

Data Sheet

OLICLINOMEL®

OliClinomel N4-550, OliClinomel N5-800, OliClinomel N6-900, OliClinomel N7-1000.

OliClinomel N4-550 E, OliClinomel N5-800 E, OliClinomel N6-900 E, OliClinomel N7-1000 E.

Description

Appearance prior to reconstitution:

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

After reconstitution, OliClinomel is a milk-like homogeneous liquid. OliClinomel is a hypertonic emulsion. The osmolality and energy contents of the formulations are as follows:

Formulation	Osmolality mOsmol/kg	Energy content KJ/L (kcal/L)	Formulation	Osmolality mOsmol/kg	Energy content KJ (kcal)
OliClinomel N4-550	760	2550 (610)	OliClinomel N4-550E	825	2550 (610)
OliClinomel N5-800	1060	3825 (915)	OliClinomel N5-800E	1155	3825 (915)
OliClinomel N6-900	1295	4243 (1015)	OliClinomel N6-900E	1370	4243 (1015)
OliClinomel N7-1000	1710	5016 (1200)	OliClinomel N7-1000E	1760	5016 (1200)

Composition

Lipid emulsion, amino acid solution and glucose solution presented in the form of a 3-compartment bag.

There are eight different formulations of OliClinomel, four with electrolytes and four without electrolytes. The general compositions of the formulations are summarised in the following table:

Without electrolytes & calcium	With electrolytes	Nitrogen¹	Lipid emulsion²	Amino acid solution³	Glucose solution⁴
OliClinomel N4-550	OliClinomel N4-550E	3.6g/L	10%	5.5%	20%
OliClinomel N5-800	OliClinomel N5-800E	4.6g/L	20%	7%	25%
OliClinomel N6-900	OliClinomel N6-900E	5.6g/L	20%	8.5%	30%
OliClinomel N7-1000	OliClinomel N7-1000E	6.6g/L	20%	10%	40%

¹ Prefixes N4, N5, N6, N7 refer to rounded up content of nitrogen, expressed as g/L.

² Contains refined olive oil (80%) and soya oils (20%)

³ Contains 15 L-series amino acids and electrolytes if present

⁴ Contains calcium if present

For the detailed formulations, refer to Appendix 1.

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

Pharmacology

Pharmacological actions

This is a 3-in-1 admixture 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.

Formulations denoted with an "E" i.e. OliClinomel N4-550 E, OliClinomel N5-800 E, OliClinomel N6-900 E, and OliClinomel N7-1000 E, contain electrolytes.

The formulations without electrolytes i.e. OliClinomel N4-550, OliClinomel N5-800, OliClinomel N6-900, and OliClinomel N7-1000, allow individual electrolyte intake to be adapted to meet specific requirements.

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 (80 g/L).

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 amounts of alpha tocopherol which, combined with a moderate PUFA intake, contributes to improve vitamin E status and reduce lipid peroxidation.

Pharmacokinetic properties

The ingredients of the emulsion for infusion (amino acids, glucose, lipids and electrolytes if applicable) 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.

Most of the lipid particle sizes are in the range of chylomicrons (0.08-0.6 micrometers) with the mean diameter of less than 0.45 micrometers.

However, it may contain a small fraction (up to 2.5%) of particles having a diameter of more than 1 micrometer.

Clinical Trials

Oliclinomel N4-E and N7-E have been used in two (2) small open, non-comparative clinical studies to evaluate the ease of use, the safety and the nutritional efficiency of the product. A total of 19 and 16 subjects respectively undergoing gastrointestinal surgery were evaluated for a period of 5 days of total parenteral nutrition following surgery. The evaluation of clinical and safety parameters, and ease of use demonstrated that Oliclinomel provides satisfactory means of delivery nutrition to selected patients.

Indications

Parenteral nutrition for adults and children above 2 years of age when oral or enteral nutrition is impossible, insufficient or contraindicated.

Contraindications

Use of OliClinomel 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.
- known hypersensitivity to any ingredient, egg, soya proteins/products, amino acids, olive products, components of the container or to any of the active substances or excipients.
- 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).
- severe renal insufficiency without the possibility of haemofiltration or dialysis.
- severe hepatic insufficiency.
- congenital abnormalities of amino acid metabolism that involve any of the constituent amino acids.
- severe blood coagulation disorders.
- severe hyperlipidemia or severe disorders of lipid metabolism characterised by hypertriglyceridemia.
- severe hyperglycemia, which requires more than 6 units insulin/hr.

- acute pulmonary oedema, hyperhydration, uncompensated cardiac insufficiency and hypotonic dehydration.
- high and pathological plasma concentration of one of the electrolytes (sodium, potassium, magnesium, calcium and/or phosphorus) included in OliClinomel, when present.

Precautions

Special clinical monitoring is required at the beginning of any intravenous infusion. Should any abnormalities occur, the infusion must be stopped.

Any signs of anaphylactic reaction (as for example fever, shivering, skin rash, dyspnoea, etc.) should be cause for immediate discontinuation of the infusion.

Do not administer OliClinomel N5-800, OliClinomel N6-900, OliClinomel N7-1000, OliClinomel N5-800 E, OliClinomel N6-900 E, or OliClinomel N7-1000 E through a peripheral vein.

Excess addition of iron may result in the destabilization of lipid emulsions. Iron should not be added to OLICLINOMEL unless the stability has been confirmed.

Excess addition of calcium and phosphorus may result in the formation of calcium phosphate precipitates that could lead to vascular occlusion.

Infection and sepsis may occur as a result of the use of intravenous catheters to administer parenteral nutrition, poor maintenance of catheters and immunosuppressive effects of illness, drugs and parenteral formulations. Vascular access sepsis is a complication that may occur in patients receiving parenteral nutrition. Careful symptomatic and laboratory monitoring for fever/chills, leukocytosis, technical complications with the access device and hyperglycaemia can help recognise early infections. Patients who require parenteral nutrition are often predisposed to infectious complications due to malnutrition and/or their underlying disease state. The occurrence of septic complications can be decreased with heightened emphasis on aseptic technique in catheter placement, maintenance as well as aseptic technique in nutritional formula preparation.

Reduced ability to remove the lipids contained in OliClinomel may result in a "fat overload syndrome" which may be caused by overdose or by regular doses, but may also occur at the start of an infusion administered according to instructions, and is associated with a sudden deterioration in the patient's clinical condition. The fat overload syndrome is characterised by: hyperlipidemia, fever, liver fatty infiltration, hepatomegaly, deteriorating liver function, anaemia, leukopenia, thrombocytopenia, coagulation disorders and coma. All of these symptoms are reversible when the lipid emulsion infusion is stopped.

Refeeding severely undernourished patients may result in the refeeding syndrome that is characterised 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 in series in order to avoid the possibility of air embolism due to residual air contained in the first bag.

Extravasation has been reported with the administration of OLICLINOMEL.

Use with caution in the following circumstances

Caution should be exercised in administering OliClinomel to patients with increased osmolarity, adrenal insufficiency, heart failure or pulmonary dysfunction. Fluid imbalance, electrolytic or metabolic disorders must be corrected before starting the infusion.

Gastrointestinal

Elevated liver enzymes and cholestasis have been reported with OLICLINOMEL.

Endocrine and Metabolism

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.

Serum triglyceride concentrations and the ability of the body to metabolize lipids must be checked regularly. If a lipid metabolism abnormality is suspected, monitoring of serum triglycerides is recommended as clinically necessary.

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

Renal

Use with caution in patients with renal insufficiency. Fluid and electrolyte status should be closely monitored in these patients.

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

Azotemia has been reported with OLICLINOMEL

Check the following before use

Plasma triglyceride levels and clearance should be monitored daily. The triglyceride concentration in serum during infusion should not exceed 3 mmol/L. Infusion should only be started when serum triglyceride levels have returned to baseline level.

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

Although there is a natural content of trace elements and vitamins in the product, the levels are insufficient to meet body requirements and these should be added to prevent deficiencies from developing.

Those OliClinomel products that do not contain electrolytes i.e. OliClinomel N4-550, OliClinomel N5-800, OliClinomel N6-900, and OliClinomel N7-1000, any such additions must be defined and supplementation provided depending on these requirements.

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

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

When making additions, the final osmolarity of the admixture must be measured before administration. The admixture obtained should be administered through a central or peripheral venous line depending on its final osmolarity. If the final admixture, 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, colorless or slightly yellow, practically free of visible particles and the lipid emulsion is a homogenous liquid with a milky appearance.

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, serum triglycerides, acid/base balance, blood glucose, liver and kidney function and blood count, including platelets and coagulation parameters throughout treatment.

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.

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 hyperammonemia (see corresponding section).
- renal insufficiency, particularly if hyperkalemia is present; risk of developing or worsening metabolic acidosis and hyperazotemia if extra-renal waste removal is not being performed (see corresponding section).
- 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.
- anaemia.
- hyperlipidemia (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 (children over 2 years)

No interaction studies have been performed with OLICLINOMEL.

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

When administered to children more than 2 years old, 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.

Carcinogenicity, mutagenicity and impairment of fertility

Tests for carcinogenicity, mutagenicity and effects on fertility have not been conducted with OliClinomel.

Use in pregnancy

The safety of administration of OliClinomel during pregnancy has not been established. No reproductive toxicity studies with OliClinomel have been carried out in animals, and its use in pregnancy is not recommended.

Use in lactation

No clinical data are currently available on the use of OliClinomel in breastfeeding women. Following intravenous infusion, most of the active ingredients contained in OliClinomel are expected to be excreted in human milk. The safety of administration of OliClinomel during lactation has not been established. The prescriber should consider the benefit/risk relationship before administering OliClinomel to breastfeeding women.

Interactions

No interaction studies have been performed with OLICLINOMEL.

Compatibility with other drugs and nutrients

Any additions (including vitamins) may be made into the reconstituted admixture (after the non-permanent seals have been opened and the contents of the 3 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). (See Preparation for administration).

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-stabilise the lipid emulsion. "Breaking" or "oiling out" of the emulsion can be visibly identified by accumulation of yellowish droplets or particles in the admixture.

Excess addition of iron may result in the destabilization of lipid emulsions. Iron should not be added to OLICLINOMEL unless the stability has been confirmed.

Do not administer this emulsion before, simultaneously with or after blood through the same equipment (infusion tubing) because of the risk of pseudoagglutination.

Ceftriaxone must not be co-administered with calcium-containing IV solutions, because of the risk of precipitation of ceftriaxone-calcium salt.

Soybean oil has a natural content of vitamin K1 that may counteract the anticoagulant activity of coumarin (or coumarin derivatives including warfarin).

Due to the potassium content of OLICLINOMEL, special care should be taken in patients simultaneously treated with potassium saving diuretics or with ACE inhibitors in view of the risk of hyperkalemia.

Compatibility with administration sets

Check compatibility with solutions administered simultaneously through the same giving set, catheter or cannula.

Phthalate plasticisers are extracted from PVC bags and administration sets by intravenous fat emulsions. PVC bags and administration sets should not be used for

delivery of OliClinomel or of solutions containing OliClinomel. Administration sets made from non-plasticised materials are recommended.

Effects on laboratory tests

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).

Adverse Reactions

Potential undesirable effects may occur as a result of inappropriate use: for example, overdose, excessively fast infusion rate (see corresponding sections).

Immediate reactions

At the beginning of the infusion, any of the following abnormal signs evoking a hypersensitivity reaction should be cause for immediate discontinuation of the infusion: sweating, shivering, cephalgia, dyspnoea.

Delayed reactions

During long-term parenteral nutrition containing fat emulsions, the following adverse reactions have been observed:

Hepato-biliary disorders:

- increase of alkaline phosphatase, bilirubin and transaminases (ALT & AST)
- hepatomegaly
icterus
- cholestasis

Blood and lymphatic system disorders:

- thrombocytopenia reported in children receiving lipid infusions
- thrombophlebitis 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 or by regular doses, but may also occur at the start of an infusion administered according to instructions, and is associated with a sudden deterioration in the patient's clinical condition.

The fat overload syndrome is characterised by: hyperlipidemia, fever, liver fatty infiltration, hepatomegaly, deteriorating liver function, anaemia, leukopenia, thrombocytopenia, coagulation disorders and coma.

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

Adverse Reactions from Clinical Trials:

OLICLINOMEL N4-550E, N7-1000E and N8-800* have been used in three clinical studies to evaluate the ease of use, safety and the nutritional efficiency of the product. The pooled data (64 patients) evaluated from these three studies indicated the following adverse reactions.

Clinical Trial Adverse Reactions	
System Organ Class (SOC)	Preferred MedDRA Term
Immune System Disorders	Hypersensitivity
Nervous System Disorders	Headache
Gastrointestinal Disorders	Diarrhoea
Renal and Urinary Disorders	Azotemia
General Disorders and Administrative Site Conditions	Chills Infusion site extravasation Infusion site pain Infusion site swelling Infusion site vesicles
Investigations	Hepatic enzyme increased Gamma-glutamyltransferase increased Blood triglycerides increased Blood alkaline phosphates increased

*N8-800 is not registered in Australia

Data concerning the post-marketing experience are available as Periodic Safety Reports from February 2001 up until end August 2005. It is estimated that approximately 1,088,175 patients have received the product. In the relevant period 51 suspected ADE cases have been reported, with a total of 95 symptoms. This reveals a low level of ADEs - 1/21,000 treatments. The most frequent class of symptom of suspected ADE case represented were: general disorders and administration site conditions (22% of symptoms), infections and infestations (12%), gastrointestinal disorders (11%), and skin and subcutaneous tissue disorders (9%).

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.

Nervous System Disorders: tremor

Gastrointestinal Disorders: abdominal pain, vomiting, nausea

Hepato-biliary Disorders: hepatic enzyme abnormal, hepatitis cholestasis, cholestasis, jaundice, blood bilirubin increased

Skin and Subcutaneous Tissue Disorders: erythema, hyperhidrosis

Musculoskeletal, Connective Tissue and Bone Disorders: musculoskeletal pain, back pain, chest pain, pain in extremity, muscle spasm

General Disorders and Administrative Site Conditions: catheter site phlebitis, injection site swelling, injection site oedema, localised oedema, oedema peripheral, pyrexia, feeling hot, hyperthermia, malaise, inflammation

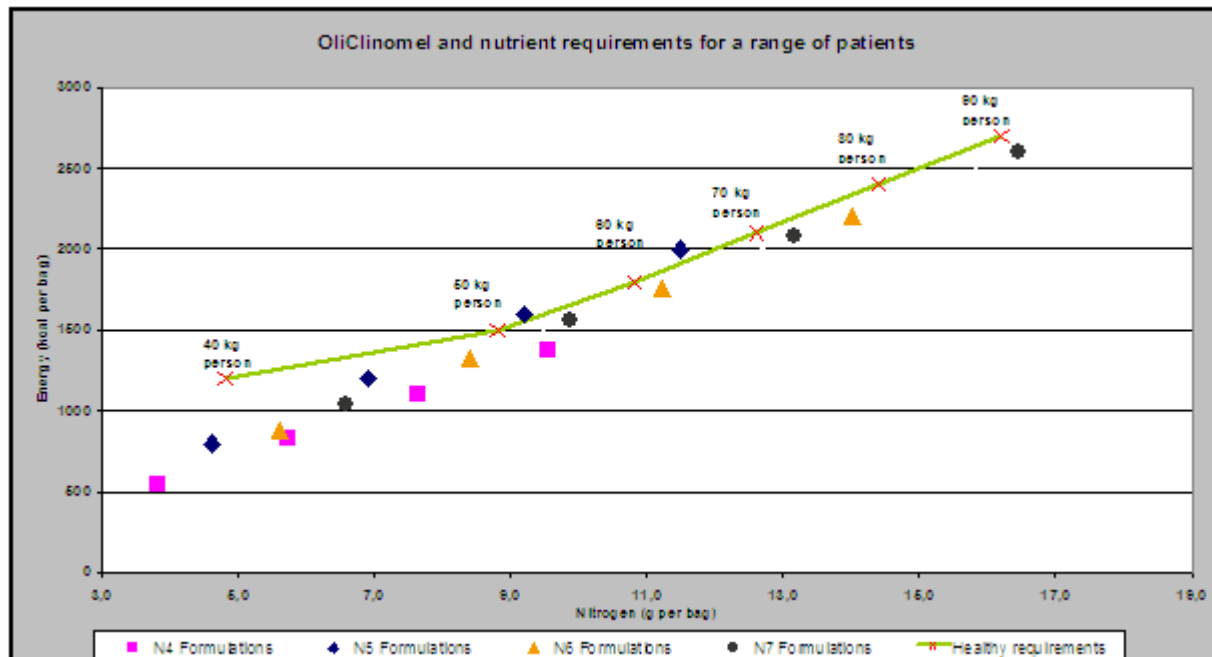
Investigations Not Listed-Covered under other SOCS: hyperglycemia, blood glucose increased

Dosage and Administration

Dosage

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

As shown in the Figure below, the OliClinomel range covers the normal adult requirements. The formulation of OliClinomel to be used should be selected according to the specific needs of the patient.



Adult:

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

Energy requirements vary depending on the patient's nutritional state and level of catabolism. On average these are 25 to 40 kcal/kg/day.

Maximum daily dose: The maximum daily dose for adults for the different formulations is shown in the following table.

Formulation	Maximum daily dose ml/kg body weight	Amino acids g/kg	Lipids g/kg	Glucose g/kg	Maximum daily dose mL/70kg patient
OliCinomel N4-550 & N4-550E	40	0.88	0.8	3.2	2800
OliClinomel N5-800 & N5-800E	40	1.12	1.6	4.0	2800
OliClinomel N6-900 & N6-900E	40	1.36	1.6	4.8	2800
OliClinomel N7-1000 5 N7-1000E	36	1.44	1.44	5.76	2520

Children above two years of age:

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.

Dosage: 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: The maximum daily dose for children for the different formulations is shown in the following table.

Formulation	Maximum daily dose ml/kg	Amino acids g/kg	Lipids g/kg	Glucose g/kg
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OliCinomel N4-550 & N4-550E	100	2.2	2	8
OliClinomel N5-800 & N5-800E	75	2.1	3	7.5
OliClinomel N6-900 & N6-900E	75	2.55	3	9
OliClinomel N7-1000 & N7-1000E	75	3	3	12

As a general rule do not exceed doses of 3 g/kg/day of amino acids and/or 17 g/kg/day of glucose and/or 3 g/kg/day of lipids, except in particular cases.

Flow Rate and Duration

The recommended duration of the parenteral nutrition infusion is between 12 and 24 hours. Treatment with parenteral nutrition may be continued for as long as is required by the patient's clinical conditions.

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

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

Maximum infusion rate:

As a general rule, the infusion rates in the table below should not be exceeded.

Formulation	Maximum infusion rate mL/kg/hr	Amino acids g/kg/hr	Lipids g/kg/hr	Glucose g/kg/hr
OliCinomel N4-550 & N4-550E	3	0.06	0.06	0.24
OliClinomel N5-800 & N5-800E	2.5	0.07	0.1	0.25
OliClinomel N6-900 & N6-900E	2.0	0.07	0.08	0.24
OliClinomel N7-1000 & N7-1000E	1.5	0.06	0.06	0.24

Route of Administration

OliClinomel N4-550 and OliClinomel N4-550 E may be administered by intravenous administration through a central or peripheral vein.

Administered OliClinomel N5-800, OliClinomel N6-900, OliClinomel N7-1000, OliClinomel N5-800 E, OliClinomel N6-900 E, OliClinomel N7-1000 E by intravenous administration only through a central vein.

Method of preparation: OliClinomel N4-550, OliClinomel N5-800, OliClinomel N6-900, and OliClinomel N7-1000 do not contain electrolytes. Although there is a natural content of trace elements and vitamins in the product, the levels are insufficient to meet body requirements. OliClinomel N4-550, OliClinomel N5-800, OliClinomel N6-900, and OliClinomel N7-1000 can be used as such or after supplementation with electrolytes, trace elements or vitamins, when required (see corresponding sections).

OliClinomel N4-550 E, OliClinomel N5-800 E, OliClinomel N6-900 E, and OliClinomel N7-1000 E do contain electrolytes. Although there is a natural content of trace elements and vitamins in the product, the levels are insufficient to meet body requirements. OliClinomel N4-550 E, OliClinomel N5-800 E, OliClinomel N6-900 E, and OliClinomel N7-1000 E can be used as such or after supplementation with electrolytes, trace elements or vitamins, when required (see corresponding sections).

Electrolytes: In those OliClinomel preparations that contain no electrolytes, the following concentrations of electrolytes must not be exceeded for each litre of the final admixture.

- sodium: 150 mmol/L
- potassium: 150 mmol/L
- magnesium: 5.60 mmol/L
- calcium: 5 mmol/L

Electrolytes: If additional electrolytes are added over and above those already contained in OliClinomel N4-550 E, OliClinomel N5-800 E, OliClinomel N6-900 E, and OliClinomel N7-1000 E in no event should the following concentrations of electrolytes be exceeded per litre of the final admixture.

- sodium: 150 mmol/L
- potassium: 150 mmol/L
- magnesium: 5.60 mmol/L
- calcium: 5 mmol/L

Trace elements and vitamins: Defined adult and paediatric trace elements and vitamins formulations for parenteral nutrition are available. Care should be taken to select the appropriate product for supplementation of the admixture.

Preparation for Administration

a. To open

- 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, colorless or slightly yellow, practically free of visible particles and the lipid emulsion is a homogenous 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

Any additions (including vitamins) may be made into the reconstituted admixture (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 admixture has been reconstituted (before opening the non-permanent seals and before mixing the solutions and the emulsion).

OliClinomel N4-550, OliClinomel N5-800, OliClinomel N6-900, and OliClinomel N7-1000 may be supplemented with

- electrolytes: stability has been demonstrated up to a total quantity of 150 mmol/L of sodium, 150 mmol/L of potassium, 5.6 mmol/L of magnesium and 5 mmol/L of calcium in the 3-in-1 admixture.
- organic phosphate: stability has been demonstrated for additions of up to 22 mmol/L for a 1000 mL bag, 14.7 mmol/L for a 1500mL bag, 11 mmol/L for a 2000mL bag, and 8.8 mmoml/L for a 2500mL bag.

- trace elements and vitamins (Thiamin, Riboflavin, Nicotinamide, Pyrodoxine, Pantothenic acid, Ascorbic acid, Biotin, Folic acid, Cyanocobalamin, Vitamin A, Vitamin D, Vitamin E, Vitamin K1): stability has been demonstrated up to the recommended daily dose.

OliClinomel N4-550 E, OliClinomel N5-800 E, OliClinomel N6-900 E, and OliClinomel N7-1000 E may be supplemented with:

- electrolytes: take account of the electrolytes already present in the bag: 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 3-in-1 admixture.
- Micro-nutrient additions must be performed under aseptic conditions.
- organic phosphate: stability has been demonstrated for additions of up to 22 mmol/L for a 1000 mL bag, 14.7 mmol/L for a 1500mL bag, 11 mmol/L for a 2000mL bag, and 8.8 mmoml/L for a 2500mL bag.
- trace elements and vitamins (Thiamin, Riboflavin, Nicotinamide, Pyrodoxine, Pantothenic acid, Ascorbic acid, Biotin, Folic acid, Cyanocobalamin, Vitamin A, Vitamin D, Vitamin E, Vitamin K1): stability has been demonstrated up to the recommended daily dose.

These additions are made into the injection site of the bag using a needle:

- prepare the injection site of the bag,
- puncture the injection site of the bag 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.

After reconstitution mixing of the preparation of admixtures, the bag may be stored as detailed in the Presentation section. Once the administration port has been broken or the overpouch opened, the content must be used immediately and must never be stored for a subsequent infusion.

For single use only.

Do not reconnect any partially used bag.

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

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

Overdosage

In the event of inappropriate administration (overdose and/or infusion rate higher than recommended), signs of hypervolemia and acidosis may occur. Excessively fast administration of Total Parenteral Nutrition (TPN) solutions, including OLICLINOMEL, has resulted in severe and fatal consequences.

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 corresponding section).

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

Presentation

Container

The three-compartment bag is a multi-layer plastic bag packaged in an oxygen barrier outer packaging. An oxygen absorber is added between the inner bag and the over wrap; discard the sachet after removing the over wrap. The inner layer plastic material consists of EVA (ethylene-vinyl acetate) and is compatible with lipids.

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 5.5% amino acid solution + 400 mL of 20% glucose solution + 200 mL of 10% lipid emulsion). Carton with 6 bags

1500 mL in a three-compartment bag (600 mL of 5.5% amino acid solution + 600 mL of 20% glucose solution + 300 mL of 10% lipid emulsion). Carton with 4 bags

2000 mL in a three-compartment bag (800 mL of 5.5% amino acid solution + 800 mL of 20% glucose solution + 400 mL of 10% lipid emulsion). Carton with 4 bags

2500 mL in a three-compartment bag (1000 mL of 5.5% amino acid solution + 1000 mL of 20% glucose solution + 500 mL of 10% lipid emulsion). Carton with 2 bags

Not all pack sizes may be marketed.

Shelf life

24 months if the overpouch is not damaged.

It is recommended that OliClinomel be 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 2°-8°C followed by a maximum of 48 hours at temperatures not exceeding 25°C.

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

For specific admixtures, chemical and physical in-use stability has been demonstrated for 7 days at 2 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, in a licensed compounding centre.

Separation of the product (gravity dispersion or "creaming") may occur after the emulsion has been stored a period of time without agitation. It should only be necessary to invert the bag 2 or 3 times before use. The product must not be used if the emulsion has a yellow appearance, or is seen to contain yellow droplets of oil. Do not use if shaking does not result in a uniform emulsion.

Storage condition

Store below 25°C.

Do not freeze.

Protect from light.

Store in overpouch.

Medicine Classification

General Sales Medicine.

Name and Address

Baxter Healthcare Limited
33 Vestey Drive
Mt Wellington
Auckland

Date of Preparation

9 July 2009

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APPENDIX 1

Note: Not all formulations and pack sizes may be marketed.

Composition of a 1000 mL bag:

COMPONENTS	OliClinomel N4-550 E	OliClinomel N5-800 E	OliClinomel N6-900 E	OliClinomel N7-1000 E
Active ingredients:				
Refined soya-bean oil + refined olive oil*	20.00 g	40.00 g	40.00 g	40.00 g
• L-alanine	4.56 g	5.80 g	7.04 g	8.28 g
• L-arginine	2.53 g	3.22 g	3.91 g	4.60 g
• Glycine	2.27 g	2.89 g	3.50 g	4.12 g
• L-histidine	1.06 g	1.34 g	1.63 g	1.92 g
• L-isoleucine	1.32 g	1.68 g	2.04 g	2.40 g
• L-leucine	1.61 g	2.05 g	2.48 g	2.92 g
• L-lysine	1.28 g	1.62 g	1.97 g	2.32 g
• (as hydrochloride)	(1.60) g	(2.03 g)	(2.46 g)	(2.90 g)
• L-methionine	0.88 g	1.12 g	1.36 g	1.60 g

• L-phenylalanine	1.23 g	1.57 g	1.90 g	2.24 g
• L-proline	1.50 g	1.90 g	2.31 g	2.72 g
• L-serine	1.10 g	1.40 g	1.70 g	2.00 g
• L-threonine	0.92 g	1.18 g	1.43 g	1.68 g
• L-tryptophan	0.40 g	0.50 g	0.61 g	0.72 g
• L-tyrosine	0.09 g	0.11 g	0.14 g	0.16 g
• L-valine	1.28 g	1.62 g	1.97 g	2.32 g
• Sodium acetate 3H ₂ O	0.98 g	2.45 g	2.45 g	2.45 g
• Sodium glycerophosphate, 5 H ₂ O	2.14 g	2.14 g	2.14 g	2.14 g
• Potassium chloride	1.19 g	1.79 g	1.79 g	1.79 g
• Magnesium chloride 6H ₂ O	0.45 g	0.45 g	0.45 g	0.45 g
• Glucose	80.00 g	100.00 g	120.00 g	160.00 g
• (as glucose monohydrate)	(88.00 g)	(110.00 g)	(132.00 g)	(176.00 g)
• Calcium chloride 2H ₂ O	0.30 g	0.30 g	0.30 g	0.30 g
Other ingredients:				
Purified egg phosphatides	1.20 g	2.40 g	2.40 g	2.40 g
• Glycerol	2.25 g	4.50 g	4.50 g	4.50 g
• Sodium oleate	0.03 g	0.06 g	0.06 g	0.06 g
• Sodium hydroxide	qs pH	qs pH	qs pH	qs pH
• Acetic acid	qs pH	qs pH	qs pH	qs pH
• Hydrochloric acid	qs pH	qs pH	qs pH	qs pH
• Water for injections	qs volume	qs volume	qs volume	qs volume

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

One of the active ingredients, soya oil, may contain ascorbyl palmitate as an antioxidant, (free radical scavenger), in the concentration of ≤ 0.15 mg per gram of oil.

COMPONENTS	OliClinomel N4-550	OliClinomel N5-800	OliClinomel N6-900	OliClinomel N7-1000
<u>Active ingredients:</u>				
• Refined soya-bean oil + refined olive oil*	20.00 g	40.00 g	40.00 g	40.00 g
• L-alanine	4.56 g	5.80 g	7.04 g	8.28 g
• L-arginine	2.53 g	3.22 g	3.91 g	4.60 g
• Glycine	2.27 g	2.89 g	3.50 g	4.12 g
• L-histidine	1.06 g	1.34 g	1.63 g	1.92 g
• L-isoleucine	1.32 g	1.68 g	2.04 g	2.40 g
• L-leucine	1.61 g	2.05 g	2.48 g	2.92 g
• L-lysine	1.28 g	1.62 g	1.97 g	2.32 g
• (as hydrochloride)	(1.60 g)	(2.03 g)	(2.46 g)	(2.90 g)
• L-methionine	0.88 g	1.12 g	1.36 g	1.60 g
• L-phenylalanine	1.23 g	1.57 g	1.90 g	2.24 g
• L-proline	1.50 g	1.90 g	2.31 g	2.72 g
• L-serine	1.10 g	1.40 g	1.70 g	2.00 g
• L-threonine	0.92 g	1.18 g	1.43 g	1.68 g
• L-tryptophan	0.40 g	0.50 g	0.61 g	0.72 g
• L-tyrosine	0.09 g	0.11 g	0.14 g	0.16 g
• L-valine	1.28 g	1.62 g	1.97 g	2.32 g
• Glucose	80.00 g	100.00 g	120.00 g	160.00 g
• (as glucose monohydrate)	(88.00 g)	(110.00 g)	(132.00 g)	(176.00 g)
<u>Other ingredients:</u>				
• Purified egg phosphatides	1.20 g	2.40 g	2.40 g	2.40 g
• Glycerol	2.25 g	4.50 g	4.50 g	4.50 g
• Sodium oleate	0.03 g	0.06 g	0.06 g	0.06 g

• Acetic acid	qs pH	qs pH	qs pH	qs pH
• Hydrochloric acid	qs pH	qs pH	qs pH	qs pH
• Sodium hydroxide	qs pH	qs pH	qs pH	qs pH
• Water for injections	qs volume	qs volume	qs volume	qs volume

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

One of the active ingredients, soya oil, may contain ascorbyl palmitate as an antioxidant, (free radical scavenger), in the concentration of ≤ 0.15 mg per gram of oil.

After the contents of the three compartments have been mixed, the 3-in-1 admixture for each of the bag presentations provides the following:

For OliClinomel N4-550:

Per bag	1 litre	1.5 litres	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
Phosphate (mmol)**	1.5	2.3	3	3.8
Acetate (mmol)	13	20	26	33
Chloride (mmol)	9	13	18	22
pH	6	6	6	6
Osmolarity	690	690	690	690

(mOsm/l)				
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** Phosphates provided by the lipid emulsion

For OliClinomel N4-550E:

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 (mOsm/l)	750	750	750	750

** Including phosphates provided by the lipid emulsion

For OliClinomel N5-800:

Per bag	1 litre	1.5 litres	2 litres	2.5 litres
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Nitrogen (g)	4.6	6.9	9.2	11.6
Amino acids (g)	28	42	56	70
Glucose (g)	100	150	200	250
Lipids (g)	40	60	80	100
Total calories (kcal)	915	1370	1825	2280
Non-protein calories (kcal)	800	1200	1600	2000
Glucose calories (kcal)	400	600	800	1000
Lipid calories (kcal)	400	600	800	1000
Non-protein calorie/nitrogen ratio (kcal/g N)	174	174	174	174
Phosphate (mmol)**	3	4.5	6	7.5
Acetate (mmol)	25	38	50	63
Chloride (mmol)	11	17	22	28
pH	6	6	6	6
Osmolarity (mOsm/l)	940	940	940	940

** Phosphates provided by the lipid emulsion

For OliClinomel N5-800E:

Per bag	1 litre	1.5 litres	2 litres	2.5 litres
Nitrogen (g)	4.6	6.9	9.2	11.6
Amino acids (g)	28	42	56	70
Glucose (g)	100	150	200	250
Lipids (g)	40	60	80	100
Total calories (kcal)	915	1370	1825	2280
Non-protein calories (kcal)	800	1200	1600	2000
Glucose calories (kcal)	400	600	800	1000
Lipid calories	400	600	800	1000

(kcal)				
Non-protein calorie/nitrogen ratio (kcal/g N)	174	174	174	174
Sodium (mmol)	32	48	64	80
Potassium (mmol)	24	36	48	60
Magnesium (mmol)	2.2	3.3	4.4	5.5
Calcium (mmol)	2	3	4	5
Phosphate (mmol)**	10	15	20	25
Acetate (mmol)	49	74	98	122
Chloride (mmol)	44	66	88	110
pH	6	6	6	6
Osmolarity (mOsm/l)	995	995	995	995

** Including phosphates provided by the lipid emulsion

For OliClinomel N6-900:

Per bag	1 litre	1.5 litres	2 litres	2.5 litres
Nitrogen (g)	5.6	8.4	11.2	14.0
Amino acids (g)	34	51	68	85
Glucose (g)	120	180	240	300
Lipids(g)	40	60	80	100
Total calories (kcal)	1015	1525	2030	2540
Non-protein calories (kcal)	880	1320	1760	2200
Glucose calories (kcal)	480	720	960	1200
Lipid calories (kcal)	400	600	800	1000
Non-protein calorie/nitrogen ratio (kcal/g N)	157	157	157	157
Phosphate	3	4.5	6	7.5

(mmol)**				
Acetate (mmol)	31	47	62	78
Chloride (mmol)	14	20	27	34
pH	6	6	6	6
Osmolarity (mOsm/l)	1100	1100	1100	1100

** Phosphates provided by the lipid emulsion

For OliClinomel N6-900E:

Per bag	1 litre	1.5 litres	2 litres	2.5 litres
Nitrogen (g)	5.6	8.4	11.2	14.0
Amino acids (g)	34	51	68	85
Glucose (g)	120	180	240	300
Lipids (g)	40	60	80	100
Total calories (kcal)	1015	1525	2030	2540
Non-protein calories (kcal)	880	1320	1760	2200
Glucose calories (kcal)	480	720	960	1200
Lipid calories (kcal)	400	600	800	1000
Non-protein calorie/nitrogen ratio (kcal/g N)	157	157	157	157
Sodium (mmol)	32	48	64	80
Potassium (mmol)	24	36	48	60
Magnesium (mmol)	2.2	3.3	4.4	5.5
Calcium (mmol)	2	3	4	5
Phosphate (mmol)**	10	15	20	25
Acetate (mmol)	53	79	106	132
Chloride (mmol)	46	69	92	115
pH	6	6	6	6

Osmolarity (mOsm/l)	1160	1160	1160	1160
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** Including phosphates provided by the lipid emulsion

For OliClinomel N7-1000:

Per bag	1 litre	1.5 litres	2 litres	2.5 litres
Nitrogen (g)	6.6	9.9	13.2	16.5
Amino acids (g)	40	60	80	100
Glucose (g)	160	240	320	400
Lipids (g)	40	60	80	100
Total calories (kcal)	1200	1800	2400	3000
Non-protein calories (kcal)	1040	1560	2080	2600
Glucose calories (kcal)	640	960	1280	1600
Lipid calories (kcal)	400	600	800	1000
Non-protein calorie/nitrogen ratio (kcal/g N)	158	158	158	158
Phosphate (mmol)**	3	4.5	6	7.5
Acetate (mmol)	37	56	74	93
Chloride (mmol)	16	24	32	40
pH	6	6	6	6
Osmolarity (mOsm/l)	1400	1400	1400	1400

** Phosphates provided by the lipid emulsion

For OliClinomel N7-1000E:

Per bag	1 litre	1.5 litres	2 litres	2.5 litres
Nitrogen (g)	6.6	9.9	13.2	16.5
Amino acids (g)	40	60	80	100
Glucose (g)	160	240	320	400
Lipids (g)	40	60	80	100

Total calories (kcal)	1200	1800	2400	3000
Non-protein calories (kcal)	1040	1560	2080	2600
Glucose calories (kcal)	640	960	1280	1600
Lipid calories (kcal)	400	600	800	1000
Non-protein calorie/nitrogen ratio (kcal/g N)	158	158	158	158
Sodium (mmol)	32	48	64	80
Potassium (mmol)	24	36	48	60
Magnesium (mmol)	2.2	3.3	4.4	5.5
Calcium (mmol)	2	3	4	5
Phosphate (mmol)**	10	15	20	25
Acetate (mmol)	57	86	114	143
Chloride (mmol)	48	72	96	120
pH	6	6	6	6
Osmolarity (mOsm/l)	1450	1450	1450	1450

** Including phosphates provided by the lipid emulsion