

OliClinomel

(Triple chambered parenteral nutrition bag)

1st complete range of 3 compartment bags containing ClinOleic 20%

1. NAME OF THE MEDICINAL PRODUCT

OliClinomel N4-550E (1000 ml & 2000 ml)

OliClinomel N7-1000E (1000 ml & 2000 ml)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The medicinal products are presented in the form of a 3-compartment bag.

There are four presentations, which have the different volumes.

Compartment	1000 ml	2000 ml
Lipid emulsion	200 ml	400 ml
Amino acid solution	400 ml	800 ml
Glucose solution	400 ml	800 ml

Composition of a 1000 ml bag (g)	N4-550E	N7-1000E
Refined olive oil + refined soya oil*	20.00	40.00
Alanine	4.56	8.28
Arginine	2.53	4.60
Glycine	2.27	4.12
Histidine	1.06	1.92
Isoleucine	1.32	2.40
Leucine	1.61	2.92
Lysine	1.28	2.32
(As lysine hydrochloride)	(1.60)	(2.90)
Methionine	0.88	1.60
Phenylalanine	1.23	2.24
Proline	1.50	2.72
Serine	1.10	2.00
Threonine	0.92	1.68
Tryptophan	0.40	0.72
Tyrosine	0.09	0.16
Valine	1.28	2.32
Sodium Acetate, 3H ₂ O	0.98	2.45
Sodium glycerophosphate, 5H ₂ O	2.14	2.14
Potassium chloride	1.19	1.79
Magnesium chloride, 6H ₂ O	0.45	0.45
Anhydrous glucose	80.00	160.00
(As glucose monohydrate)	(88.00)	(176.00)
Calcium chloride, 2H ₂ O	0.30	0.30

* Mixture of refined olive oil (approximately 80%) and refined soya oil (approximately 20%)

For the excipients, see 6.1

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

Per 1000 ml mixture	N4-550E	N7-1000E
Nitrogen (g)	3.6	6.6
Amino acids (g)	22	40
Total calories (kcal)	610	1200
Non-protein calories (kcal)	520	1040
Glucose calories (kcal)	320	640
Lipid calories (kcal)	200	400
Non-protein calorie/nitrogen ratio (kcal/g N)	144	158
Sodium (mmol)	21	32
Potassium (mmol)	16	24
Magnesium (mmol)	2.2	2.2
Calcium (mmol)	2	2
Phosphate (mmol)**	8.5	10
Acetate (mmol)	30	57
Chloride (mmol)	33	48
pH	6	6
Osmolarity (mOsm/l)	750	1450

** Phosphates provided by the lipid emulsion

3. PHARMACEUTICAL FORM

After reconstitution: emulsion for infusion.

Appearance before reconstitution:

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

Appearance after reconstitution:

- Homogenous liquid with a milky appearance.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

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

4.2. POSOLOGY AND METHOD OF ADMINISTRATION

POSOLOGY

The dosage depends on metabolic requirements, energy expenditure and the patient's clinical condition.

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

In adults

Requirements

Average nitrogen requirements are 0.16 to 0.35 g/kg/day (approximately 1 to 2 g of amino acids/kg/day).

Maximum daily dose

OliClinomel N4-550E:

The maximum daily dose is 40ml/kg body weight (equivalent to 0.88 g of amino-acids, 3.2 g of glucose and 0.8 g of lipids per kg), i.e. 2,800 ml of the emulsion for infusion for a patient weighing 70 kg.

OliClinomel N7-1000E:

The maximum daily dose is 36 ml/kg body weight (equivalent to 1.44 g of amino-acids, 5.76 g of glucose and 1.44 g of lipids per kg), i.e. 2,250 ml of the emulsion for infusion for a patient weighing 70 kg.

In children above two years of age (In children above two years of age under non-exclusive parenteral nutrition)

Requirements

Average nitrogen requirements are 0.35 to 0.45 g/kg/day (approximately 2 to 3 g of amino acids/kg/day).

Energy requirements vary depending on the patient's age, nutritional state and level of catabolism. On average these range between 60 and 110 kcal/kg/day.

Posology

The dosage is based on fluid intake and daily nitrogen requirements.

These intakes should be adjusted to take account of the child's hydration status.

Maximum daily dose

OliClinomel N7-1000E:

75 ml/kg body weight (equivalent to 3 g amino-acids, 12 g of glucose and 3 g of lipids per kg body weight).

METHOD OF ADMINISTRATION

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

Oliclinomel N4-550E

BY INTRAVENOUS ADMINISTRATION THROUGH A CENTRAL OR PERIPHERAL VEIN

Oliclinomel N7-1000E

BY INTRAVENOUS ADMINISTRATION THROUGH A CENTRAL VEIN

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

The administration flow rate should be adjusted to take account of the dose being administered, the characteristics of the final mixture being infused, the daily volume intake and the duration of the infusion (see section 4.4).

Normally, the flow rate should be increased gradually during the first hour.

Maximum infusion rate

As a general rule, do not exceed:

OliClinomel N4-550E:

3 ml/kg/hour of the emulsion for infusion, i.e. 0.06 g of amino-acids, 0.24 g of glucose and 0.06 g of lipids per kg body weight per hour.

OliClinomel N7-1000E:

1.5 ml/kg/hour of the emulsion for infusion, i.e. 0.06 g of amino-acids, 0.24 g of glucose and 0.06 g of lipids per kg body weight per hour.

Additions

These products contain electrolytes. They contain neither trace elements nor vitamins. OliClinomel can be used as such or after supplementation with electrolytes, trace elements or vitamins, when required. (see sections 4.4 and 6.6).

Electrolytes

If electrolytes are added in OliClinomel over and above contained in OliClinomel with electrolytes, in no event should the following concentrations of electrolytes be exceeded per litre of the final mixture (see also section 4.4).

- Sodium: 150 mmol/l
- Potassium: 150 mmol/l
- Magnesium: 5.60 mmol/l
- Calcium: 5 mmol/l

Trace elements and vitamins

There are authorized formulae for adults, which are mutually exclusive.

Paediatric formulations are required for children.

4.3. CONTRAINDICATIONS

Use of OLICLINOMEL is contraindicated in the following situations:

- In premature neonates, infants and children less than 2 years old, as the calorienitrogen ratio and energy supply are inappropriate.
- Known hypersensitivity to egg or soya proteins or to any other ingredient.
- Severe renal insufficiency without the possibility of haemofiltration or dialysis.
- Severe hepatic insufficiency.
- Congenital abnormalities of amino acid metabolism.
- Severe blood coagulation disorders.
- Severe hyperlipidaemia.
- Hyperglycemia, which requires more than 6 units insulin/h.
- For formulation with electrolytes: High and pathological plasma concentration of one of the electrolytes included in the product.

The general contraindications for administrating an intravenous infusion are as follows:

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

4.4. SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE

Water and electrolyte equilibration disorders and metabolic disorders must be corrected before starting the infusion.

The osmolarity of the final admixture after additions must be defined before administration.

Caution should be exercised in administering OliClinomel to patients with increased osmolarity, adrenal insufficiency, heart failure or pulmonary dysfunction.

Strict aseptic conditions must be observed when the catheter is inserted or handled all along infusion.

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

Normally, the flow rate should be increased gradually during the first hour.

This medicinal product contains Soya oil, which may rarely cause severe hypersensitivity reactions.

The infusion must be stopped immediately if any abnormal signs or symptoms of an allergic reaction (such as fever, shivering, skin rashes or respiratory difficulties) develop.

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

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) and if the amino acids solution and the glucose solution are clear, and if the lipid emulsion is homogeneous.

After opening the bag, the content must be used immediately and must never be stored for a subsequent infusion.

Monitor water and electrolyte balance, serum osmolarity, acid/base balance, blood glucose and liver function tests throughout treatment.

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

Serum triglycerides concentrations must not exceed 3 mmol/l during the infusion. These concentrations should not be determined before a minimum of a 3-hour period of continuous infusion 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 triglycerides concentrations have returned to normal values.

In addition, regular clinical and laboratory tests are required particularly in cases of:

- Amino acid metabolism disorders.
- Hepatic insufficiency because of the risk of developing or worsening neurological disorders associated with hyperammonaemia (see section 4.3).
- Renal insufficiency, particularly if hyperkalaemia is present; risk of developing or worsening metabolic acidosis and hypernitrogenaemia if extra-renal waste removal is not being performed (see section 4.3).
- Metabolic acidosis (administration of carbohydrates is not recommended in the presence of lactic acidosis).
- Diabetes mellitus: monitoring of glucose concentrations, glucosuria, ketonuria and, where applicable, adjustment of insulin dosages.
- Coagulation disorders.
- Anemia.
- Hyperlipidaemia (because of the presence of lipids in the emulsion for infusion).

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

Special precautions in paediatrics

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

Oliclinomel N4-550E, & N7-1000E: When administered to children more than 2 years old, it is essential to use a bag which volume corresponds to the daily dosage.

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

4.5. INTERACTIONS WITH OTHER MEDICAMENTS AND OTHER FORMS OF INTERACTION

This emulsion for infusion must not be administered simultaneously with blood through the same infusion tubing because of the possibility of pseudo-agglutination.

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

4.6. PREGNANCY AND LACTATION

There are not at present sufficient relevant clinical findings to assess the tolerability of the ingredients in OliClinomel in women who are pregnant or breast-feeding.

In the absence of data, the prescriber must assess the risks/benefits before deciding to administer this emulsion either during pregnancy or to women who are breast-feeding.

4.7. EFFECTS ON THE ABILITY TO DRIVE AND USE MACHINES

Not applicable

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).

The effects which may occur and which require the treatment to be stopped are as follows: hyperthermia, excessive sweating, tremors, nausea, headaches, dyspnoea.

Transient rises in liver function parameters (alkaline phosphatase, transaminases, bilirubin) have been reported, particularly during long term parenteral nutrition lasting several weeks.

Hepatomegaly and jaundice have developed in rare cases.

Oliclinomel N4-550E: If a hypertonic solution is administered, thrombophlebitis may develop if peripheral veins are used.

Reduced ability to remove the lipids contained in OliClinomel may result in a "fat overload syndrome" which may be caused by overdose but may also occur at the start of an infusion according to instructions, and is associated with a sudden deterioration in the patient's clinical condition.

The fat overload syndrome is characterized by: hyperlipidaemia, fever, fatty infiltration, hepatomegaly, anaemia, leucopaenia, thrombocytopaenia, coagulation disorders and coma.

All of these symptoms are reversible when the lipid emulsion infusion is stopped.

Rare cases of thrombocytopenia have been reported in children receiving lipid infusions.

4.9. OVERDOSE

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

Hyperglycemia, glucosuria, and a 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 also section 4.8).

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

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Solutions for parenteral nutrition/mixtures

ATC code: B05 BA 10.

This is a ternary mixture enabling the nitrogen/energy balance to be maintained from the nitrogen source (L series amino acids) and energy in the form of glucose and essential fatty acids.

In addition, this formulation contains electrolytes.

The amino acid solution contains 15 L series amino acids (including 8 essential amino acids), which are indispensable for protein synthesis.

The amino acids also represent an energy source, their oxidation resulting in excretion of nitrogen in the form of urea.

The amino acid profile is as follows:

- Essential amino acids/total amino acids: 40.5%
- Essential amino acids (g)/total nitrogen (g): 2.5
- Branched-chain amino acids/total amino acids: 19%.

The carbohydrate source is glucose.

The lipid emulsion is an association of refined olive oil and refined Soya 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.

The moderate essential fatty acid (EFA) content improves the status of their upper derivatives while correcting EFA deficiency.

Olive oil contains significant amount of alpha tocopherol which, combined with a moderate PUFA intake, contributes to improve vitamin E status and reduce lipid per oxidation.

5.2. PHARMACOKINETIC PROPERTIES

The ingredients of the emulsion for infusion (amino acids, electrolytes, glucose, 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. Amino acids from food proteins, however, first pass through the vena portal before reaching 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 OliClinomel is close to that of chylomicrons and this emulsion therefore has a similar elimination rate.

5.3. PRECLINICAL SAFETY DATA

No preclinical studies have been performed on the OliClinomel finished product.

Preclinical studies performed using the solutions of amino acids and glucose contained in OliClinomel of different qualitative compositions and concentrations have not, however, revealed any specific toxicity.

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

6. PHARMACEUTICALS PARTICULARS

6.1. LIST OF EXCIPIENTS

Lipid emulsion compartment: Amino acid solution compartment:

- Purified egg lecithin • Acetic acid
 - Glycerol • Water for injections
 - Sodium oleate
- Glucose solution compartment:
- Sodium hydroxide • Hydrochloric acid
 - Water for injections • Water for injections

6.2. INCOMPATIBILITIES

All formulations:

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 with the mixture of the three components 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-stabilize the lipid emulsion.

Check compatibility with solutions administered simultaneously through the same giving 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 over wrap is not damaged.

It is recommended that the product is used immediately after the non-permanent seal between the 3 compartments have been opened.

The reconstituted emulsion has, however, been shown to be stable for a maximum of 7 days at between 2° and 8°C followed by a maximum of 48 h at temperatures not exceeding + 25°C.

After addition of supplements (electrolytes, organic phosphate, trace elements, vitamins; see section 6.6).

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 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 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.

Keep container in outer carton.

6.5. NATURE AND CONTENTS OF CONTAINERS

The three-compartment bag is a multi-layer plastic bag packaged in an oxygen barrier outer packaging. An oxygen absorber may be added inside of the over wrap. The multi-layer plastic material consists mostly of EVA (polyethylene-vinyl acetate) and is compatible with lipids.

The bag is packaged in an oxygen barrier overwrap, which contains an oxygen absorber in a sachet.

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.

After the seals have been broken, the capacity of the bag is sufficient to enable vitamins, electrolytes and trace elements to be added.

PACK SIZES:

1000 ml in a three-compartment bag (400 ml of amino acid solution + 400 ml of glucose solution + 200 ml of lipid emulsion)

Carton with 6 bags

All formulations:

1000 ml in a three-compartment bag (400 ml of amino acid solution + 400 ml of glucose solution + 200 ml of lipid emulsion)

1 bag

2000 ml in a three-compartment bag (800 ml of amino acid solution + 800 ml of glucose solution + 400 ml of lipid emulsion) (unique available volume for OliClinomel N8-800)

Carton with 4 bags

All formulations

2000 ml in a three-compartment bag (800 ml of amino acid solution + 800 ml of glucose solution + 400 ml of lipid emulsion)

1 bag

Not all pack sizes may be marketed.

6.6. INSTRUCTIONS FOR USE/HANDLING

a. To open

- Tear the protective overwrap.

All formulations

- When present, discard the oxygen absorber sachet after removing the overwrap.

All formulations:

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) and if the amino acids solution and the glucose solution are clear.

b. Mixing the solutions and the emulsion

Ensure that the product is at ambient temperature when breaking the non-permanent seals.

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 half of their length.

Mix by inverting the bag at least 3 times.

c. 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.

d. Additions

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

Vitamins may also be added into the glucose compartment before the mixture has been reconstituted (before opening the non-permanent seals and before mixing the solutions and the emulsion).

OliClinomel may be supplemented with:

- Electrolytes (for formulations with electrolytes: take account of the electrolytes when already present in the bag)

Stability has been demonstrated per litre of the ternary mixture up to a total quantity of:

- 150 mmol of sodium, 150 mmol of potassium, 5.6 mmol of magnesium, 5 mmol of calcium

Organic phosphate: stability has been demonstrated for additions of up to 22 mmol per bag

- Trace elements and vitamins:

stability has been demonstrated up to the recommended daily dose.

These additions are made into the injection site using an injection needle:

- Prepare the injection site,
- Puncture the injection site and inject,
- Mix the contents of the bag and the additives.

e. Administration

If OliClinomel has been stored at cold temperature, ensure that the product has been brought to room temperature before use.

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.

For single use only

After opening the bag the content must be used immediately, and must never be stored for a subsequent infusion.

All formulations:

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

Do not reconnect any partially used bag.

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

This product information may differ from country to country.

OliClinomel Range

	Peripheral vein		Central vein	
	Nutritional Assistance		Nutritional Assistance	Total Parenteral Nutrition
	N4-550		N7-1000	N7-1000
E = WITH ELECTROLYTES	E	E	E	E
Volume (L)	1L	2L	1L	2L
Total calories (kcal)	610	1215	1200	2400
NP (Non-protein) calories (kcal)	520	1040	1040	2080
Nitrogen (g)	3.6	7.3	6.6	13.2
NP calorie-nitrogen ratio (kcal/g N)	144	144	158	158
Glucose (g)	80	160	160	320
Lipids (g)	20	40	40	80
Carbohydrate-lipid ratio	62/38	62/38	62/38	62/38
Electrolytes (mmol)				
<i>Sodium</i>	21	42	32	64
<i>Potassium</i>	16	32	24	48
<i>Magnesium</i>	2.2	4.4	2.2	4.4
<i>Calcium</i>	2	4	2	4
<i>Phosphate</i>	8.5	17	10	20
<i>Chloride</i>	33	66	48	96
<i>Acetate</i>	30	61	57	114
Osmolarity (mosm/l)	750	750	1450	1450

	NUTRITIONAL ASSISTANCE			TOTAL PARENTERAL NUTRITION
	PERIPHERAL VEIN		CENTRAL VEIN	CENTRAL VEIN
	N4-550		N7-1000	N7-1000
E = with electrolytes	E	E	E	E
Volume (L)	1L	2L	1L	2L
Total calories (kcal)	610	1215	1200	2400
NP (Non-protein) calories (kcal)	520	1040	1040	2080
Nitrogen (g)	3.6	7.3	6.6	13.2
NP calorie-nitrogen ratio (kcal/g N)	144	144	158	158
Glucose (g)	80	160	160	320
Lipids (g)	20	40	40	80
Carbohydrate-lipid ratio	62/38	62/38	62/38	62/38
Electrolytes (mmol)	Yes	Yes	Yes	Yes
Osmolarity (mosm/L)	750	750	1450	1450