PRODUCT MONOGRAPH

CLINOLEIC 20%

Refined Olive Oil and Refined Soybean Oil Lipid Emulsion

(approximately 16%/4% w/w)

Lipid Emulsion for Intravenous Nutrition

Baxter Corporation
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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	**Dosage Form / Strength**	**Clinically Relevant Nonmedicinal Ingredients**
Intravenous	Lipid Emulsion for Infusion / 20% Refined Olive Oil and Refined Soybean Oil Lipid Emulsion (approximately 16%/4% w/w)	Egg phosphatides *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

CLINOLEIC (Refined Olive Oil and Refined Soybean Oil Lipid Emulsion) 20% is indicated for parenteral nutrition in adults when oral or enteral nutrition is not possible, insufficient, or contraindicated. As a lipid emulsion, CLINOLEIC 20% provides a source of fat (or lipids) for adult patients requiring parenteral nutrition.

Geriatrics:

Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with any differences in safety or effectiveness.

Pediatrics:

Clinical data on the use of CLINOLEIC 20% in the pediatric population are not provided.

CONTRAINDICATIONS

The use of CLINOLEIC (Refined Olive Oil and Refined Soybean Oil Lipid Emulsion) 20% is contraindicated in the following populations/situations:

- Known hypersensitivity to egg, soybean proteins, or to any active ingredient (olive or soybean oil), excipients, or components of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.
- Severe hyperlipidemia or severe disorders of lipid metabolism characterized by hypertriglyceridemia
- Hypertriglyceridemia-associated acute pancreatitis

WARNINGS AND PRECAUTIONS

General

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

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

NEVER ADD other medicinal products or electrolytes directly to CLINOLEIC (Refined Olive Oil and Refined Soybean Oil Lipid Emulsion) 20% bag (see DOSAGE AND ADMINISTRATION).

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 hyperglycemia 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 and maintenance as well as aseptic technique in nutritional formula preparation.

Fat overload syndrome has been reported with lipid products. Reduced ability to eliminate the lipids contained in CLINOLEIC 20% may result in a "fat overload syndrome", which may be caused by overdose; however, the signs and symptoms of this syndrome may also occur when the product is administered according to instructions. This syndrome is characterized by hyperlipidemia, fever, jaundice, liver fatty infiltration, hepatosplenomegaly (deteriorating liver and spleen function), and hypoxia with or without respiratory insufficiency, anemia, leucopenia, thrombocytopenia, coagulation disorders and coma.These symptoms are usually reversible when the lipid emulsion infusion is stopped.

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

Before starting the infusion, correct severe water and electrolyte equilibration disorders, severe fluid overload states, and severe metabolic disorders. Fluid status should be closely monitored in patients with pulmonary edema or heart failure.

If CLINOLEIC 20% is mixed with dextrose and/or amino acid solutions, the compatibility should be checked before administration (see section DOSAGE AND ADMINISTRATION). Formation of precipitates could result in vascular occlusion.

CLINOLEIC 20% 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 characterized 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.

Carcinogenesis and Mutagenesis

Carcinogenesis, mutagenesis and teratogenic studies were not conducted.

Cardiovascular

Fluid status should be closely monitored in patients with heart failure. The level of triglyceride should be monitored to avoid hypertriglyceridemia when administering CLINOLEIC 20% in patients with acute myocardial infarction.

Endocrine and Metabolism

Serum triglyceride concentrations and the ability of the body to metabolize lipids must be monitored regularly. If a lipid metabolism abnormality is suspected, daily monitoring of serum triglycerides is recommended. Hypertriglyceridemia left untreated can lead to the development of pancreatitis, altered pulmonary function, and immune dysfunction.

Hypercholesterolemia may be caused by excessive amount of phospholipids in the parenteral formula.

Hepatic/Biliary/Pancreatic

Parenteral nutrition should be used with caution in patients with preexisting liver disease or liver insufficiency.

Liver function parameters should be closely monitored in these patients. Hepatobiliary disorders including cholestasis, hepatic steatosis, fibrosis and cirrhosis, possibly leading to hepatic failure, as well as cholecystitis and cholelithiasis are known to develop in some patients on parenteral nutrition.

The etiology of these disorders is thought to be multifactorial and may differ between patients. Patients developing abnormal laboratory parameters or other signs of hepatobiliary disorders should be assessed early by a clinician knowledgeable in liver diseases in order to identify possible causative and contributory factors, and possible therapeutic and prophylactic interventions.

Immune

Hypersensitivity to the constituents of the parenteral nutrition formulation such as egg and soybean proteins, olive or soybean oil, excipients, or components of the container may occur. See CONTRAINDICATIONS.

Renal

Use with caution in patients with renal insufficiency.

Respiratory

Lipid emulsions should be given cautiously to patients with acute respiratory distress syndrome

Special Populations

Pregnant Women:

There are no adequate data on use of CLINOLEIC 20% in pregnant women. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing CLINOLEIC 20%.

Nursing Women:

There are no adequate data on use of CLINOLEIC 20% in lactating women. Physicians should carefully consider the potential risks and benefits for each specific patient before prescribing CLINOLEIC 20%.

Monitoring and Laboratory Tests

Monitor serum triglycerides, fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, blood count, including platelets, and coagulation parameters, throughout treatment. Daily monitoring is recommended during initiation of parenteral nutrition and until the patient and laboratory measurements are stable.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse drug reactions occurred with similar frequencies and in similar proportions of patients treated with CLINOLEIC 20% or refined soybean oil lipid emulsion as evidenced by data obtained from 261 adult patients treated with CLINOLEIC 20% in 14 completed clinical efficacy and safety studies. The most frequent adverse drug reactions noted for CLINOLEIC (Refined Olive Oil and Refined Soybean Oil Lipid Emulsion) 20% in clinical trials were nausea/vomiting and muscle spasm, .

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 1 reflects adverse reactions from exposure to CLINOLEIC 20% in 261 adult patients in 14 active-controlled studies with refined soybean oil lipid emulsions. None of the adverse drug reactions were considered serious reactions.

Table 1: Incidence and rate of ADRs per preferred term (Incidence rate ≥1%) in CLINOLEIC Studies

		CLINOLEIC N=261		Refined Soybean Oil Lipid Emulsion N= 248	
		N*	%	N*	%
Gastrointestinal disorders					
	Vomiting / Nausea	17	6.5	7	3.2
	Abdominal distension	3	1.1	1	0.4
Investigations	Blood triglycerides increased	4	1.5	4	1.6
	Blood bilirubin increased**	3	1.1	1	0.4
	Liver function test abnormal***	24	9.2	2	0.8
Metabolism and nutrition disorders	Cell death	4	1.5	2	0.8
	Hyperglycemia	9	3.4	1	0.4
	Hypoproteinaemia	7	2.7	6	2.4
	Hyperlipidemia	6	2.3	1	0.4
Musculoskeletal and connective tissue disorders	Muscle spasms	6	2.3	4	1.6
Vascular disorders	Mean arterial pressure decreased	3	1.1	3	1.2
Hepatobiliary disorders	Cholestasis	3	1.1	0	0
General disorders and administration site conditions	Asthenia	3	1.1	1	0.4

*Number of patients reporting this ADR.
** Includes Bilirubin Conjugated Increased
***includes reports of Hepatic Function Abnormal, Hepatic Enzyme Increased, Blood Alkaline Phosphatase Increased, Gamma Glutamyl Transferase Increased, Blood Alkaline Phosphatase Abnormal, Gamma Glutamyl Transferase Abnormal

In an open-label, non-comparative study of patients with chronic intestinal failure treated with CLINOLEIC 20% for at least six months, two of 13 patients experienced a reaction considered possibly related to the study treatment (fever suspected to be linked to line infection, and severe pneumonia resulting in death). All patients in this study had severe digestive diseases and were dependent on supplemental parenteral nutrition (to meet their required fat/lipids needs) for 1 to 9 years prior to entry into the clinical trial.

Less Common Clinical Trial Adverse Drug Reactions (<1%) for CLINOLEIC

Blood and lymphatic system disorders: Leukopenia

Gastrointestinal disorders: Abdominal pain,, Epigastric discomfort

General disorders and administration site conditions: Malaise, Pyrexia

Hepatobiliary disorders: Cytolytic hepatitis

Investigations: Pancreatic enzyme increased

Musculoskeletal and connective tissue and bone disorders: Back pain

Vascular disorders: Circulatory collapse, Hot flush, Hypotension

Respiratory, thoracic, and mediastinal disorders: Dyspnea

Post-Market Adverse Drug Reactions

In addition to the adverse reactions noted in clinical trials, the following adverse reactions have been reported in the post-marketing experience. These reactions are listed by MedDRA System Order Class (SOC), then by Preferred Term in order of severity.

BLOOD AND LYMPHATIC SYSTEM DISORDERS: Thrombocytopenia

IMMUNE SYSTEM DISORDERS: Hypersensitivity

GASTROINTESTINAL DISORDERS: Diarrhea

SKIN AND SUBCUTANEOUS DISORDERS: Urticaria, Pruritus

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS: Chills

INVESTIGATIONS: International normalized ratio decreased

Class / Other Reactions

Other adverse reactions associated with similar products include:

Fat overload syndrome, Thrombocytopenia

Hepatic failure, Hepatic cirrhosis, Hepatic fibrosis, Cholestasis, Hepatic steatosis,

Cholecystitis, Cholelithiasis

DRUG INTERACTIONS

Overview

No interaction studies have been performed with CLINOLEIC (Refined Olive Oil and Refined Soybean Oil Lipid Emulsion) 20%.

Drug-Drug Interactions

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

Drug-Food Interactions

No CLINOLEIC 20% - food interaction studies have been performed.

Drug-Herb Interactions

No CLINOLEIC 20% - herb interaction studies have been performed.

Drug-Laboratory Interactions

CLINOLEIC 20% may interfere with the results of certain laboratory tests (for example, bilirubin, lactate dehydrogenase, oxygen saturation, blood hemoglobin) if the blood sample is taken before the lipids are eliminated (these are generally eliminated after a period of 5 to 6 hours without receiving lipids). Potential assay interference associated with lipemia should be considered when interpreting the results of lipemic samples.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Dosing of CLINOLEIC (Refined Olive Oil and Refined Soybean Oil Lipid Emulsion) 20% is based on the energy requirements of the individual patient. Lipids present only one component in parenteral nutrition. For complete parenteral nutrition, concomitant supplementation with amino acids, carbohydrates, electrolytes, vitamins, and trace elements is necessary.

Lipid content: CLINOLEIC 20% contains 200 g/L of lipids (200 mg/mL), corresponding to a content of 40 g/L essential fatty acids.

Care must be taken in co-administering the components of parenteral nutrition. If CLINOLEIC (Refined Olive Oil and Refined Soybean Oil Lipid Emulsion) 20% is to be used as a component of parenteral nutrition, compatibility of the resulting infusion should be evaluated and ensured prior to administration to the patient.

Recommended Dose and Dosage Adjustment

The dosage depends on energy expenditure, and the patient's clinical status (degree of stress and daily fatty acid needs) , body weight, and ability to metabolize CLINOLEIC 20%, as well as additional energy given orally/enterally. Therefore the dosage should be individualized and the bag size chosen accordingly.

The maximum daily dose of CLINOLEIC 20% should be based on individual total nutritional requirements and patient tolerance.

Adults

The usual dosage is 1 to 2 g lipids/kg/day. The initial infusion rate must be slow and not exceed 0.1 g lipids or 0.5 mL (10 drops) per minute for 10 minutes then gradually increased until reaching the required rate after half an hour.

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 **OVERDOSAGE**).

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.

	Per kg of body weight	**For a 70 kg Adult**
Usual lipid dosage	1 to 2 g/kg/day	70 to 140 g/day
Infused volume of CLINOLEIC 20%	5 to 10 mL/kg/day	350 to 700 mL/day

Never exceed 0.15 g lipids/kg/hour (0.75 mL/kg/hour).

Missed Dose

In the event of a missed dose, the infusion should be restarted at the recommended dose and flow rate. Doses should NOT be doubled.

Administration

For instructions for preparation and handling of the emulsion for infusion see **SPECIAL HANDLING INSTRUCTIONS**.

Intravenous infusion:

When administered as a component of parenteral nutrition (with dextrose and amino acids) the central or peripheral venous route should be chosen, depending on the osmolarity of the final infusate.

When infused alone as a support to oral or enteral nutrition complementary CLINOLEIC 20% can be administered via central or peripheral vein.

The compatibility with solutions administered simultaneously via a common end section must be ensured.

Treatment with parenteral nutrition may be continued for as long as is required by the patient's clinical conditions. Monitoring of laboratory and clinical parameters is recommended (see **WARNINGS AND PRECAUTIONS** and Monitoring and Laboratory Tests).

When administered as a component of parenteral nutrition, the compatibility of the components and stability of the admixture must be checked before administration to the patient. Admixing should be accompanied by gentle agitation during preparation under strict aseptic conditions.

When preparing an admixture that includes CLINOLEIC 20%, the final osmolarity of the mixture should be measured before administration via a peripheral vein.

If the final mixture is hypertonic, it may cause irritation of the vein when administered into a peripheral vein.

OVERDOSAGE

For suspected cases of drug overdose, contact the regional poison control centre.

In the event of overdose, fat overload syndrome may result (see WARNINGS AND PRECAUTIONS). Stop the infusion to allow lipids to clear from serum. The effects are usually reversible after the lipid emulsion infusion is stopped. If medically appropriate, further intervention may be indicated.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Fatty acids (lipids) are important energy sources for the body. The human body cannot synthesize omega-6 (linoleic acid and derivatives) or omega-3 (α-linolenic acid and derivatives) polyunsaturated fatty acids and requires these from the diet. Fatty acids are also important as substrates for membranes, precursors for bioactive molecules (such as prostaglandins), and as regulators of gene expression.

A clinical study examined the metabolism of CLINOLEIC in 6 healthy adult males using indirect calorimetry and measurement of plasma clearance. The subjects received CLINOLEIC or the comparator refined soybean oil lipid emulsion (0.1 g/kg/hour over 5 hours) using a crossover design. Analysis of the data showed no significant difference between the treatments in terms of energy expenditure measured by indirect calorimetry, and lipid metabolism and clearance (i.e. fatty acid profile and triglyceride levels).

Pharmacodynamics

CLINOLEIC (Refined Olive Oil and Refined Soybean Oil Lipid Emulsion) 20% is a mixture of refined olive oil and refined soybean oil (ratio approximately 16/4 w/w), 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 may improve utilisation of infused essential fatty acids for synthesis of higher derivative fatty acids.

Olive oil contains significant amounts of alpha-tocopherol that contributes to vitamin E status.

Pharmacokinetics

The elimination rate of lipid emulsions depends on particle size, fatty acid composition, apolipoprotein content of the lipid globules, lipoprotein lipase activity, and hepatic lipase activity. The maximal removal capacity (K1) for the lipid emulsion found for CLINOLEIC 20% in normal volunteers is 176 ± 16 mg/kg/hr. In CLINOLEIC 20%, the size of the lipid particles is close to that of chylomicrons and this emulsion therefore has a similar elimination rate).

Metabolism and excretion: Triglycerides are metabolized to carbon dioxide and excreted by the lungs.

In a study that examined the metabolism of CLINOLEIC in 6 healthy adult males (for study design see ACTION AND CLINICAL PHARMACOLOGY, Mechanism of Action) amounts of carbon dioxide produced versus the amount of oxygen consumed (assessed by indirect calorimetry) were similar in the CLINOLEIC and the refined soybean oil lipid emulsion treatment groups.

In the clinical study C89 CSW 6/3 08F, there was a trend for a better status of the upper derivatives (Σn 6 >18 + 18:3n-6) in the plasma phospholipids fraction in the CLINOLEIC group compared to the refined soybean oil lipid emulsion. The status of upper derivatives of the n-3 series (C >18, sum (n-3)) remained lower than normal values for both lipid emulsions. (For study design, see Part II: SCIENTIFIC INFORMATION, CLINICAL TRIALS.)

Special Populations and Conditions

Pharmacokinetic data have not been obtained in special patient populations or conditions.

STORAGE AND STABILITY

Store at room temperature (15 to 30ºC). Do not freeze. Store in protective overpouch.

SPECIAL HANDLING INSTRUCTIONS

Before opening the overpouch, check the colour of the oxygen indicator. Compare it to the reference colour printed next to the OK symbol and depicted in the printed area of the indicator label. 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.

To open

Remove the protective overpouch.

Discard the oxygen absorber / oxygen indicator sachet.

Confirm the integrity of the bag. Use only if the bag is not damaged and if the lipid emulsion is an homogeneous liquid with a milky appearance, with no visible oil droplets at the surface.

Additions

Never make any additions directly to the bag.

Preparation of the Infusion

For single use only. Aseptic conditions must be observed.

Suspend the bag.

Remove the plastic protector from the administration port.

Insert the spike of the infusion set into the administration port.

Administration

For single use only. Aseptic conditions must be observed.

Use administration sets and lines that do not contain di-2-ehtylhexyl phthalate (DEHP).

Use of a final filter is recommended during administration of all parenteral nutrition solutions.

Do not use filters of less than 1.2 micron pore size with lipid emulsions. Do not use the EXACTAMIX Inlet H938173 with an EXACTAMIX compounder to transfer CLINOLEIC 20% injection. This inlet spike has been associated with dislodgement of the administration port membrane into the CLINOLEIC 20% injection bag.

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

Do not reconnect any partially used bag.

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

Any unused product or waste material must be discarded.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CLINOLEIC (Refined Olive Oil and Refined Soybean Oil Lipid Emulsion) 20% is presented in a non-Polyvinyl Chloride (PVC) bag and contains a mixture of refined olive oil (approximately 16%) and refined soybean oil (approximately 4%).

List of excipients

Purified egg phosphatide
Glycerol
Sodium oleate
Sodium hydroxide for pH adjustment
Nitrogen
Water for injections

Packaging

The bag is a multi-layer non-PVC bag fitted with an injection port and with an administration port for insertion of the spike of the infusion set. The inner (contact) layer of the bag material is made of a blend of polyolefinic copolymers and is compatible with lipid emulsions. Other layers are made of poly-ethylene vinyl acetate and of a copolyester.

To protect from air contact, the bag is packaged in an oxygen barrier overpouch, which contains an oxygen absorber / oxygen indicator sachet.

Pack sizes:

100 mL in bag: Box of 24 or 10 units.
250 mL in bag: Box of 20 or 10 units.
350 mL in bag: Box of 12 or 10 units.
500 mL in bag: Box of 12 or 10 units.
1000 mL in bag: Box of 6 units.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

CLINOLEIC (Refined Olive Oil and Refined Soybean Oil Lipid Emulsion) 20% contains a mix of refined olive oil and refined soybean oil.

Proper Name Chemical Name	Molecular Formula and Molecular Mass	Structural Formula	Physicochemical Properties
Olive oil, refined	Complex mixture of triglycerides; predominant fatty acids in olive oil are oleic, palmitic and linoleic. Approximately 870 depending on the fatty acid composition.	CH_2-OCO-R_1 | CH-OCO-R_2 | CH_2-OCO-R_3 where R_1, R_2 and R_3 represent the fatty acids linked to the glycerol moiety of the triglyceride.	Clear, colourless or greenish-yellow, transparent liquid, practically insoluble in ethanol (96%), miscible with light petroleum (50°C to 70°C). When cooled, it begins to become cloudy at 10°C and becomes a butter-like mass at about 0°C. It has a relative density of about 0.913.
Soybean oil, refined	Complex mixture of triglycerides; predominant fatty acids in soybean oil are linoleic, oleic, palmitic and linolenic. Approximately 870 depending on the fatty acid composition.	CH_2-OCO-R_1 | CH-OCO-R_2 | CH_2-OCO-R_3 where R_1, R_2 and R_3 represent the fatty acids linked to the glycerol moiety of the triglyceride.	Clear, pale yellow, liquid, miscible with light petroleum (50°C to 70°C), practically insoluble in alcohol. It has a relative density of about 0.922 and a refractive index of about 1.475.

Energy content: 2000 kcal/L

Osmolarity approx.: 270 mOsmol/L

pH: 6 to 8

Molecular Mass: composition **Approximately 870 g/mol depending on the fatty acid**

CLINICAL TRIALS

Fifteen (15) studies in adult patients are reported for CLINOLEIC (Refined Olive Oil and Refined Soybean Oil Lipid Emulsion) 20%, of which eight (8) were for short-term and seven (7) for long-term administration. The short-term studies included a total of 364 patients, of which 187 were given CLINOLEIC 20% and the long-term studies included a total of 158 patients, of which 87 were given CLINOLEIC 20%. In all of the clinical trials performed, there were 12 deaths among 274 patients infused with CLINOLEIC 20% and 9 deaths among 249 patients treated with comparative lipid emulsions. None were considered by the investigator to be related to the lipid emulsion.

There were two pivotal studies, C89 CSW 6/3 08F and C89 CSQW 6/3 10F. Patients were given parenteral nutrition for reasons that included gastrointestinal or other surgeries, severe digestive diseases, and chronic illness. Parenteral nutrition was exclusive in one of the studies and represented more than 50% of nutritional intake in the other study. In both studies, the lipid emulsion was administered as part of a ternary parenteral nutrition mixture that included amino acids, dextrose, electrolytes, vitamins and trace elements according to patient needs.

Study demographics and trial design

Summary of patient demographics for clinical trials in parenteral nutrition

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
C89 CSW 6/3 08F	Randomised, open label, multicentre study	1.88 ± 0.09 g/kg/day for the CLINOLEIC group 1.81 ± 0.07 g/kg/day for the refined soybean oil lipid emulsion group IV Mean 22 days for both groups	ITT population CLINOLEIC n=23 refined soybean oil lipid emulsion n=23	CLINOLEIC 32 ± 15.0 years refined soybean oil lipid emulsion 30 ± 14.1 years Overall (17-75 years)	CLINOLEIC 16 M, 7 F refined soybean oil lipid emulsion 15 M, 8 F
C89 CSW 6/3 10F	Randomised, open label, multicentre study Supplement to oral / enteral nutrition	0.91 ± 0.07 g/kg/day for the CLINOLEIC group 0.95 ± 0.12 g/kg/day for the refined soybean oil lipid emulsion group IV Mean 202 days for the CLINOLEIC group Mean 145 days for the refined soybean oil lipid emulsion group	ITT population CLINOLEIC n=12 refined soybean oil lipid emulsion n=10	CLINOLEIC 58 ± 14.9 years (32-81) refined soybean oil lipid emulsion 60 ± 9.2 years (47-75)	CLINOLEIC 7 M, 5 F refined soybean oil lipid emulsion 5 M, 5 F

Study results

Results of study C89 CSW 6/3 08F in parenteral nutrition

Primary Endpoints	Results
Nutritional criteria	Improvement of anthropometry and biological nutritional status (albumin, total protein, gamma globulin) in both groups (difference not significant)
Plasma triglyceride levels	No significant differences in plasma triglyceride levels.
Plasma phospholipids fraction	Significant difference between the two groups ($p < 0.0001$) with regard to the change in oleic acid (C18:1n-9) and linoleic acid (C18:2n-6): - Increase in oleic acid and decrease in linoleic acid in CLINOLEIC group. - Decrease in oleic acid and increase in linoleic acid in refined soybean oil lipid emulsion group.

Results of study C89 CSW 6/3 10F in parenteral nutrition

Primary Endpoints	Results
Clinical tolerance	Anthropometric criteria (weight, mid-arm circumference, triceps skin fold) showed similar improvement in both groups.
Biological tolerance (hepatic and lipid parameters, haematology, phosphocalcic homeostasis, biochemical parameters)	Results for lipid parameters (e.g., plasma triglycerides, total cholesterol, HDL cholesterol, phospholipids) showed no significant differences between groups. Results for hepatic parameters (e.g., AST, ALT, alkaline phosphatase, GGT) showed no significant differences between groups. No significant differences between groups in haematology, plasma proteins, phosphocalcic homeostasis or biochemical parameters.

The study results demonstrated that the efficacy and safety of CLINOLEIC 20% is similar in nutritional efficacy to the refined soybean oil lipid emulsions in providing parenteral nutrition to patients when oral or enteral nutrition is not possible, insufficient or contraindicated.

DETAILED PHARMACOLOGY

Three comparative pharmacologic studies have been performed in healthy volunteers with CLINOLEIC (Refined Olive Oil and Refined Soybean Oil Lipid Emulsion) 20% or refined soybean oil lipid emulsion administered intravenously.

The first study examined the metabolism of the two lipid emulsions in six healthy males at a dose of 0.1 g/kg/h lipid emulsion with glucose and amino acids solutions over 5

hours. The changes were evaluated by measuring energy expenditure by indirect calorimetry and lipid metabolism and clearance (i.e., free fatty acid and triglyceride levels). Analysis of the data showed no significant difference between the two treatments in terms of indirect calorimetry, triglyceride levels, or free fatty acids. Glycerol was significantly higher following treatment with CLINOLEIC 20%.

The analysis of free fatty acids and fatty acids in the triglyceride fraction (TG-FAs) showed significant differences, which essentially reflect the composition of the 2 emulsions:

- TG-FAs: An increase in oleic acid with smaller increases in linoleic acid and palmitic acid following administration of CLINOLEIC 20%. α-Linolenic acid remained stable.
- TG-FAs: An increase in linoleic acid with smaller increases in oleic acid and palmitic acid following administration of refined soybean oil lipid emulsion. α-Linolenic acid remained stable.

The fatty acid profile of the free fatty acids and the triglycerides was similar between treatment groups.These results demonstrated that the levels of triglycerides and free fatty acids, as well as the metabolism, of CLINOLEIC 20% were similar to those of refined soybean oil lipid emulsion. The differences found in the fatty acid profiles essentially reflect the composition of the 2 emulsions. The clinical and biological tolerance of both emulsions was satisfactory.

The second study was performed to examine the in vivo elimination of triglyceride-rich particles after intravenous administration of 2 different emulsions. In a randomized cross-over design, six healthy male volunteers were iv administered CLINOLEIC 20% and a refined soybean oil lipid emulsion 20%. Test emulsions were administered as a single bolus injection (0.1 g/kg TG) followed by an infusion of 0.25 g/kg for 1 hour. The decline in plasma TG was followed during an additional 1 hour period. Olive oil triglycerides exhibited slower elimination than the soybean oil triglycerides. A lower maximal removal capacity (K1) and lower fractional catabolic rate (K2) were measured with the olive-oil-containing emulsion than with the refined soybean oil lipid emulsion. The K1 values were 176.3 ± 16.3 mg/kg/hr in the CLINOLEIC 20% group and 217.9 ± 29.4 mg/kg/hr in the refined soybean oil lipid emulsion group ($p < 0.05$). The K2 values were 1.83 ± 0.43%/min for CLINOLEIC 20% and 3.0 ± 0.48%/min for refined soybean oil lipid emulsion ($p < 0.05$). Clearance (K1) of the olive oil emulsion was inversely related to hepatic lipase activity ($r = -0.85$; $p < 0.05$). Clearance (K1) of the refined soybean oil lipid emulsion was related to the initial plasma triglyceride concentration (r =

-0.84; $p < 0.05$), but not to lipolytic activity. In vivo apolipoprotein CII levels decreased similarly with both emulsions. It was concluded, based upon the kinetics of triglyceride elimination, that hepatic lipase activity was more important in the elimination of olive oil emulsions than refined soybean oil lipid emulsion. The faster elimination of refined soybean oil lipid emulsion suggested an additional elimination pathway, such as uptake by the reticulo-endothelial system (RES).

The third study investigated the effects on intravenous administration of CLINOLEIC 20% and the refined soybean oil lipid emulsion on biliary secretion and jejunal absorption of bile acids. This randomized, crossover, double-blind study was conducted in 9 healthy male subjects. After a 3 hour saline infusion, one of the test emulsions or saline were infused at 100 mL/hr for 4 hours (lipid dose 0.29 g/kg/hr).

No significant differences were observed between the 2 emulsions or saline with regard to secretion of bile acids, cholesterol, or phospholipids. No significant differences were noted between treatments in the jejunal absorption of bile acids. Serum lipids rose significantly on infusion of both lipid emulsions. The concentrations of triglycerides and free cholesterol were higher with CLINOLEIC 20% than with refined soybean oil lipid emulsion 20%. The results suggested that there was a different mechanism for lipid clearance for each emulsion.

TOXICOLOGY

Single-dose Toxicity

Single-dose toxicity was investigated in the mouse and rat to compare the LD_{50} of CLINOLEIC (Refined Olive Oil and Refined Soybean Oil Lipid Emulsion) 20% with that of 20% refined soybean oil lipid emulsion.

LD_{50} values were comparable at around 100-112 mL/kg (corresponding to approximately 20 g lipid/kg) in both species with rapid infusion.

Repeat-Dose Toxicity

CLINOLEIC 20% was administered to rats and dogs by intravenous infusion in studies lasting up to 91 days. The key studies conducted are presented in the table below.

Repeated Dose Toxicity Studies

Type of Study	Species and Strain	Method of Administration	Duration of Dosing	Doses
30 Day toxicity study in the rat	Rat Sprague Dawley CD (Charles River)	IV infusion	30 days	CLINOLEIC 20% 90 mL/kg/day at a rate of 1.2 mL/kg/min (18 g/kg/day) refined soybean oil lipid emulsion 20% 18 g/kg/day
30 Day toxicity study in the rat	Rat Sprague Dawley CD (Charles River)	IV infusion	30 days	CLINOLEIC 20% 75 mL/kg/day at a rate of 1.5 mL/kg/min (15 g/kg/day) refined soybean oil lipid emulsion 20% 15 g/kg/day
90 Day toxicity study in the rat	Rat Sprague Dawley CD (Charles River)	IV infusion	90 days	CLINOLEIC 20% 15, 30 and 60 mL/kg/day at a rate of 2 mL/kg/min (3, 6, and 12 g/kg/day) refined soybean oil lipid emulsion 20% 12 g/kg/day
30 Day toxicity study in the dog	Dog Beagle	IV infusion	30 days	CLINOLEIC 20% 45 mL/kg/day at a rate of 0.2 mL/kg/min (9 g/kg/day) refined soybean oil lipid emulsion 20% 9 g/kg/day
30 Day toxicity study in the dog	Dog Beagle	IV infusion	30 days	CLINOLEIC 20% 60 mL/kg/day at a rate of 0.2 mL/kg/min (12 g/kg/day) refined soybean oil lipid emulsion 20% 12 g/kg/day
91 Day toxicity study in the dog	Dog Beagle	IV infusion	91 days	CLINOLEIC 20% 15, 22.5, 30 mL/kg/day 0.2 mL/kg/min (3, 4.5, and 6 g/kg/day) refined soybean oil lipid emulsion 20% 6 g/kg/day

The toxicological changes associated with the daily intravenous administration of CLINOLEIC 20% at 15-18 g/kg/day to rats and 9-12 g/kg/day to dogs for 30 consecutive days were comparable to those of refined soybean oil lipid emulsion 20%, the reference

refined soybean oil lipid emulsion used in the studies, and were consistent with the anticipated effects of excess lipid administration. The effects typically included decreased food consumption, hematuria (rats), mild regenerative anemia and thrombocytopenia, increased hepatic enzymes, hepatocellular and splenic macrophage vacuolation, hepatic and splenic macrophage pigmentation, interstitial and tubular nephritis (rat) and renal tubular vacuolation (dog).

The doses administered in the 30 day repeated dose toxicology studies were 6.0-7.2 times (rat) or 3.6-4.8 times (dog) the maximum clinical dose of 2.5 g/kg/day recommended by American Society of Parenteral and Enteral Nutrition (ASPEN), 2004 Guidelines on Safe Practices for Parenteral Nutrition.

Likewise, when CLINOLEIC was administered intravenously for 90-91 consecutive days to rats at 3-12 g/kg/day and to dogs at 3-6 g/kg/day (1.2-4.8 times and 1.2-2.4 times the maximum clinical dose, respectively), treatment-related changes were limited to the anticipated effects of excess lipid administration as in the 30 day studies and were dose-dependent. With the exception of the lipoid pigment present in hepatic and splenic macrophages, all treatment-related changes were demonstrated to be reversible following treatment withdrawal.

Studies on the carcinogenic potential, reproductive and developmental toxicity, and genotoxic potential of CLINOLEIC 20% have not been performed.

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PART III: CONSUMER INFORMATION

CLINOLEIC 20%
Refined Olive Oil and Refined Soybean Oil Lipid Emulsion
(approximately 16%/4% w/w)

Lipid Emulsion for Intravenous Nutrition

This leaflet is part III of a three-part "Product Monograph" published when CLINOLEIC 20% was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about CLINOLEIC 20%. Contact your doctor or pharmacist if you have any questions about the product.

ABOUT THIS MEDICATION

What the medication is used for:
CLINOLEIC 20% is as a source of calories and essential fatty acids when you are unable to take food by mouth.

CLINOLEIC 20% must only be used under medical supervision.

What it does:
The use of CLINOLEIC 20% is a way to ensure an adequate intake of calories and essential fatty acids and thus helps to prevent or treat malnutrition.

When it should not be used:
Do not use CLINOLEIC 20%, if:

- You are allergic to any ingredients (such as egg and soybean proteins, olive or soybean oil). (See **What the important nonmedicinal ingredients are**.)
- Your body has severe problems metabolizing (breaking down) lipids or fats.
- You have very high levels of fats in your blood.
- You have acute pancreatitis (severe inflammation of pancreas) in association with hyperlipidemia (high blood fat levels)

What the medicinal ingredient are:
CLINOLEIC 20% is a lipid (fat) emulsion for intravenous infusion. Each 1000 mL contains 200 g of a mixture of refined olive oil (approximately 160 g) and refined soybean oil (approximately 40 g).

What the important nonmedicinal ingredients are:
Egg Phosphatides, Glycerol, Sodium Oleate and Water for Injection. A small quantity of Sodium Hydroxide may be used to adjust the acidity of the solution.

What dosage forms it comes in:
CLINOLEIC 20% is supplied in a bag which contains either 100 mL, 250 mL, 350 mL, 500 mL or 1000 mL of emulsion.

WARNINGS AND PRECAUTIONS

BEFORE you use CLINOLEIC 20%, talk to your doctor or pharmacist if:

- You are allergic to any ingredients (such as egg and soybean proteins, olive or soybean oil). (See **What the important nonmedicinal ingredients are**.)
- You have acute respiratory distress syndrome (difficulty in breathing)
- You have kidney or liver problems.
- You have severe problems metabolizing (breaking down) lipids or fats OR you have high levels of fat in your blood.
- You are taking any other medicines on a regular basis.
- You are pregnant or intend to become pregnant.
- You are breastfeeding or intend to breastfeed.

In all cases, your doctor will base his/her decision to give you this medicine on factors such as age, weight and clinical condition, together with the results of any te sts that he/she has performed. Always be sure to check with your doctor if anything about your condition changes.

Your doctor will need to monitor how you are doing while you are on this medicine. This means that you will need to have laboratory tests done on a routine basis.

INTERACTIONS WITH THIS MEDICATION

No interaction studies have been performed.

If you are taking a blood thinning agent of the coumarin type (like warfarin), you should talk to your doctor or pharmacist. Olive and soybean oils in CLINOLEIC 20% have a natural content of Vitamin K1 that may counteract the anticoagulant activity of coumarin derivatives, including warfarin.

PROPER USE OF THIS MEDICATION

CLINOLEIC 20% is given in a hospital or managed care facility, or at home under the supervision of a doctor or other health care professional.

After appropriate training and with the agreement of your medical team, you may be able to administer the product yourself. Your doctor's instructions must be followed exactly when taking CLINOLEIC 20%.

Administration:

Preparation:
a.) The product is packaged in a multi-layer bag, fitted with an injection port and with an administration port for insertion of the spike of the infusion set. To protect from air contact, the bag packaged in an oxygen barrier overpouch, which contains an oxygen absorber / oxygen indicator sachet. Do not use the EXACTAMIX Inlet H938173 with an EXACTAMIX compounder to transfer CLINOLEIC 20% injection. This inlet spike has been associated with dislodgement of the administration port membrane into the CLINOLEIC 20% injection bag.

b.) Before opening the overpouch, check the colour of the oxygen indicator. Compare it to the reference colour printed next to the OK symbol and shown on the printed area of the indicator label. 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.

c.) To open: Remove the protective overpouch.
Discard the oxygen absorber / oxygen indicator sachet.
Confirm the integrity of the bag. Use only if the bag is not damaged and if the lipid emulsion is an evenly distributed liquid with a milky appearance and with no visible oil droplets at the surface.

d.) To administer:
- Aseptic conditions must be followed (cleaning of hands).
- Suspend the bag.
- Remove the plastic protector from the administration set.
- Insert the spike of the infusion set into the administration port of the bag.
- Use of a final filter (not less than 1.2 micron pore size) is recommended during administration of all parenteral nutrition solutions
- Use contents immediately.
- Never make any additions directly to the bag.
- Your health care professional will provide instructions on preparation of site, a route of administration (central or peripheral venous route), and specify a flow rate corresponding to your needs and medical condition.
- ClinOleic should only be used once. Discard unused portion, do not reuse partially used bag, Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

Usual dose:
Your doctor will decide how much of the treatment you will need and how long it will be given to you. The dose will depend on your nutritional requirements and on the reason you are being given the treatment.

The emulsion will usually be given to you via a plastic tube which will be placed very carefully into the vena cava, a larger vein in your chest. Non-nutritional intravenous solutions and blood may be given through this tube (but generally not at the same time).

Your doctor will provide any other specific instructions corresponding to your needs and medical condition.

Always use CLINOLEIC 20% exactly as your doctor has told you to. You should check with your doctor if you are not sure.

Overdose:
If your dose is too high CLINOLEIC 20% content may increase the fats in your blood which may result in fever and a worsening of your health that may require hospitalization.

To prevent these events occurring, your doctor will regularly monitor your condition and test your blood and urine parameters.

In case you feel you have been administered too much or have taken too much CLINOLEIC 20%, contact your doctor, hospital emergency department or the regional poison control centre.

Missed Dose:
If you miss or forget to take one or more doses of CLINOLEIC 20%, contact your doctor as soon as possible. Your doctor will instruct you about how to re-start your treatment and what flow rate to use.

DO NOT take a double dose to make up for forgotten individual doses.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

If you notice any changes in the way you feel during or after the treatment, tell your doctor or another member of your medical team immediately.

The tests your doctor will perform while you are taking the medicine should minimise the risk of side effects.

If any abnormal signs or symptoms of an allergic reaction develop, such as fever, shivering/chills, skin rashes or hives, severe headache or breathing difficulties, you must stop the infusion immediately.

If any side effect gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor or a member of your medical team right away.

You may suffer fat overload syndrome while taking CLINOLEIC 20%. Contact your doctor if you suffer symptoms such as fever, jaundice (yellowing of the skin or eyes).

There have been reports of liver problems and liver failure in patients who take similar products as part of an intravenous nutrition therapy. If you suffer symptoms such as nausea, vomiting, abdominal pain, dark stool, yellowing of the skin or eyes, contact your doctor immediately.

Other side effects could occur as listed. Notify your doctor immediately should other side effects be encountered.

The most frequent adverse drug reactions noted for CLINOLEIC 20% in clinical trials were nausea/vomiting and muscle spasm. Other reactions that occurred in at least 1 in every 100 patients included increased blood triglycerides, , hyperglycemia (increased blood sugar), and decreased mean arterial pressure and hypotension (low blood pressure).

Occasionally, reddening and stinging may occur at the point where the tubing enters your body. If you notice this, tell your doctor or nurse immediately.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	**Fever**			√
	Shivering			√
	Skin rashes			√
	Breathing difficulties			√
	Severe headache			√

This is not a complete list of side effects. For any unexpected effects while taking CLINOLEIC 20%, contact your doctor or a member of your medical team or pharmacist.

HOW TO STORE IT

Store at room temperature (15 to 30ºC). Do not freeze. Store in protective overpouch.

Do not use CLINOLEIC 20% after the expiry date which is printed on the container and the outer packaging (MM/YYYY). The expiry date refers to the last day of that month.

Once you have broken the seal on the administration port, use the bag within 12 hours. Do not keep the unsealed bag longer than 24 hours. Do not re-use a partially empty bag.

This medicine must be at room temperature to be administered.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to:Canada Vigilance Program
    Health Canada
    Postal Locator 0701D
    Ottawa ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of the side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Baxter Corporation at: 1-888-719-9955 .

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