1 ClinOleic (emulsion for infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ClinOleic is a sterile fat emulsion with the following composition:

Active Ingredients	
Olive oil (refined)	Approximately 80%
Soya oil (refined)	Approximately 20%

One of the active ingredients, soya oil, contains ascorbyl palmitate as an antioxidant (free radical scavenger), in the concentration of 0.15mg/g of oil.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Emulsion for infusion (intravenous).

Appearance

ClinOleic is a milk-like homogeneous liquid.

Osmolality

ClinOleic is an isotonic emulsion. It has an osmolality of approximately 345mOsmL/kg water and energy content of 8.360MJ (2,000kcal)/L.
Final pH is between 6.0 – 8.0.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Parenteral nutrition when oral or enteral nutrition is impossible, insufficient or contraindicated.

4.2 Dose and method of administration

The dosage depends on energy expenditure, the patient's clinical status, body weight, and ability to metabolise ClinOleic, as well as additional energy given orally/enterally. Therefore, the dosage should be individualised and the bag size chosen accordingly. The maximum daily dose of ClinOleic should be based on individual total nutritional requirements and patient tolerance.

Dosage

Note: the percentage (%) of lipid in the ClinOleic formulation is expressed in weight by volume (w/v). That is, 5mL of ClinOleic contains 1g of lipid.

Adults:

The dosage is 1 to a maximum of 2g lipids/kg/day.
Never exceed 0.15g lipids/kg/hour (0.75mL/kg/hour).

	Adults per kg of body weight	**70kg adult**
Usual lipid dosage	1 to 2g/kg/day	70 to 140g/day
Infused volume of **ClinOleic**	5 to 10mL/kg/day	350 to 700mL/day

Children:
It is recommended not to exceed a daily dose of 3g lipids/kg of body weight and an infusion rate of 0.15g lipids/kg of body weight/hour.
Daily dose should be increased gradually during the first week of administration.

Premature newborns and low birth weight infants:
The use of ClinOleic is restricted to premature infants of 28 weeks gestational age or more.
The initial daily dose should be 0.5 - 1.0g lipids/kg of body weight. The dose may be increased by 0.5 - 1.0g lipids/kg of body weight every 24 hours up to a daily dose of 2.0g lipids/kg of body weight.

Flow rate and duration
The administration flow rate must be adjusted taking into account the dose being administered, the daily volume intake, and the duration of the infusion. The recommended duration of infusion for a parenteral nutrition bag is between 12 and 24 hours, depending on the clinical situation. Treatment with parenteral nutrition may be continued for as long as is required by the patient's condition.

Adults:
The initial infusion rate must be slow and not exceed 0.1g lipids or 0.5mL (10 drops) per minute for 10 minutes then gradually increased until reaching the required rate after half an hour.

Children:
ClinOleic should be administered as a continuous 24h/day infusion.
It is recommended not to exceed an infusion rate of 0.15g lipids/kg of body weight/hour.
Daily dose should be increased gradually during the first week of administration.

Premature newborns and low birth weight infants:
ClinOleic should be administered as a continuous 24h/day infusion.

Route of administration
Intravenous infusion only:
- When used in premature newborns, low birth weight infants and children, the solution (in bags and administration sets) should be protected from light exposure after admixture through administration (see section 4.4).
- When administered as part of a complete nutrition admixture (with glucose and amino acids), the central or peripheral venous route should be chosen depending on the osmolarity of the final admixture.
- In rare cases, when infused alone as a complementary support to oral or enteral nutrition, ClinOleic can be administered via central or peripheral vein.

When preparing an admixture that includes ClinOleic (see *Preparation for Administration* below), the final osmolarity of the mixture should be measured before administration via a peripheral vein. If the mixture is hypertonic, it may cause irritation of the vein when administered into a peripheral vein.

ClinOleic infusion does not contain an antimicrobial agent. To avoid the risk of microbial contamination, infusion should be commenced as soon as practicable after the preparation of an admixture. As with all parenteral administration, particularly infusions, strict aseptic technique should be used at all times. ClinOleic intravenous infusion is for single use only in a single patient.

Method of preparation
The order of mixing is critical to ensure compatibility and stability of admixtures containing ClinOleic. Use aseptic technique all the way through the compounding processes. Thorough mixing after the addition of each component is essential. ClinOleic and other components of Parenteral Nutrition do

not contain anti-microbial agents. Therefore, once mixed, the admixtures should be administered over a period not exceeding 24 hours.

ClinOleic may be combined with other nutrients by adding the emulsion to a mixture of amino acids and glucose in fixed proportions.

Thus for example, an extemporaneous formulation made of amino acid, Synthamin® 9, with electrolytes (500mL), Glucose solution 10% (375mL) and ClinOleic (250mL) could be prepared without the risk of instability. Some combinations of 3-in-1 Total Parenteral Nutrition (TPN) admixtures are shown in the table below.

Recommended 3-in-1 TPN admixtures (Synthamin® (w/e), Glucose and ClinOleic)			
Amino Acid (mL) *	**Glucose (mL)**	**ClinOleic (mL)**	**Total Vol (mL)**
Synthamin 9 (500)	Glucose 10% (375)	**ClinOleic** (250)	1125
Synthamin 9 (500) Synthamin 17 (500)	Glucose 10% (125) Glucose 20% (125)	**ClinOleic** (250)	1500
Synthamin 9 (250)	Glucose 10% (188)	**ClinOleic** (250)	688
Synthamin 17 (400)	Glucose 20% (95)	**ClinOleic** (250)	745
Synthamin 9 (425)	Glucose 30% (400) Glucose 50% (200)	**ClinOleic** (200)	1225
Synthamin 17 (625)	Glucose 50% (425)	**ClinOleic** (200)	1250
Synthamin 9 (250)	Glucose 50% (250)	**ClinOleic** (250)	750
Synthamin 17 (375)	Glucose 70% (150)	**ClinOleic** (250)	775
Synthamin 9 (250) Synthamin 13 (250)	Glucose 30% (125) Glucose 50% (125)	**ClinOleic** (250)	1000
* All amino acid solutions contain electrolytes [Note: w/e=with electrolytes]			

The order of admixing of the above components should be approached by minimising a sudden change in the negative charge of the emulsion. Firstly, mix the glucose infusion with the amino acid infusion. ClinOleic emulsion can then be added into this admixture. Finally the electrolyte complements then trace elements can be added.

As the lipid emulsion is negatively charged, do not add electrolytes or trace elements directly into ClinOleic emulsion as they destabilise the emulsion. The recommended sequence for adding electrolytes is monovalent, divalent, and trivalent ions. Phosphate salts must always be added prior to calcium salts as discussed below.

The inclusion of calcium and phosphate ions in a TPN admixture requires special attention to a possible formation of calcium phosphate precipitate, which is affected by pH, temperature, calcium salt, sequence of calcium and phosphate addition to the admixtures and concentration of calcium and phosphates ions. The limits of these electrolytes should be less than, or equal to, 5.0mmol/L for calcium and phosphates should not exceed a concentration of 30mmol/L from all sources. At pH 7.0 and above the addition of NaH_2PO_4 to calcium gluconate solution results in a precipitation of $CaHPO_4$, that is, the equilibrium between $[H_2PO_4]^{-1}$ and $[HPO_4]^{-2}$ is shifted to the $[HPO_4]^{-2}$ side.

At pH of 4.1, phosphate ions are predominantly in the form of monobasic phosphate, whilst at a higher pH, it occurs in a form of dibasic phosphate ions. Taking into consideration that the glucose infusion has a pH in the range 3.2 – 6.5, and in order to minimise a formation of dibasic phosphate ions, the sodium monobasic phosphate should be added to the glucose infusion in the early stage of the compounding of a TPN admixture. Then, this admixture is added to the amino acid infusion,

which has a buffer capacity and no charge effects at pH 5 – 6. This is followed by the addition of the lipid emulsion to the obtained admixture. Finally, calcium gluconate is added at the end of the TPN compounding process.

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 shake 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.

For instructions on product preparation before administration, and additions, see section 6.6.

4.3 Contraindications

- Known hypersensitivity to egg or soybean proteins or to any of the ingredients, including the lipid emulsion and/or excipients.
- Severe hyperlipidaemia or severe disorders of lipid metabolism characterised by hypertriglyceridaemia and non-corrected metabolism disorders including lactic acidosis and uncompensated diabetes.
- Severe sepsis.
- Severe liver disease.
- Blood coagulation disorders, thrombophlebitis.
- Acute and chronic renal failure, in absence of specific studies, there is insufficient data to justify its use in acute/chronic renal failure.
- Myocardial infarction.

4.4 Special warnings and precautions for use

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

Allergic reactions

The infusion must be stopped immediately if any signs or symptoms of an allergic reaction develop.

Infections

Patients who require parenteral nutrition are often predisposed to infectious complications due to malnutrition and/or their underlying disease state.

Infection and sepsis may occur as a result of the use of intravenous catheters to administer parenteral formulations, or poor maintenance of catheters and contaminated solutions.

Immunosuppression and other factors such as hyperglycaemia, malnutrition and/or their underlying disease state may predispose patients to infectious complications.

The occurrence of septic complications can be decreased with heightened emphasis on aseptic technique in catheter placement and maintenance, as well as aseptic technique in the preparation of the nutritional formula.

Careful monitoring of signs, symptoms, and laboratory test results (including fever, chills, leuko-cytosis, and hyperglycaemia), and frequent checks of the access device for technical complications can help recognise early infections.

Fat overload syndrome

Fat overload syndrome has been reported with similar products. This may be caused by inappropriate administration (e.g. overdose and/or infusion rate higher than recommended, see section 4.9); however, the signs and symptoms of this syndrome may also occur when the product is administered according to instructions. The reduced or limited ability to metabolise the lipids contained in ClinOleic accompanied by prolonged plasma clearance may result in a fat overload syndrome. This syndrome is associated with a sudden deterioration in the patient's clinical condition and is characterised by findings such as fever, anaemia, leukopaenia, thrombocytopaenia, coagulation disorders, hyper-lipidaemia, liver fatty infiltration (hepatomegaly), deteriorating liver function and central nervous system manifestations (e.g. coma). The syndrome is usually reversible when the infusion of the lipid emulsion is stopped.

Refeeding syndrome

ClinOleic is administered as part of a parenteral nutrition regimen. Refeeding severely undernourished patients with parenteral nutrition may result in the refeeding syndrome. The syndrome is characterised by the intracellular shift of potassium, phosphorus and magnesium 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.

Fat emulsions should be administered simultaneously with carbohydrates and amino acids to avoid metabolic acidosis.

Never make additions directly to the ClinOleic bag. If ClinOleic is mixed with glucose and/or amino acid solutions, the compatibility should be checked before administration (see section 4.2). Formation of precipitates could result in vascular occlusion.

To avoid air embolism due to possible residual gas contained in the primary bag, do not connect flexible bags in series (see section 4.2). Air embolism can result if residual gas in the bag is not fully evacuated prior to administration if the flexible bag is pressurised to increase flow rates. Use of a vented intravenous administration set with the vent in the open position could result in air embolism.

Use with caution in the following circumstances

Fat metabolism may be disturbed in uncompensated diabetes. The use of ClinOleic in patients with diabetes mellitus has not been investigated. If ClinOleic is administered the elimination of fat should be monitored daily.

Check the following before/during treatment

Water/fluid balance and overload states, electrolytic or metabolic disorders should be corrected before administration of ClinOleic.

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

During short-term or long-term intravenous nutrition, alkaline phosphatase and total bilirubin should be checked at regular intervals, depending on the health status of the patient.

Monitor serum triglycerides, fluid and electrolyte status, acid/base balance, serum osmolarity, blood glucose, liver and kidney function, and blood count, including platelet and coagulation parameters, throughout treatment.

Fluid status should be closely monitored in patients with pulmonary oedema or heart failure.

Use in hepatic impairment
The use of ClinOleic in patients with chronic liver disease without systemic failure has not been evaluated. If parenteral nutrition is to be used in patients with pre-existing liver disease or insufficiency, liver function parameters as well as liver condition should be closely followed when using ClinOleic. Hetapobiliary disorders including cholestasis, hepatic steatosis, fibrosis and cirrhosis, possibly leading to hepatic failure, as well as cholecystitis and cholelithiasis are known to develop in some patients on parenteral nutrition. The aetiology of these disorders is thought to be multifactorial and may differ between patients. Patients developing abnormal laboratory parameters (see *Effect on Laboratory Tests* below) or other signs of hepatobiliary disorders should be assessed early by a clinician knowledgeable in liver diseases in order to identify possible causative and contributory factors, and possible therapeutic and prophylactic interventions. See section 4.3.

Use in renal impairment
See section 4.3.

Paediatric use
Extremely premature and/or very low birth-weight infants receiving ClinOleic should be under the close supervision of a neonatologist. Clinical experience exists for administration of ClinOleic for up to 7 days in neonates and up to 2 months in children.

ClinOleic should be administered with caution in the case of neonatal hyperbilirubinaemia (total serum bilirubin > 200µmol/L). Total bilirubin levels should be monitored closely.

Light exposure of solutions for intravenous parenteral nutrition, after admixture with trace elements and/or vitamins, may have adverse effects on clinical outcome in neonates, due to generation of peroxides and other degradation products. When used in premature newborns, low birth weight infants and children, ClinOleic should be protected from ambient light after admixture until administration is complete (see section 4.2).

Effects on laboratory tests
The lipids contained in ClinOleic may interfere with the results of certain laboratory tests (e.g. bilirubin, lactate dehydrogenase, oxygen saturation, haemoglobin) if the blood sample is taken before the lipids are eliminated. Administered lipids are generally eliminated from the bloodstream after a period of 5 to 6 hours following discontinuation of administration.

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed with ClinOleic.

Olive and soybean oils have a natural content of vitamin K1 that may counteract the anticoagulant activity of coumarin derivatives, including warfarin.

Compatibility with other medicines and nutrients
Complete information about incompatibilities is not available.

- Electrolytes or medication should not be added directly to the lipid emulsion.
- If it is necessary to introduce additives to a solution containing ClinOleic, first verify the compatibility and then mix thoroughly before administration to the patient.
- The compatibility of medicines intended for administration by the Y-site of an infusion containing ClinOleic, must first be established.

ClinOleic may be included as a component of parenteral nutrition admixtures incorporating carbohydrates and amino acids where compatibility and stability have been established before administration to the patient. Admixing should be accompanied by gentle agitation during preparation under strict aseptic conditions. The addition of polyvalent electrolytes to an admixture requires thorough review of the interaction of calcium and phosphate. This review should be made before compounding is initiated, due to the possible interaction between the calcium and the phosphate.

In the case of Synthamin amino acid solutions with electrolytes, the limits of these electrolytes should be less than, or equal to, 5.0mmol/L for calcium, and phosphates should not exceed a concentration of 30mmol/L from all sources.

Absolute solubility of calcium/phosphate in parenteral admixtures is dependent upon many factors, including the concentration of amino acids in the admixture. Reference should be made to calcium/phosphate solubility curves (appropriate to the amino acid in use), published by the amino acid solution manufacturers, to determine the solubility limits before admixing commences.

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

Compatibility with containers and administration sets
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 ClinOleic or of solutions containing ClinOleic. Bags made from ethyl vinyl acetate (EVA) and administration sets made from non-plasticised materials are recommended.

4.6 Fertility, pregnancy and lactation

Fertility
Tests for effects on fertility have not been conducted with Clinoleic.

Use in pregnancy (Pregnancy Category – exempt)
The safety of administration of ClinOleic during pregnancy has not been established. No reproductive toxicity studies with ClinOleic have been carried out in animals, and its use in pregnancy is not recommended.

Breast-feeding
The safety of administration of ClinOleic during lactation has not been established. Therefore, ClinOleic should be used during lactation only if clearly needed.

4.7 Effects on ability to drive and use machines

The effects of ClinOleic on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 Undesirable effects

During administration of parenteral nutrition fat emulsions, two types of adverse reactions can occur:

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 of fat emulsions, the following adverse reactions have been observed:

HEPATO-BILIARY DISORDERS: increase of alkaline phosphatase, bilirubin and transaminases (ALT & AST), hepatomegaly, icterus.

BLOOD AND LYMPHATIC SYSTEM DISORDERS: thrombocytopenia.

Of the clinical trials performed with ClinOleic, a summary of the serious adverse events (SAE) are summarised in the table below. Over a period from November 1995 to November 2003, sixteen (16) SAE's were reported in clinical studies. Of the 16 AE's, seven (7) were not related, one (1) possibly related and one (1) unlikely related to the product administration. The total number of units used during this period was 1,325,117.

To date, two (2) spontaneous adverse events were reported.

Adverse Reactions report by System Organ Class classification. Post-marketing experience, PSUR 1995-2003.		
System Organ Classification	**Sources**	
	Clinical Trials	**Spontaneous**
Serious adverse events		
1. Body as a whole	8 (8/16 = 50%)	
• Fever	1 N/R	
• Septicaemia	3 N/R	
• Sepsis	4 N/R	
• Allergic reaction		1 P/R
2. Central Nervous System	3 (3/16 = 19%)	0
• Cerebral oedema	1 N/R	
• Convulsion	1 N/R	
3. Respiratory system	2 (2/16 = 16%)	0
• Pneumonia (fatal)	1 P/R	
• Respiratory insufficiency	1 U/R	
4. Cardiovascular system	2 (2/16 = 16%)	
• Arrhythmia	1 N/R	
• Increased blood level of immunosuppressant drug		1 N/R
5. Musculo-skeletal system	1 (1/16 = 6%)	0
• Bone necrosis	1 N/R	
TOTAL	16	0
N/R – Not Related P/R – Possibly Related U/R – Unlikely Related		

In addition to the adverse reactions noted above, the following adverse reactions have been reported in clinical trials.

BLOOD AND LYMPHATIC SYSTEM DISORDERS: leukopaenia.

METABOLISM AND NUTRITION DISORDERS: hyperglycaemia, diabetes mellitus inadequate control, hypoproteinaemia, hyperlipidaemia (including hypertriglyceridaemia).

VASCULAR DISORDERS: mean arterial pressure decreased, circulatory collapse, hypotension, hot flush.

RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS: dyspnoea.

GASTROINTESTINAL DISORDERS: vomiting, nausea, abdominal pain, abdominal distension, epigastric discomfort.

HEPATOBILIARY DISORDERS: cholestasis, hepatic function abnormal, cytolytic hepatitis.

MUSCULOSKELETAL AND CONNECTIVE TISSUE AND BONE DISORDERS: muscle spasms, back pain.

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: pyrexia, asthenia, malaise.

INVESTIGATIONS: blood bilirubin increased, bilirubin conjugated increased, hepatic enzyme increased, liver function test abnormal, pancreatic enzyme increased, blood triglycerides increased.

Post-marketing adverse effects
The following additional adverse reactions have been reported in the post-marketing experience:

GASTROINTESTINAL DISORDERS: diarrhoea.

SKIN AND SUBCUTANEOUS TISSUE DISORDERS: pruritus

INVESTIGATIONS: International Normalised Ratio decreased.

IMMUNE SYSTEM DISORDERS: hypersensitivity with the manifestations of rash and dyspnoea.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continuing monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphv.otago.ac.nz/reporting/

4.9 Overdose
In case of overdose (an abnormal rise in triglyceride levels during infusion of fat) where any of the following reactions occur, fat infusion should be stopped to allow lipids to clear from serum, or if necessary, continue the infusion at a reduced dosage: general symptoms such as fever or evocating an haemodynamic instability, emesis, algia, liver function abnormalities, hepato or splenomegalia, haemostasis disorders, hyperlipidaemia, hypersensitivity and fat overload syndrome (see section 4.4). The effects are usually reversible after the lipid infusion is stopped. If medically appropriate, further intervention may be indicated.

For advice on the management of overdose please contact the National Poisons Centre on phone number: 0800 764 766 [0800 POISON] in New Zealand (or 131126 in Australia).

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group
Lipid emulsion for parenteral nutrition

ATC code
B05BA02

Mechanism of action
ClinOleic provides a moderate proportion of essential fatty acids (EFA), which probably facilitates their utilisation. The combination of olive and soya oils allows a content of fatty acids in an approximate ratio of:

- Saturated fatty acids: 15% (SFA).
- Mono-unsaturated fatty acids: 65% (MUFA).
- Essential Poly-unsaturated fatty acids: 20% (EPUFA).

For patients requiring complete parenteral nutrition, complementary carbohydrates, amino acids, electrolytes, vitamins, and trace elements supplements are required.

ClinOleic is a source of energy; the high-energy content of the emulsion enables the administration of a large quantity of calories in a small volume. ClinOleic also contains glycerol for isotonicity. Egg lecithin supplies phosphorus and choline.

Physiochemical properties
The relative density of ClinOleic is in the range of 0.983 – 0.989.

Refined olive oil:
CAS number 8001-25-0.

Refined soya oil:
CAS number 8001-22-7.

Clinical trials
ClinOleic has been used in a number of small clinical trials generally using Intralipid as a comparative agent. The numbers enrolled in these trials were small and they are not suitable for data pooling or meta-analysis or for demonstrating non-inferiority to the comparator. The studies were of variable duration. The studies usually measured fatty acid composition of plasma lipid fractions. Of the population studied, 32% of the adults were aged over 65 years old.

The 2 pivotal studies enrolled 59 infants and children aged under 11 years old.

- Study CT 2402/P14/93/F ("Ricour Study"), double-blind, randomised, parallel group, measured the level of fatty acids in plasma phospholipids (primary efficacy variable) and compared the long-term efficacy and safety of ClinOleic (n = 9) to Intralipid 20% (n = 9) in children and infants who needed prolonged Parenteral Nutrition (PN) at home or hospital. Seventeen patients aged from 1 to 9 years old were exposed for 2 months and 1 patient was exposed for 1 month.

The results of the study are shown in the following table:

Primary efficacy variable: fatty acids in plasma phospholipids		
	Day 0	**Day 60**
Oleic acid (C18: n-9) (p = 0.0023)		
ClinOleic	10.7	14.5
Intralipid	9.2	9.9
Linoleic acid (C18: 2n-6) (p = 0.0001)		
ClinOleic	16.6	13.9
Intralipid	17.6	20.2
C20: 4n-6/C18: 2n-6 (p = 0.0001)		
ClinOleic	0.58	0.70
Intralipid	0.59	0.45
n-6 metabolites/C18: 2n-6 (p = 0.0001)		
ClinOleic	0.82	0.96
Intralipid	0.83	0.64

- Study CT 2402/P15/94/G ("Koletzko Study"), double-blind, randomised, parallel group, compared the efficacy and safety of ClinOleic (n = 22) to Intralipid 20% (n = 20) in premature infants requiring lipid based Total Parenteral Nutrition (TPN) for 7 days. Forty-two premature infants aged -gestational age- 28 to 36 weeks ± 6 days were exposed.

The results are shown in the following table:

Primary efficacy variable: n-6 and n-3 metabolites fatty acids; mead acid; arachidonic acid.		
	Day 0	**Day 8**
n-6 metabolites (p = 0.19)		
ClinOleic	16.8	13.3
Intralipid	17.7	13.0
n-3 metabolites (p = 0.73)		
ClinOleic	3.39	2.73
Intralipid	3.68	3.09
Mead acid (C20: 3n-9) (p = 0.03)		
ClinOleic	1.15	1.04
Intralipid	0.72	0.20
Arachidonic acid (C20: 4n-6) (p = 1.0)		
ClinOleic	13.3	9.2
Intralipid	14.1	9.5

Tolerability of the emulsions in the treatment and control groups was similar.

5.2 Pharmacokinetic properties

In ClinOleic, most of the lipid particle sizes are in the range of chylomicrons (0.08 - 0.6µm) with the mean diameter of less than 0.45µm. However, it may contain a small fraction (up to 2.5%) of particles having a diameter of more than 1µm.

5.3 Preclinical safety data

Genotoxicity

Tests for mutagenicity have not been conducted with Clinoleic.

Carcinogenicity

Tests for carcinogenicity have not been conducted with Clinoleic.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ClinOleic contains the following excipients:

Excipients (in 1000mL)	
Egg lecithin (purified egg phospholipids)	12g
Glycerol	22.5g
Sodium oleate	0.3g
Nitrogen	q.s.
Sodium hydroxide	q.s.
Water for Injection	q.s. to 1000mL

6.2 Incompatibilities

Refer to section 4.5.

6.3 Shelf life

18 months from date of manufacture. The expiry date can be found on the packaging.

6.4 Special precautions for storage

Store product at or below 25°C. Do not freeze, protect from light.

6.5 Nature and contents of container

ClinOleic is presented as a multi-layer plastic bag packaged in an oxygen barrier over wrap in the following pack sizes:
100mL (box of 10 or 24 units)
250mL (box of 10 or 20 units)
350mL (box of 10 or 12 units)
500mL (box of 10 or 12 units)
1000mL (box of 6 units).

Note: Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicine or waste material should be disposed of in accordance with local requirements.

Preparation for administration

Bag

Store in protective overwrap.

PLEASE NOTE: As lipid emulsions are oxygen sensitive, an oxygen indicator affixed to an oxygen absorber is added between the inner bag and the over wrap. The oxygen indicator shows whether oxygen has entered the packaging due to damage of the overwrap. The oxygen indicator should be inspected before removing the overwrap; compare it to the reference colour printed next to the OK symbol and depicted in the printed area of the indicator label. If oxygen enters the overwrap and is not absorbed by the oxygen absorber, the oxygen indicator changes colour. Do not use the product if the colour of the oxygen indicator does not correspond to the reference colour printed next to the OK symbol.

The oxygen indicator mixture may appear biphasic, as it is a suspension of a solid in a liquid. Once it is determined that the product is safe to use, the oxygen absorber/indicator should be discarded.

Do not use plastic containers in series connection. Such use could result in embolism due to residual air drawn from the primary container before administration of the fluid from the secondary container is completed.

To open:

- Tear the protective over wrap.
- Confirm the integrity of the bag.
- Use only if the bag is not damaged and the emulsion is a homogenous liquid with a milky appearance.

Positioning the infusion:

- Suspend the bag.
- Remove the plastic protector from the administration outlet.
- Firmly insert the infusion spike into the administration outlet.

Additions:
If it is necessary to introduce additives, verify the compatibility and mix thoroughly before administration to the patient. Additions must be performed under aseptic conditions. Never make any additions directly to the bag; 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 (see *Method of Preparation* above).

All opened bags must be used immediately and not be stored for further use.

The use of a final filter is recommended during administration of all parenteral nutrition solutions, where possible.

For single use only.

Do not store partially used bags, discard partially used bags and destroy all accessory parts after use.

Do not re-connect partially used bags.

When used in premature newborns, low birth weight infants and children, protect from light exposure when admixtures include trace elements and/or vitamins, after admixture through administration. Exposure of ClinOleic to ambient light after admixture generates peroxides and other degradation products that can be reduced by photoprotection (see section 4.4).

7 MEDICINE SCHEDULE

General Sale Medicine.

8 SPONSOR

ClinOleic is distributed in New Zealand by:
Baxter Healthcare Ltd
33 Vestey Drive
Mt Wellington
Auckland 1060.

Baxter Healthcare Ltd
PO Box 14 062
Panmure
Auckland 1741

Phone (09) 574 2400.

ClinOleic is distributed in Australia by:
Baxter Healthcare Pty Ltd
1 Baxter Drive
Old Toongabbie, NSW 2146.

9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:
24 January 2004.

10 DATE OF REVISION OF THE TEXT

15 July 2020.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Formatting, spacing
2	Added 'approximately' to active ingredients.
6.1	Excipients re-ordered.
4.2	Under section - Preparation for administration (Bag): Addition of "Store in protective overwrap". Changing the sentence structure to improve clarity, from "As lipid emulsions are oxygen sensitive, an oxygen absorber and oxygen indicator are added … "to "As lipid emulsions are oxygen sensitive, an oxygen indicator affixed to an oxygen absorber is added …".

Based on Australian PI most recent amendment 15 June 2020 and CCSI404 2019 0612.

Please refer to the Medsafe website (www.medsafe.govt.nz) for most recent data sheet.