Bar code

Baxter

OliClinomel N4-550 E

Emulsion for infusion

1. SUMMARY OF PRODUCT CHARACTERISTICS

OliClinomel N4-550E, emulsion for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

This medicinal product is presented in the form of a 3-compartment bag. There are four presentations, which have the following different volumes:

Compartment	1000 ml	1500 ml	2000 ml	2500 ml
Lipid emulsion	200 ml	300 ml	400 ml	500 ml
Amino acid solution	400 ml	600 ml	800 ml	1000 ml
Glucose solution	400 ml	600 ml	800 ml	1000 ml

Composition of a 1000ml bag:

Active substances	10% lipid emulsion compartment (corresponding to 10g/100ml) (200ml)	5.5% amino acid solution compartment (corresponding to 5.5g/100ml) (400ml)	20% glucose solution compartment (corresponding to 20g/100ml) (400ml)
Refined olive oil + refined soya bean oil*	20.00 g		
Alanine		4.56 g	
Arginine		2.53 g	
Glycine		2.27 g	
Histidine		1.06 g	
Isoleucine		1.32 g	
Leucine		1.61 g	
Lysine		1.28 g	
(As Lysine hydrochloride)		(1.60 g)	
Methionine		0.88 g	
Phenylalanine		1.23 g	
Proline		1.50 g	
Serine		1.10 g	
Threonine		0.92 g	
Tryptophan		0.40 g	
Tyrosine		0.09 g	
Valine		1.28 g	
Sodium acetate, $3H_2O$		0.98 g	
Sodium glycerophosphate, $5H_2O$		2.14 g	
Potassium chloride		1.19 g	
Magnesium chloride, $6H_2O$		0.45 g	
Glucose			80.00 g
(As Glucose monohydrate)			(88.00) g

Calcium chloride, $2H_2O$			0.30 g

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

For full list of the excipients, see section 6.1

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

Per bag	**1 litre**	**1.5 litre**	**2 litres**	**2.5 litres**
Nitrogen (g)	3.6	5.4	7.3	9.1
Amino acids (g)	22	33	44	55
Glucose (g)	80	120	160	200
Lipids(g)	20	30	40	50
Total calories (kcal)	610	910	1215	1520
Non-protein calories (kcal)	520	780	1040	1300
Glucose calories (kcal)	320	480	640	800
Lipid calories (kcal)	200	300	400	500
Non-protein calorie/nitrogen ratio (kcal/g N)	144	144	144	144
Sodium (mmol)	21	32	42	53
Potassium (mmol)	16	24	32	40
Magnesium (mmol)	2.2	3.3	4.4	5.5
Calcium (mmol)	2	3	4	5
Phosphate (mmol)**	8.5	13	17	21
Acetate (mmol)	30	46	61	76
Chloride (mmol)	33	50	66	83
pH	6	6	6	6
Osmolarity (mOsmol/l)	750	750	750	750

** Including phosphates provided by the lipid emulsion.

3. PHARMACEUTICAL FORM

After reconstitution:
Emulsion for infusion.

Appearance prior to reconstitution:

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Parenteral nutrition for adults and children greater than 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 the patient's energy expenditure, clinical status, body weight and the ability to metabolize the constituents of OliClinomel, as well as additional energy intake or proteins taken orally enterally; therefore the bag size chosen accordingly.

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

Maximum daily dose

The maximum daily dose should not be exceeded in adult and paediatric patients. 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 adults

Requirements:
Average nitrogen requirements are 0.16 to 0.35g/kg/day (approximately 1 to 2 g of amino acids/kg/day).
Energy requirements vary depending on the patient's nutritional status and level of catabolism. On average these are 20 to 40 kcal/kg/day.

Maximum daily dose
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, 0.84 mmol of sodium and 0.64 mmol of potassium per kg), i.e. 2800 ml of the emulsion for infusion for a patient weighing 70kg.

In adolescent and children greater than two years of age

There have been no studies performed in the paediatric population.

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.
Daily fluid, nitrogen, and energy requirements continuously decrease with age.
The guidelines for maximal recommended hourly rate of infusion and volume per day for pediatric patients are:

Maximum Daily Dose

	2 to 11 years	12 to 18 years
Constituent	OLICLINOMEL N4E Max Daily Dose[a]	OLICLINOMEL N4E Max Daily Dose[a]

Fluids (mL/kg/d)	50	50
Amino acids (g/kg/d)	1.1	1.1
Glucose (g/kg/d)	4.0	4.0
Lipids (g/kg/d)	1.0	1.0
Total energy (kcal/kg/d)	30.5	30.5

[a]: Magnesium concentration is the limiting factor for maximum daily dose in both age groups

Maximum Hourly Rate

Constituent	2 to 11 years OLICLINOMEL N4E Max Hourly Rate[a]	12 to 18 years OLICLINOMEL N4E Max Hourly Rate[a]
Fluid (mL/kg/h)	4.5	3.0
Amino acids (g/kg/h)	0.09	0.07
Glucose (g/kg/h)	0.36	0.24
Lipids (g/kg/h)	0.09	0.06

[a]: Glucose concentration is the limiting factor for maximum hourly rate in both age groups

Method and duration of administration

For single use only.

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

Appearance after reconstitution: homogenous liquid with a milky appearance.

For instructions for preparation and handling of the emulsion for infusion, see section 6.6 “Special precautions for disposal and other handling”.

BY INTRAVENOUS ADMINISTRATION THROUGH A CENTRAL OR PERIPHERAL VEIN (due to the low osmolarity of OliClinomel).

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

The administration flow rate must be adjusted taking into account the dose being administered, 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 in adults:
As a general rule, do not exceed 3.0 ml/kg/hour of the emulsion for infusion, i.e. 0.06 g amino acids, 0.24 g glucose and 0.06 g lipids /kg body weight / hour.

As a general rule, do not exceed infusion rates of 0.10 g/kg/hour amino acids and/or 0.25 g/kg/hour glucose and/or 0.15 g/kg/hour lipids, except in particular cases.

4.3 Contraindications

The use of OliClinomel N4-550E is contraindicated in the following situations:

- In premature neonates, infants and children less than 2 years old, as the calorie-nitrogen ratio and energy supply are inappropriate;
- Hypersensitivity to egg, soya-bean, peanut proteins, or corn/corn products (see Section 4.4), or to any other active substance 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;
- 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, including OliClinomel N4-550E, 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, dyspnoea or bronchospasm) develop. This medicinal product contains soybean oil and egg phosphatide. Soybean and egg proteins may cause hypersensitivity reactions. Cross allergic reactions between soybean and peanut proteins have been observed.

Oliclinomel N4-550E contains glucose derived from corn, which may cause hypersensitivity reactions in patients with allergy to corn or corn products (see section 4.3).

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.

Ceftriaxone must not be mixed or administered simultaneously with any calcium-containing IV solutions even via different infusion lines or different infusion sites because of the risk of precipitation of ceftriaxone-calcium salt.

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. Alternatively, infusion of TPN solution could be stopped for the period of ceftriaxone infusion, considering the advice to flush infusion lines between solutions (see section 4.5 and 6.2).If the same infusion line is used for sequential administration, the line must be thoroughly flushed with a compatible fluid between infusions. This only applies to products containing electrolytes.

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). Precipitates have been reported even in the absence of

phosphate salt in the solution. Precipitation distal to the in-line filter and suspected precipitate formation in the blood stream have 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 pulmonary 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 destabilization of the lipid emulsion could result in vascular occlusion (see section 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 tests 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.

Metabolic complications may occur if the nutrient intake is not adapted to the patient's requirements of the patient 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.

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

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

"Fat overload syndrome has been reported with the administration of Oliclinomel and similar products. The reduced or limited ability to metabolize the lipids contained in OliClinomel N4-550E may result in a "fat overload syndrome", which may be caused by overdose, but the signs and symptoms of this syndrome may also occur when the product is administered according to instructions (see also Section 4.8 and Section 4.9).

In the event of hyperglycaemia, the rate infusion rate of OliClinomel N4-550E must be adjusted and/or insulin administered.

While OliClinomel N4-550E can be administered through a peripheral vein, thrombophlebitis may develop. 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 should 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. (See section 6.6)

Caution should be exercised in administering OliClinomel N4-550E to patients with increased osmolarity, adrenal insufficiency, heart failure or pulmonary dysfunction.

Refeeding severely undernourished patients may result in the refeeding syndrome that is characterized by the shift of potassium, phosphorus and magnesium intracellularly as the patient becomes anabolic. Thiamine deficiency and fluid retention may also develop. Careful monitoring and slowly increasing nutrient intakes, while avoiding overfeeding can prevent these complications. This syndrome has been reported with similar products.

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

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 balance, 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

Exercise 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 presence of lipids in the emulsion for infusion. Regular clinical and laboratory tests are required.
- Amino acid metabolism disorders.

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 OLICLINOMEL N4-550E, 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. If there is any deterioration of the affected area (continued pain, necrosis, ulceration, suspected compartment syndrome), surgery should be consulted immediately.

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.

Special precautions in paediatrics

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

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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 any calcium-containing IV solutions including Oliclinomel N4-550E through the same or even via different infusion lines or different infusion sites because of the risk of precipitation of ceftriaxone-calcium salt. 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).

OliClinomel N4-550E contains vitamin K, naturally present in lipid emulsions. The amount of vitamin K in recommended doses of OliClinomel N4-550E are not expected to influence effects of coumarin derivatives.

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

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

Because of the potassium content of OliClinomel N4-550E, 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 and cyclosporine in view of the risk of hyperkalemia.

4.6 Fertility, pregnancy and lactation

There are not at present sufficient relevant clinical findings to assess the tolerability of the ingredients in OliClinomel N4-550E 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 ability to drive and use machines

There are no data on the effects on the ability to operate and use automobile or other heavy machinery.

4.8 Undesirable effects

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

At the beginning of the infusion, any abnormal signs or symptoms of an allergic reaction (eg. sweating, fever, shivering, headache, skin rashes, dyspnoea, bronchospasm) should be cause for immediate discontinuation of the infusion.

4.8.1. Adverse Reactions from Clinical Trials

OLICLINOMEL N4-550E, N7-1000E, and N8-800 have been used in four (4) clinical studies. Three (3) studies evaluated the ease of use and the safety, and the nutritional efficiency of the product with 2 of the 3 studies in patients undergoing gastrointestinal surgery for gastric cancer. The third study was in hospitalized patients with various diagnoses requiring parenteral nutrition (31% surgery, 23% trauma, 51% medical patients). The medical patients had a variety of disorders that included cardiac, respiratory, gastrointestinal, metabolic, nervous system, infectious, renal, and neoplastic disease. The last study was to assess the safety and efficacy of OLICLINOMEL and was in patients admitted to a surgical service. Of those, 86.3% underwent surgery (most were abdominal surgery for gastrointestinal disease).

The data evaluated from these four studies (total number of patients = 286) was pooled and indicated the following adverse reactions as related to OLICLINOMEL.

Clinical Trial Adverse Reactions			
System Organ Class (SOC)	**Preferred MedDRA Term**	**Frequency**	**Frequency Percent**

			age [*]
IMMUNE SYSTEM DISORDERS	**Hypersensitivity**	Uncommon	0.7%
METABOLISM AND NUTRITION DISORDERS	**Hyperglycaemia**	Common	1.4%
NERVOUS SYSTEM DISORDERS	**Dizziness**	Uncommon	0.7%
	Headache	Uncommon	0.3%
GASTROINTESTINAL DISORDERS	**Nausea**	Common	9.5%
	Diarrhoea	Common	1.7%
	Vomiting	Common	1.4%
	Abdominal pain	Uncommon	0.7%
HEPATOBILIARY DISORDERS	**Hepatic function abnormal**[†]	Common	4.2%
RENAL AND URINARY DISORDERS	**Azotaemia**[‡]	Uncommon	0.7%
GENERAL DISORDERS AND ADMINISTRATIVE SITE CONDITIONS	**Infusion site swelling**[#]	Very common	11.9%
	Infusion site pain[‖]	Common	4.5%
	Infusion site extravasation	Common	1.4%
	Chest discomfort	Common	1.4%
	Infusion site reaction	Common	1.0%
	Pyrexia	Uncommon	0.3%

	Infusion site vesicles	Uncommon	0.3%
	Malaise	Uncommon	0.7%
	Chills	Uncommon	0.3%
INVESTIGATIONS	**Gamma-glutamyltransferase increased**	Common	5.2%
	Hepatic enzyme increased[Δ]	Common	4.5%
	Blood alkaline phosphatase increased	Common	1.4%
	Blood triglycerides increased[◊]	Common	1.4%
	Heart rate irregular	Uncommon	0.3%

*Frequency categories: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10,000 to < 1/1000); and very rare (< 1/10,000).

† Includes reports of liver disorder.

‡ Includes reports of blood urea increased.

Includes reports of swelling, injection site swelling, effusion, puncture site swelling.

‖ Includes reports of tenderness.

Δ Includes reports of aspartate aminotransferase increased, alanine aminotransferase increased, and transaminases increased.

◊ Includes report of hyperlipidemia.

4.8.2. Post-Marketing Adverse Reactions

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

IMMUNE SYSTEM DISORDERS: Bronchospasm (as part of an allergic reaction)

METABOLISM AND NUTRITION DISORDERS: Fat overload syndrome

NERVOUS SYSTEM DISORDERS: Tremor

HEPATOBILIARY DISORDERS: Cholestasis, Jaundice

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Erythema, Hyperhidrosis

MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS: Musculoskeletal pain, Back pain, Muscle spasm, Pain in extremity

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Catheter site phlebitis, Infusion site oedema, Chest pain/discomfort, Feeling hot, Localized oedema, Oedema peripheral, Inflammation, Necrosis/Ulcer

INVESTIGATIONS: Blood bilirubin increased, Hepatic enzymes abnormal

4.8.3. Other (Class) Reactions

The following has been reported with other similar products:

- Pulmonary vascular precipitates (Pulmonary vascular emboli and Pulmonary distress) (see Section 4.4)

Fat overload syndrome (very rare)

Fat overload may be caused by inappropriate administration (e.g. overdose and/or infusion rate higher than recommended; 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 metabolize the lipids in OliClinomel, accompanied by prolonged plasma clearance may result in a "fat overload syndrome". This syndrome is associated with a sudden change in the patient's clinical condition, and is characterized by findings such as hyperlipidaemia, fever, fatty infiltration of the liver, hepatomegaly, deteriorating liver function, anaemia, leukopenia, thrombocytopenia, coagulation disorders and central nervous system manifestations (e.g. coma), requiring hospitalization. These symptoms are reversible if the lipid emulsion is discontinued.

- Vascular disorders (frequency not known – cannot be estimated from the available data): Pulmonary vascular precipitates (pulmonary vascular embolism and respiratory distress)

Paediatric population
Thrombocytopenia has been reported in children receiving lipid infusions.

4.9 Overdose

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

An excessively fast administration of total parenteral nutrition (TPN) solutions, including OliClinomel N4-550E, may result in serious or fatal consequences (See section 4.4 " Special warning and precautions for use").

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

Excessively fast infusion or administration of an inappropriate large volume may cause nausea, vomiting, chills, chest pain, headache, heart rate irregular or tachycardia, and electrolyte disturbances.

In such situations, the infusion should be stopped immediately.

The reduced or limited ability to metabolize the 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/mixed nutrition, ATC code: B05BA10.

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 acid: 19%
- The carbohydrate source is Dextrose (glucose) (80 g/l).

The lipid emulsion 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.

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 peroxidation.

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 porta 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 N4-550E 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 finished product, OliClinomel N4-550E. Preclinical studies performed using the solutions of amino acids and glucose contained in OliClinomel N4-550E of different qualitative composition and concentrations have not, however, revealed any specific toxicity.

Preclinical toxicity studies performed using the lipid emulsion contained in OliClinomel N4-550E have identified the changes , which are conventionally found with a high intake of a lipid emulsion: fatty liver, thrombocytopenia and elevated cholesterol.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Lipid emulsion compartment:

- Purified egg phosphatide
- Glycerol
- Sodium oleate
- Sodium hydroxide (for pH adjustment)
- Water for injection

Amino acid solution compartment:

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

Glucose solution compartment:

- Hydrochloric acid (for pH adjustment)
- Water for injection

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 or formation of precipitates) (See Section 6.6).

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 formation of calcium phosphate precipitates.
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-stabilise the lipid emulsion.

Ceftriaxone must not be mixed or administered simultaneously with intravenous calcium-containing solutions, including Oliclinomel N4-550E, 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).

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.

Oliclinomel N4-550E contains calcium ions which pose additional risk of coagulation precipitates in citrate anticoagulated/preserved blood or components.

6.3 Shelf life

2 years if the overpouch is not damaged.

It is recommended that the product is used immediately after the non-permanent seals 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°C and +8°C, followed by a maximum of 48h 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 temperatures between 2°C and 8°C followed by 48 hours at temperatures 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.
Store in overpouch.
Keep container in the outer carton in order to protect from light.
For storage of the reconstituted emulsion, see Section 6.3.

6.5 Nature and contents of container

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

The bag is packaged in an oxygen barrier overpouch, 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 3-compartment bag (400 ml 5.5% amino acid solution (corresponding to 5.5g/100ml) + 400 ml 20% glucose solution (corresponding to 20g/100ml) + 200 ml 10% lipid emulsion (corresponding to 10g/100ml))
Carton with 6 bags per carton.

1000 ml in a 3 compartment bag (400 ml 5.5% amino acid solution (corresponding to 5.5g/100ml)+ 400 ml 20% glucose solution (corresponding to 20g/100ml) + 200 ml 10% lipid emulsion (corresponding to 10g/100ml))
1 bag

1500 ml in a 3-compartment bag (600 ml 5.5% amino acid solution (corresponding to 5.5g/100ml) + 600 ml 20% glucose solution (corresponding to 20g/100ml) + 300 ml 10% lipid emulsion (corresponding to 10g/100ml))
Carton with 4 bags

1500 ml in a 3 compartment bag (600 ml 5.5% amino acid solution (corresponding to 5.5g/100ml)+ 600 ml 20% glucose solution (corresponding to 20g/100ml) + 300 ml 10% lipid emulsion (corresponding to 10g/100ml))
1 bag

2000 ml in a three-compartment bag (800 ml 5.5% amino acid solution (corresponding to 5.5g/100ml) + 800 ml 20% glucose solution (corresponding to 20g/100ml) + 400 ml 10% lipid emulsion (corresponding to 10g/100ml))
Carton with 4 bags

2000 ml in a 3 compartment bag (800 ml 5.5% amino acid solution (corresponding to 5.5g/100ml)+ 800 ml 20% glucose solution (corresponding to 20g/100ml) + 400 ml 10% lipid emulsion (corresponding to 10g/100ml))
1 bag]

2500ml in a three-compartment bag (1000 ml 5.5% amino acid solution (corresponding to 5.5g/100ml) + 1000 ml 20% glucose solution (corresponding to 20g/100ml) + 500 ml 10% lipid emulsion (corresponding to 10g/100ml))
Carton with 2 bags

2500 ml in a 3 compartment bag (1000 ml 5.5% amino acid solution (corresponding to 5.5g/100ml)+ 1000 ml 20% glucose solution (corresponding to 20g/100ml) + 500 ml 10% lipid emulsion (corresponding to 10g/100ml))
1 bag

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

a. <u>To open</u>

- Tear the protective overpouch.

- When present, discard the oxygen absorber sachet after removing the overpouch.
- Confirm the integrity of the bag and of the non-permanent seals.
- Use only if the bag is not damaged, if the non-permanent seals are intact (i.e. no mixture of the contents of the three compartments) and if the amino acids solution and the glucose solution are clear, colourless or slightly yellow, practically free of visible particles and if the lipid emulsion is a homogeneous liquid with a milky appearance.

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

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 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).

When making additions to the formulation, the final osmolarity of the mixture should be measured before administration via a peripheral vein.OliClinomel N4-550E may be supplemented with:

Electrolytes: electrolytes already present in the bag should be taken into account. Stability has been demonstrated up to a total quantity of 150 mmol of sodium, 150 mmol of potassium, 5.6 mmol of magnesium and 5 mmol of calcium per litre of the ternary mixture.
Organic phosphate: stability has been demonstrated for additions of up to 15 mmol per bag.

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

Compatibility for other additives is available upon request.

Additions must be performed by qualified personnel under aseptic conditions. These additions are made into the

injection site using a needle:
- Prepare the injection site.
- Puncture the injection site and inject.
- Mix the contents of the bag and the additives.

e. Administration

For single use only

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

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

After opening the bag, the contents must be used immediately. The opened bag must never be stored for a subsequent infusion.
Do not reconnect any partially used bag.
Do not connect bags in series in order to avoid the possibility of air embolism due to air contained in the primary bag. Any unused product or waste material and all necessary devices must be discarded.
Do not store any partially used bags and discard all devices after use.

7. MANUFACTURER ADDRESS

Baxter S.A. Boulevard Rene Branquart 80, B-7860, Lessines, Belgium

8. DATE OF REVISION OF THE TEXT

August 2020