 g
L-Arginine	4.34 g	6.51 g	8.68 g
L-Aspartic acid	1.28 g	1.92 g	2.56 g
L-Glutamic acid	2.21 g	3.32 g	4.42 g
Glycine	3.07 g	4.60 g	6.14 g
L-Histidine	2.64 g	3.97 g	5.29 g
L-Isoleucine	2.21 g	3.32 g	4.42 g
L-Leucine	3.07 g	4.60 g	6.14 g
L-lysine acetate (equivalent to Lysine)	4.88 g (3.48 g)	7.31 g (5.23 g)	9.75 g (6.97 g)
L-Methionine	2.21 g	3.32 g	4.42 g
L-Phenylalanine	3.07 g	4.60 g	6.14 g
L-Proline	2.64 g	3.97 g	5.29 g
L-Serine	1.75 g	2.62 g	3.50 g
L-Threonine	2.21 g	3.32 g	4.42 g
L-Tryptophan	0.74 g	1.10 g	1.47 g
L-Tyrosine	0.11 g	0.17 g	0.22 g
L-Valine	2.83 g	4.25 g	5.66 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 monohydrate (equivalent to anhydrous glucose)	154.00 g (140.00 g)	231.00 g (210.00 g)	308.00 g (280.00 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 the full list of excipients, see section 6.1.

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

	Contents per bag		
	1000 mL	**1500 mL**	**2000 mL**
Lipids	40 g	60 g	80 g
Amino acids	44.3 g	66.4 g	88.6 g
Nitrogen	7.0 g	10.5 g	14.0 g
Glucose	140.0 g	210.0 g	280.0 g
Energy:			
Total calories approx.	1140 kcal	1710 kcal	2270 kcal
Non-protein calories	960 kcal	1440 kcal	1920 kcal
Glucose calories	560 kcal	840 kcal	1120 kcal
Lipid calories[a]	400 kcal	600 kcal	800 kcal
Non-protein calories / nitrogen ratio	137 kcal/g	137 kcal/g	137 kcal/g
Glucose / lipid calories ratio	58/42	58/42	58/42
Lipid / total calories	35%	35%	35%
Electrolytes:	4	5	6
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	45 mmol	67 mmol	89 mmol
Chloride	45 mmol	68 mmol	90 mmol
pH	5.8 – 6.8	5.8 – 6.8	5.8 – 6.8
Osmolality	1225 – 1495 mosm/kg	1225 – 1495 mosm/kg	1225 – 1495 mosm/kg

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

OLEUNOR N7E, emulsion for infusion is indicated for parenteral nutrition for adults and children older than 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.

4.2 Posology and method of administration

Posology

The appearance of the product after mixing the 3 compartments is a milk-like emulsion.

OLEUNOR Peri-N4E 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).

Fluid balance, blood glucose, and serum electrolytes should be monitored before and during administration (see sections 4.4, 4.5, 4.6 and 4.8).
The patient's ability to eliminate fat and metabolise nitrogen and glucose, and the nutritional requirements should govern the dosage and infusion rate, see section 4.4.
The dose should be individualised with regard to the patient's clinical condition and body weight (bw).
The maximum daily dose varies with the clinical condition of the patient and may even change from day to day.

Dosage

The recommended maximum daily dose of 40 mL/kg bw/day, mentioned below, should not be exceeded. Due to the static composition of the multi-compartment 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, any volume (dose) adjustments must take into consideration the resultant effect this will have on the dosing of all other nutrient components of OLEUNOR Peri-N4E.

In adults

The dosage depends on the patient's energy expenditure, clinical status, body weight and the ability to metabolise the constituents of OLEUNOR Peri-N4E, as well as

additional energy or proteins provided orally/enterally; therefore, the bag size shouldbe chosen accordingly.

The average daily requirements are:

- The requirements are 0.10-0.15 g nitrogen/kg bw/day (0.6-0.9 g amino acids/kg bw/day) in the normal nutritional state or in conditions with mild catabolic stress. In patients with moderate to high metabolic stress with or without malnutrition, the requirements are in the range of 0.15-0.25 g nitrogen/kg bw/day (0.9-1.6 g amino acids/kg bw/day). In some very special conditions (e.g. burns or marked anabolism) the nitrogen need may be even higher.
- 20 to 40 kcal / kg.
- 20 to 40 mL fluid / kg, or 1 to 1.5 mL per expended kcal.

Maximum daily dose
For OLEUNOR Peri-N4E, the maximal daily dose is defined by fluid intake, 40 mL/kg, corresponding to 1 g/kg amino acids, 3 g/kg glucose, 1.2 g/kg lipids, 0.8 mmol/kg sodium and 0.6 mmol/kg potassium. For a 70 kg patient, this would be equivalent to 2800 mL OLEUNOR Peri-N4E per day, resulting in an intake of 70 g amino acids, 210 g glucose and 84 g lipids (i.e., 1680 non-protein kcal and 1960 total kcal). In obese patients the dose should be based on the estimated ideal weight.

Infusion rate
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.
The maximum infusion rate for glucose is 0.25 g/kg bw/h, for amino acid 0.1 g/kg bw/h, and for fat 0.15 g/kg bw/h.
For OLEUNOR Peri-N4E, the maximal infusion rate is 3.2 mL/kg/hour, corresponding to 0.08 g/kg/hour amino acids, 0.24 g/kg/hour glucose and 0.10 g/kg/hour lipids.

<u>In children greater than 2 years of age and adolescents.</u>
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 OLEUNOR Peri-N4E, 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 OLEUNOR Peri-N4E, in both age groups, the magnesium concentration is the limiting factor for daily dose. In the 2 to 11 year age group, the lipid concentration is the limiting factor for hourly rate. In the 12 to 18 year age group, the glucose 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]	OLEUNOR	Recommended[a]	OLEUNOR

		Peri-N4E Max Vol		Peri-N4E Max Vol
Maximum Daily Dose				
Fluids (mL/kg/d)	60 – 120	45	50 – 80	45
Amino acids (g/kg/d)	1 – 2 (up to 2.5)	1.16	1 – 2	1.1
Glucose (g/kg/d)	1.4 – 8.6	3.4	0.7 – 5.8	3.4
Lipids (g/kg/d)	0.5 – 3	1.4	0.5 – 2 (up to 3)	1.4
Total energy (kcal/kg/d)	30 - 75	31.5	20 - 55	31.5
Maximum Hourly Rate				
OLEUNOR Peri-N4E (mL/kg/h)		4.3		3.2
Amino acids (g/kg/h)	0.20	0.11	0.12	0.08
Glucose (g/kg/h)	0.36	0.33	0.24	0.24
Lipids (g/kg/h)	0.13	0.13	0.13	0.10

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

Method and duration of administration

For single use only. Intravenous use, infusion into a peripheral or central vein.

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

After reconstitution, the mixture is milk-like, homogenous liquid, showing no phase separation.

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

Due to its low osmolarity, OLEUNOR Peri-N4E can be administered through a peripheral or 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 OLEUNOR Peri-N4E is contraindicated in the following situations:
- In premature neonates, infants and children less than 2 years of age.
- Hypersensitivity to egg, soybean, 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 characterized by hypertriglyceridaemia.
- Severe hyperglycaemia.
- Severe hepatic insufficiency, hepatic coma.
- Severe renal insufficiency without access to hemofiltration or dialysis.
- Severe blood coagulation disorders.
- Hemophagocytotic syndrome.
- Acute shock.
- General contraindications to infusion therapy: acute pulmonary oedema, hyperhydration, and decompensated cardiac insufficiency.
- Unstable conditions (e.g. severe post-traumatic conditions, uncompensated diabetes mellitus, acute myocardial infarction, stroke, embolism, metabolic acidosis, severe sepsis, hypotonic dehydration and hyperosmolar coma)
- 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 phospholipids. Soybean and egg proteins may cause hypersensitivity reactions. Cross-allergic reactions between soybean and peanut proteins have been observed.

OLEUNOR Peri-N4E 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 infusion 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 a 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 be 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 destabilization of the lipid emulsion could result in vascular occlusion (see sections 6.2 and 6.6).

Hyponatraemia
Treatment with intravenous fluids having a lower sodium concentration than the patient’s serum sodium may cause hyponatremia (see section 4.2). Children, patients with reduced cerebral compliance, patients with non-osmotic vasopressin release (e.g. in acute illness, trauma, post-operative stress, central nervous system diseases), and patients exposed to vasopressin agonists and other drugs that can lower serum sodium (see section 4.5) are at particular risk of acute hyponatraemia. Acute hyponatraemia can lead to acute brain oedema and life-threatening brain injury.
Severe water and electrolyte equilibration disorders (e.g. abnormally high or low serum levels of the electrolytes), 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 medicines. Careful monitoring of signs, symptoms and laboratory test results for fever/chills, leukocytosis, technical complications with the access device and hyperglycaemia 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.

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.

When involving an extremity, the concerned limb should be elevated.

Depending on the extravasated product (including the product(s) being mixed with OLEUNOR Peri-N4E, 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 peripheral or 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 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 ahould 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 OLEUNOR Peri-N4E 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 OLEUNOR Peri-N4E must be adjusted and/or insulin administered.

Thrombophlebitis may develop if peripheral veins are used. The catheter insertion site must be monitored daily for local signs of thrombophlebitis.

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. 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 OLEUNOR Peri-N4E 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 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.
The amount of individual electrolytes to be added is governed by the clinical condition of the patient and by frequent monitoring of serum levels.

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.

OLEUNOR Peri-N4E 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 older than 2 years of age, it is essential to use a bag that has a volume corresponding to the daily dosage.

OLEUNOR Peri-N4E 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.

Maximal infusion rate is 4.3 mL/kg/hour in children 2 to 11 years of age and 3.2 mL/kg/hour in children 12 to 18 years of age.
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.

OLEUNOR Peri-N4E 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 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 OLEUNOR Peri-N4E, through the same infusion line (e.g., Y-site).
However, ceftriaxone and calcium-containing solutions may be administered sequentially of one another if the infusion lines are thoroughly flushed between the infusions with a compatible fluid (see sections 4.4 and 6.2).

OLEUNOR Peri-N4E contains vitamin K, naturally present in lipid emulsions. The amount of vitamin K in recommended doses of OLEUNOR Peri-N4E are not expected to influence effects of coumarin derivatives.

Due to the potassium content of OLEUNOR Peri-N4E, 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 hyperkalemia.

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.

Drugs that can increase the risk for hyponatremia

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no clinical data from the use of OLEUNOR Peri-N4E in pregnant women. No animal reproductive studies have been preformed with OLEUNOR Peri-N4E (see section 5.3). Taking into account the use and indications of OLEUNOR Peri-N4E, the product may be considered during pregnancy, if necessary. OLEUNOR Peri-N4E should only be given to pregnant women after careful consideration. When OLEUNOR Peri-N4E is administrated to pregnant women during labour, particularly if administered in combination with oxytocin, there may be an increased risk for hyponatraemia (see section 4.4, 4.5 and 4.8).

Breastfeeding
There is insufficient information on the excretion of OLEUNOR Peri-N4E components/metabolites in human milk. Parenteral nutrition may become necessary during breast-feeding. OLEUNOR Peri-N4E 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

Not relevant.

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 similar parenteral nutrition emulsions for infusion in a randomized, 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 impossible) were included and treated; patients in the group receiving the medicinal product received up to 40 mL/kg/d of the medicinal product over 5 days. The pooled

data from clinical trials and the postmarketing experience indicate the following adverse drug reactions (ADRs) related to <*Parenteral nutrition Peri-N4E*>.

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[a]
Metabolism and nutrition disorders	Decreased appetite	Common[a]
	Hypertriglyceridaemia	Common[a]
	Hospital Acquired Hyponatraemia**	Not known
Gastrointestinal disorders	Abdominal pain	Common[a]
	Diarrhoea	Common[a]
	Nausea	Common[a]
	Vomiting	Not known[b]
Vascular disorders	Hypertension	Common[a]
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]
Nervous system disorders	Hyponatraemic encephalopathy**	Not known

[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 a parenteral nutrition emulsion for infusion with an identical composition.
** Hospital acquired hyponatraemia may cause irreversible brain injury and death due to development of acute hyponatraemic encephalopathy (see sections 4.2 and 4.4).

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 reactions 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, sub-section "Hepatobiliary disorders")
- 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 (for example 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 OLEUNOR Peri-N4E 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 (for example 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 Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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, headache, hot flush, hyperhidrosis 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.

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.

OLEUNOR N7E'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 OLEUNOR N7E 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 OLEUNOR N7E (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 OLEUNOR N7E have been performed. The constituents/metabolites of OLEUNOR N7E are substances which occur naturally in the organism. There are no non-clinical data considered relevant to clinical safety beyond data included in other sections of the SmPC.

Preclinical toxicity studies performed using similar combinations of substances as in the lipid emulsion 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 with similar solutions for parenteral nutrition containing solutions of amino acids and glucose 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 B, sodium hydroxide (*for pH adjustment*), water for injections.

Compartment of amino-acid solution with electrolytes:
acetic acid, glacial (*for pH adjustment*), water for injections.

Compartment of glucose solution with calcium:
hydrochloric acid, concentrated (*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 destabilize 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.

OLEUNOR Peri-N4E contains calcium ions which pose an additional risk of coagulation in case of precipitation in blood or blood components containing a citrate preservative / anticoagulant.

Ceftriaxone must not be mixed or administered simultaneously with intravenous calcium-containing solutions, including OLEUNOR Peri-N4E, 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, OLEUNOR Peri-N4E should not be administered through the same infusion line or mixed together with ampicillin or fosphenytoin. Ceftriaxone and calcium-containing solutions can be administered sequentially, one after another, if different infusion lines or sites are used or if the lines of infusion are

replaced or have been thoroughly rinsed between the infusions with a compatible fluid.
Check compatibility with solutions administered simultaneously through the same administration set, catheter, or cannula.

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

6.3 Shelf life

24 months if the overwrap is not damaged.

After reconstitution

It is recommended that the product be used immediately after the peelabe seals between the 3 compartments have been opened. However, physical stability of the reconstituted emulsion 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, the reconstituted solution should be used immediately. If not used immediately, storage times and conditions, after mixing and prior to use, are the sole 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.

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 sole 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

Do not freeze.
This medicinal product does not require any special storage conditions.
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 polypropylene soft bag with peelable seals, appropriate for parenteral nutrition solutions, allowing the mixing of the three solutions prior to administration upon breakage of the seals.

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.

To prevent contact with oxygen, the bag is packaged in a suitable overpouch under vacuum with an oxygen absorber sachet citing between the overpouch and the bag, so as to further assure the complete absence of oxygen.

Pack sizes N7E:

1000 mL bag: 1 carton with 6 bags
1500 mL bag: 1 carton with 4 bags
2000 mL bag: 1 carton with 4 bags

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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, showing no phase separation.

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 milk-like homogeneous liquid, showing no phase separation

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.

OLEUNOR N7E may be supplemented with electrolytes according to the tables below:

Per 1000 mL			
	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 (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:

To perform an addition:
- Aseptic conditions must be respected.
- 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 respected.
- 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

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