

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CLINOLIPID safely and effectively. See full prescribing information for CLINOLIPID.

CLINOLIPID (lipid injectable emulsion), for intravenous use

Initial U.S. Approval: 1975

RECENT MAJOR CHANGES

Boxed Warning (Removed)	5/2023
Indication and Usage (1)	4/2024
Dosage and Administration (2.4)	4/2024
Contraindication (4)	5/2023
Warnings and Precautions (5.1, 5.2)	5/2023
Warnings and Precautions (5.9)	4/2024

INDICATIONS AND USAGE

CLINOLIPID is indicated in adults and pediatric patients, including term and preterm neonates, as a source of calories and essential fatty acids for parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated. (1)

DOSAGE AND ADMINISTRATION

- Use a 1.2 micron in-line filter when administering to a patient. (2.1)
- For infusion into a central or peripheral vein. (2.2)
- See full prescribing information for administration and admixing instructions. (2.2, 2.3)
- CLINOLIPID Pharmacy Bulk Package is only indicated for use in pharmacy admixture programs for the preparation of three-in-one or total nutrition admixtures. (2.2)
- Protect the admixed parenteral solution from light. (2.3)
- Recommended dosage depends on age, energy expenditure, clinical status, body weight, tolerance, ability to metabolize and eliminate lipids, and consideration of additional energy given to the patient. (2.4)
- For information on the age-appropriate infusion rate, see the full prescribing information. (2.4, 5.1)

Age	Initial Dose	Maximum Dose
Birth to 2 years of age (including preterm and term neonates)	0.5 to 1 g/kg/day	3 g/kg/day
Pediatric patients 2 to less than 12 years of age	1 to 2 g/kg/day	3 g/kg/day
Pediatric patients 12 to 17 years of age	1 g/kg/day	3 g/kg/day
Adults	1 to 1.5 g/kg/day	2.5 g/kg/day

DOSAGE FORMS AND STRENGTHS

Injectable emulsion:

- 20% (20 g/100 mL) (0.2 g/mL) of lipid in 100 mL single-dose flexible container (3)
- 20% (50 g/250 mL) (0.2 g/mL) of lipid in 250 mL single-dose flexible container (3)

- 20% (100 g/500 mL) (0.2 g/mL) of lipid in 500 mL single-dose flexible container (3)
- 20% (200 g/1,000 mL) (0.2 g/mL) of lipid in 1,000 mL Pharmacy Bulk Package (3)

CONTRAINDICATIONS

- Known hypersensitivity to egg, soybean, peanut, or any of the active or inactive ingredients. (4)
- Severe disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglycerides >1,000 mg/dL). (4, 5.7)

WARNINGS AND PRECAUTIONS

- Clinical Decompensation with Rapid Infusion of Intravenous Lipid Emulsion in Neonates and Infants:** Acute respiratory distress, metabolic acidosis, and death after rapid infusion of intravenous lipid emulsions have been reported. (5.1, 8.4)
- Parenteral Nutrition-Associated Liver Disease:** Increased risk in patients who receive parenteral nutrition for greater than 2 weeks, especially preterm neonates. Monitor liver tests: if abnormalities occur, consider discontinuation or dosage reduction. (5.2, 8.4)
- Hypersensitivity Reactions:** Monitor for signs or symptoms. Discontinue infusion if reactions occur. (5.3)
- Risk of Infections, Fat Overload Syndrome, Refeeding Syndrome, Hypertriglyceridemia, and Essential Fatty Acid Deficiency:** Monitor for signs and symptoms; monitor laboratory parameters. (5.4, 5.5, 5.6, 5.7, 5.9)
- Aluminum Toxicity:** Increased risk in patients with renal impairment, including preterm neonates. (5.8, 8.4)

ADVERSE REACTIONS

Most common ($\geq 5\%$) adverse drug reactions from clinical trials in adults were nausea and vomiting, hyperlipidemia, hyperglycemia, hypoproteinemia, and abnormal liver function tests. Most common ($\geq 5\%$) adverse reactions from clinical trials in pediatric patients were hyperbilirubinemia, patent ductus arteriosus, anemia, gastroesophageal reflux disease, bradycardia, feeding intolerance, neonatal intraventricular hemorrhage, increased alkaline phosphatase, atrial septal defect, hyponatremia, sepsis, and infantile apnea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare at 1-866-888-2472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

The anticoagulant activity of coumarin derivatives, including warfarin, may be counteracted. (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised 4/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

CLINOLIPID is indicated in adults and pediatric patients, including term and preterm neonates, as a source of calories and essential fatty acids for parenteral nutrition (PN) when oral or enteral nutrition is not possible, insufficient, or contraindicated.

2 DOSAGE AND ADMINISTRATION

2.1 Use of an Inline Filter When Administering CLINOLIPID to a Patient

Fragments of the administration port membrane could be dislodged into the bag after spiking. Use a 1.2 micron in-line filter during administration of CLINOLIPID (alone or as part of an admixture) to remove particulate matter or micro-precipitate contamination during administration of a lipid injection (alone or as part of an admixture). Particulate matter greater than 5 microns has the capability of obstructing blood flow through capillaries, which could lead to embolism and vascular occlusion. Do not use filters of less than 1.2 micron pore size with lipid emulsions.

2.2 Important Administration Instructions

Before opening the overwrap, check the color of the oxygen indicator. Compare the color of the indicator to the reference color printed next to the OK symbol depicted in the printed area of the indicator label. Do not use the product if the color of the oxygen absorber/indicator does not correspond to the reference color printed next to the OK symbol.

After opening the bag, use the contents immediately and discard unused portion.

Visually inspect that the emulsion is a homogeneous liquid with a milky appearance. Inspect for particulate matter and discoloration prior to administration, whenever solution and container permit.

Do not exceed the recommended maximum infusion rate (0.75 mL/kg/hour for pediatric patients and 0.5 mL/kg/hour for adults) [*see Dosage and Administration (2.4) and Warnings and Precautions (5.1)*].

When Administering CLINOLIPID to a Patient:

Do not connect flexible bags in series to avoid air embolism due to possible residual gas contained in the primary bag.

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.

Do not use vented administration sets with the vent in the open position. This can result in air embolism.

If CLINOLIPID is mixed with dextrose and/or amino acid solutions, check the compatibility before administration by inspecting the mixture closely for the presence of precipitates. Formation of precipitates could result in vascular occlusion.

CLINOLIPID can be administered via central or peripheral vein. When administered with dextrose and amino acids, the choice of a central or peripheral venous route should depend on the osmolarity of the final infusate.

Do not use administration sets and lines that contain di-2-ethylhexyl phthalate (DEHP).

Use only a 1.2 micron pore size in-line filter to administer CLINOLIPID. DO NOT use any size less than 1.2 micron pore size in-line filter [*see Dosage and Administration (2.1)*].

CLINOLIPID 100 mL, 250 mL and 500 mL single-dose Flexible Containers:

- After removing the overpouch, infuse immediately. If not used immediately, the product should be stored for no longer than 24 hours at no more than 25°C (77°F).

CLINOLIPID 1,000 mL Pharmacy Bulk Package:

- *For admixing use only and not for direct intravenous infusion.* Prior to administration, transfer to a separate PN container for individual patient use.
- Transfer the contents through the infusion port using a suitable sterile transfer device or dispensing set. Discard any unused contents. Discard any unused portion.
- Use the Pharmacy Bulk Package immediately for admixing after removal from overpouch. If not used immediately, the product should be stored for no longer than 24 hours at no more than 25°C (77°F).
- Once the closure is penetrated use Pharmacy Bulk Package contents within 4 hours.

2.3 Admixing Guidelines

When Admixing CLINOLIPID in the Pharmacy:

Prepare the admixture using strict aseptic techniques to avoid microbial contamination.

Do not add additives directly to CLINOLIPID. Do not add CLINOLIPID to the total parenteral nutrition container first; destabilization of the lipid may occur from such an admixture.

Do not use the EXACTAMIX Inlet REF 173 (H938173) with an EXACTAMIX compounder to transfer CLINOLIPID. This inlet spike has been associated with dislodgement of the administration port membrane into the CLINOLIPID bag. Use of EXACTAMIX Inlet REF 174 (H938174) is recommended.

The following proper mixing sequence must be followed to minimize pH related problems by ensuring that typically acidic Dextrose Injections are not mixed with lipid emulsions alone:

1. Transfer Dextrose Injection to the Total Parenteral Nutrition Admixture Container
2. Transfer Amino Acid Injection
3. Transfer Lipid Emulsion

Amino Acid Injection, Dextrose Injection and Lipid Emulsions may be simultaneously transferred to the admixture container. Use gentle agitation during admixing to minimize localized concentration effects; shake bags gently after each addition.

The prime destabilizers of emulsions are excessive acidity (such as a pH below 5) and inappropriate electrolyte content. Give careful consideration to additions of divalent cations (Ca^{++} and Mg^{++}), which have been shown to cause emulsion instability. Amino acid solutions exert buffering effects that protect the emulsion.

Inspect the admixture closely for separation of the emulsion. This can be visibly identified by a yellowish streaking or the accumulation of yellowish droplets in the admixed emulsion. The admixture should also be examined for particulates. Discard the admixture if any of the above is observed.

Protect the admixed parenteral nutrition solution from light.

2.4 Dosing Considerations

The recommended nutritional requirements of lipid and recommended dosages of CLINOLIPID to be administered to meet those requirements for pediatric and adult patients are provided in Table 1, along with recommendations for the initial and maximum infusion rates. For complete parenteral nutrition, concomitant supplementation with amino acids, carbohydrates, electrolytes, vitamins, and trace elements is necessary.

Prior to administration of CLINOLIPID, correct severe water and electrolyte disorders, severe fluid overload states, and severe metabolic disorders. Before starting the infusion, obtain serum triglyceride levels to establish the baseline value. In patients with elevated triglyceride levels, initiate CLINOLIPID injection at a lower dose, and advance in smaller increments, checking the triglyceride levels prior to each adjustment.

Adjust the infusion rate by taking into account the dose being administered, the daily volume intake, and the duration of the infusion. Do not exceed the maximum infusion rates in Table 1 [*Warnings and Precautions (5.1) and see Overdosage (10)*].

The recommended duration of infusion for a parenteral nutrition bag is between 12 and 24 hours, depending on the clinical situation. For preterm and term neonates, the recommended duration of infusion is 20 to 24 hours. Treatment with parenteral nutrition may be continued for as long as required by the patient's condition.

The maximum daily dosage of CLINOLIPID should be based on individual total nutritional requirements and patient tolerance (Table 1).

Table 1: Recommended Pediatric and Adult Dosage and Infusion Rate

Age	Nutritional Requirements	Direct Infusion Rate*	
	Recommended Initial Dosage and Maximum Dosage	Initial	Maximum
Birth to 2 years of age (including preterm and term neonates**) [see Warnings and Precautions (5.1)]	Initial 0.5 to 1 g/kg/day not to exceed 3 g/kg/day***	0.1 to 0.2 mL/kg/hour for the first 15 to 30 minutes; gradually increase to the required rate after 30 minutes	0.75 mL/kg/hour
Pediatric patients 2 to less than 12 years of age	Initial 1 to 2 g/kg/day not to exceed 3 g/kg/day***	0.2 to 0.4 mL/kg/hour for the first 15 to 30 minutes; gradually increase to the required rate after 30 minutes	0.75 mL/kg/hour
Pediatric patients 12 to 17 years of age	Initial 1 g/kg/day not to exceed 3 g/kg/day***	0.2 to 0.4 mL/kg/hour for the first 15 to 30 minutes; gradually increase to the required rate after 30 minutes	0.75 mL/kg/hour
Adults	1 to 1.5 g/kg/day not to exceed 2.5 g/kg/day***	0.2 mL/kg/hour for the first 15 to 30 minutes; if tolerated, gradually increase to the required rate after 30 minutes	0.5 mL/kg/hour

* CLINOLIPID Pharmacy Bulk Package is not intended for direct intravenous administration.

**The neonatal period is defined as including term, post-term, and preterm newborn infants. The neonatal period for term and post-term infants is the day of birth plus 27 days. For preterm infants, the neonatal period is defined as the day of birth through the expected age of delivery plus 27 days (i.e., 44 weeks post-menstrual age).

*** Daily dosage should also not exceed a maximum of 60% of total energy requirements [see *Overdosage (10)*].

3 DOSAGE FORMS AND STRENGTHS

CLINOLIPID is a sterile, homogenous, white, milky, lipid injectable emulsion supplied as:

- 20% (20 g/100 mL)(0.2g/mL) of lipid in 100 mL single-dose Flexible Container
- 20% (50 g/250 mL)(0.2g/mL) of lipid in 250 mL single-dose Flexible Container
- 20% (100 g/500 mL)(0.2g/mL) of lipid in 500 mL single-dose Flexible Container
- 20% (200 g/1,000 mL)(0.2g/mL) of lipid in 1,000 mL Pharmacy Bulk Package

4 CONTRAINDICATIONS

The use of CLINOLIPID is contraindicated in patients with the following:

- Known hypersensitivity to egg, soybean, peanut or to any of the active or inactive ingredients in CLINOLIPID [see *Warnings and Precautions (5.3)*].
- Severe disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglyceride >1,000 mg/dL) [see *Warnings and Precautions (5.7)*].

5 WARNINGS AND PRECAUTIONS

5.1 Clinical Decompensation with Rapid Infusion of Intravenous Lipid Emulsion in Neonates and Infants

In the postmarketing setting, serious adverse reactions including acute respiratory distress, metabolic acidosis, and death have been reported in neonates and infants after rapid infusion of intravenous lipid emulsions. Hypertriglyceridemia was commonly reported.

Strictly adhere to the recommended total daily dosage; the hourly infusion rate should not exceed 0.75 mL/kg/hour [see *Dosage and Administration (2.4)*].

Preterm and small for gestational age infants have poor clearance of intravenous lipid emulsion and increased free fatty acid plasma levels following lipid emulsion infusion. The risk due to poor lipid clearance should be considered when administering intravenous lipid emulsions.

Carefully monitor the infant's ability to eliminate the infused lipids from the circulation (e.g., measure serum triglycerides and/or plasma free fatty acid levels). If signs of poor clearance of lipids from the circulation occur, stop the infusion and initiate a medical evaluation [see *Warnings and Precautions (5.5, 5.7) and Overdosage (10)*].

5.2 Parenteral Nutrition-Associated Liver Disease and Other Hepatobiliary Disorders

Risk of Parenteral Nutrition-Associated Liver Disease

Parenteral nutrition-associated liver disease (PNALD), also referred to as intestinal failure-associated liver disease (IFALD), can present as cholestasis or hepatic steatosis, and may progress to steatohepatitis with fibrosis and cirrhosis (possibly leading to chronic hepatic failure). The etiology of PNALD is multifactorial; however, intravenously administered phytosterols (plant sterols) contained in plant-derived lipid emulsions, including CLINOLIPID, have been associated with development of PNALD.

Monitor liver tests in patients treated with CLINOLIPID and consider discontinuation or dosage reduction if abnormalities occur.

Other Hepatobiliary Disorders

Hepatobiliary disorders including cholecystitis and cholelithiasis have developed in some PN-treated patients without preexisting liver disease.

Monitor liver tests when administering CLINOLIPID. Patients developing signs of hepatobiliary disorders should be assessed early to determine whether these conditions are related to CLINOLIPID use.

5.3 Hypersensitivity Reactions

CLINOLIPID contains soybean oil and egg phospholipids, which may cause hypersensitivity reactions. Cross reactions have been observed between soybean and peanut. CLINOLIPID is contraindicated in patients with known hypersensitivity to egg, soybean, peanut, or any of the active or inactive ingredients in CLINOLIPID. If a hypersensitivity reaction occurs, stop infusion of CLINOLIPID immediately and initiate appropriate treatment and supportive measures.

5.4 Infections

Lipid emulsions, such as CLINOLIPID, can support microbial growth and are an independent risk factor for the development of catheter-related bloodstream infections. To decrease the risk of infectious complications, ensure aseptic techniques are used for catheter placement, catheter maintenance, and preparation and administration of CLINOLIPID.

Monitor for signs and symptoms of infection including fever and chills, as well as laboratory test results that might indicate infection (including leukocytosis and hyperglycemia). Perform frequent checks of the intravenous catheter insertion site for edema, redness, and discharge.

5.5 Fat Overload Syndrome

Fat overload syndrome is a rare condition that has been reported with intravenous lipid formulations and is characterized by a sudden deterioration in the patient's condition (e.g., fever, anemia, leukopenia, thrombocytopenia, coagulation disorders, hyperlipidemia, hepatomegaly, deteriorating liver function, and central nervous system manifestations such as coma). A reduced or limited ability to metabolize lipids, accompanied by prolonged plasma clearance (resulting in higher lipid levels), may result in this syndrome. Although fat overload syndrome has been most frequently observed when the recommended lipid dose or infusion rate was exceeded, cases have also been described when the lipid formulation was administered according to instructions.

If signs or symptoms of fat overload syndrome occur, stop CLINOLIPID. The syndrome is usually reversible when the infusion of the lipid emulsion is stopped.

5.6 Refeeding Syndrome

Administering PN to severely undernourished patients may result in the refeeding syndrome, which is characterized by intracellular shift of potassium, phosphorus, and magnesium as the patients become anabolic. Thiamine deficiency and fluid retention may also develop. To prevent these complications, closely monitor severely malnourished patients and slowly increase their nutrient intake.

5.7 Hypertriglyceridemia

The use of CLINOLIPID is contraindicated in patients with hypertriglyceridemia with serum triglyceride concentrations >1,000 mg/dL.

Patients with conditions such as inherited lipid disorders, obesity, diabetes mellitus, or metabolic syndromes have a higher risk of developing hypertriglyceridemia with the use of CLINOLIPID. In addition, patients with hypertriglyceridemia may have worsening of their hypertriglyceridemia with administration of CLINOLIPID. Excessive dextrose administration may further increase such risk.

Evaluate patients' capacity to metabolize and eliminate the infused lipid emulsion by measuring serum triglycerides before the start of infusion (baseline value) and regularly throughout treatment. If triglyceride levels are above 400 mg/dL in adults, stop the CLINOLIPID infusion and monitor serum triglyceride levels to avoid clinical consequences of hypertriglyceridemia such as pancreatitis.

To minimize the risk of new or worsening of hypertriglyceridemia, assess high-risk patients for their overall energy intake including other sources of lipids and dextrose, as well as concomitant drugs that may affect lipid and dextrose metabolism.

5.8 Aluminum Toxicity

CLINOLIPID contains no more than 25 mcg/L of aluminum.

The aluminum contained in CLINOLIPID may reach toxic levels with prolonged administration in patients with impaired kidney function. Preterm infants are at greater risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions that contain aluminum. Patients with impaired kidney function, including preterm infants, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day, accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration of total parenteral nutrition products.

5.9 Essential Fatty Acid Deficiency

In pediatric trials, EFAD was defined by calculating the Holman index (the triene [Mead acid] to tetraene [arachidonic acid] ratio; T:T ratio > 0.4). One patient treated with CLINOLIPID became at risk for EFAD (T:T ratio >0.2) after 14 days of treatment. No cases of biochemical EFAD and no cases of clinical EFAD were observed; however, the median treatment duration in three of the four pediatric trials was 15 days or less. There are insufficient data to determine whether CLINOLIPID can supply adequate amounts of essential fatty acids in patients who may need treatment for more than 15 days.

Monitor patients for laboratory evidence (e.g., abnormal fatty acid levels) and clinical symptoms of (EFAD) (e.g., skin manifestations, poor growth). Laboratory testing using the triene to tetraene ratio may not be adequate to diagnose EFAD, and assessment of individual fatty acid levels may be needed. Ensure patients are receiving recommended dosages of CLINOLIPID to prevent EFAD [*see Dosage and Administration (2.4) and Description (11)*].

5.10 Monitoring/Laboratory Tests

Routine Monitoring

Monitor fluid status closely in patients with pulmonary edema or heart failure.

Throughout treatment, monitor serum triglycerides [*see Warnings and Precautions (5.7)*], fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, blood count (including platelets), and coagulation parameters.

The lipids contained in CLINOLIPID may interfere with the results of some laboratory tests (e.g., hemoglobin, lactate dehydrogenase, bilirubin, oxygen saturation) if the blood is sampled before the lipids have cleared from the bloodstream. Conduct these tests at least 6 hours after stopping the infusion.

CLINOLIPID 20% contains Vitamin K that may counteract anticoagulant activity [*see Drug Interactions (7)*].

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Clinical Decompensation with Rapid Infusion of Intravenous Lipid Emulsion in Neonates and Infants [*see Warnings and Precautions (5.1)*]
- Parenteral Nutrition-Associated Liver Disease and Other Hepatobiliary Disorders [*see Warnings and Precautions (5.2)*]
- Hypersensitivity reactions [*see Warnings and Precautions (5.3)*]
- Infections [*see Warnings and Precautions (5.4)*]
- Fat overload syndrome [*see Warnings and Precautions (5.5)*]
- Refeeding syndrome [*see Warnings and Precautions (5.6)*]
- Hypertriglyceridemia [*see Warnings and Precautions (5.7)*]
- Aluminum toxicity [*see Warnings and Precautions (5.8)*]
- Essential Fatty Acid Deficiency [*see Warnings and Precautions (5.9)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The CLINOLIPID trials had small sample sizes and patients had a variety of underlying medical conditions both between different trials and within the individual trials. Patients had gastrointestinal diseases/dysfunction or were recovering from gastrointestinal or other surgeries, trauma, burns, or were afflicted by other chronic illness.

Adult Trials

Commonly observed adverse reactions in 261 adult patients who received CLINOLIPID were nausea and vomiting, hyperlipidemia, hyperglycemia, hypoproteinemia, and abnormal liver function tests and occurred in 2 to 10 % of patients.

The largest clinical trial in adult patients (Study 1) enrolled 48 subjects with different underlying diagnoses. Study 2 was a randomized, open label multicenter study that enrolled 22 subjects, aged 32-81 years, who required long-term parenteral nutrition.

The most common adverse reactions in Study 1 and Study 2 were infectious complications (urinary tract infection, septicemia, and fever of unknown origin), treatment emergent abnormalities on liver/gallbladder ultrasound and abnormalities of serum chemistries, principally, hepatic function tests.

Adverse reactions reported with other intravenous lipid emulsions include hyperlipidemia, hypercoagulability, thrombophlebitis, and thrombocytopenia.

Adverse reactions reported in long-term use with other intravenous lipid emulsions include hepatomegaly, jaundice due to central lobular cholestasis, splenomegaly, thrombocytopenia, leukopenia, abnormalities in liver function tests, brown pigmentation of the liver and overloading syndrome (focal seizures, fever, leukocytosis, hepatomegaly, splenomegaly, and shock).

Pediatric Trials

The safety of CLINOLIPID in pediatric patients was evaluated in Studies 3, 4, 5, and 6 [see *Clinical Studies (14.2)*].

In Study 3, EFAD was defined by calculating the Holman index (the triene [Mead acid] to tetraene [arachidonic acid] ratio; T:T ratio > 0.4). Although no patient developed EFAD, one CLINOLIPID-treated patient who had a T:T ratio that increased from < 0.2 at baseline to > 0.2 at end of study treatment was considered at risk for EFAD. This patient's arachidonic and linoleic acid levels remained within the normal range. No soybean oil lipid emulsion-treated patients had a T:T ratio \geq 0.2.

In Studies 3, 4, 5, and 6, adverse reactions occurred at similar rates in subjects treated with CLINOLIPID and the 100% soybean oil comparator. Adverse reactions that occurred in \geq 5% of patients included hyperbilirubinemia, patent ductus arteriosus, anemia, gastroesophageal reflux disease, bradycardia, feeding intolerance, neonatal intraventricular hemorrhage, increased alkaline phosphatase, atrial septal defect, hyponatremia, sepsis, and infantile apnea.

6.2 Postmarketing Experience

The following adverse reactions have been identified during use of CLINOLIPID. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: Diarrhea

Skin and Subcutaneous Tissue Disorders: Pruritus

Immune System Disorders: Hypersensitivity with the manifestations of rash and dyspnea

Investigations: International normalized ratio (INR) decreased in anticoagulated patients [*see Drug Interactions (7)*]

Hepatobiliary disorders: cholestasis

7 DRUG INTERACTIONS

No drug interaction studies have been performed with CLINOLIPID.

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Administration of the recommended dose of CLINOLIPID is not expected to cause major defects, miscarriage, or other adverse maternal or fetal outcomes. No animal reproduction studies have been conducted with lipid injectable emulsion. There are clinical considerations if CLINOLIPID is used in pregnant women [*see Clinical Considerations*].

The estimated background risk of major birth defects and miscarriage for the indicated population are unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk:

Severe malnutrition in a pregnant woman is associated with preterm delivery, low birth weight, intrauterine growth restriction, congenital malformations and perinatal mortality. Parenteral nutrition should be considered if a pregnant woman's nutritional requirements cannot be fulfilled by oral or enteral intake. It is not known whether the administration of CLINOLIPID to pregnant women provides adequate essential fatty acids to the developing fetus.

8.2 Lactation

Risk Summary

There are no data available to assess the presence of CLINOLIPID and/or its active metabolite(s) in human milk, the effects on the breastfed child or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CLINOLIPID and any potential adverse effects on the breastfed child from CLINOLIPID or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of CLINOLIPID have been established as a source of calories and essential fatty acids for PN in pediatric patients, including term and preterm neonates, when oral or enteral nutrition is not possible, insufficient, or contraindicated. Use of CLINOLIPID in pediatric patients is supported by evidence from four studies that enrolled pediatric patients, including preterm and term neonates, and additional evidence from clinical studies in adults. Use of CLINOLIPID in older pediatric patients is supported by evidence from two studies in pediatric patients up to 9 years of age treated for a median of 15 and 56 days, respectively, with additional evidence from clinical studies in adults [see Clinical Studies (14.2)]. No clinically significant cases of EFAD were observed in short term pediatric clinical studies. However, one premature neonate in study 3 became at risk for EFAD after 14 days of treatment based on a Holman Index increase above 0.2. This patient's arachidonic and linoleic acid levels remained within the normal range [see Adverse Reactions (6.1)]. Monitor pediatric patients for laboratory evidence of EFAD, including fatty acid profile (i.e., arachidonic acid) because they may be particularly vulnerable to neurologic complications if adequate amounts of essential fatty acids are not provided [see Warnings and Precautions (5.9)].

In the postmarketing setting, clinical decompensation with rapid infusion of intravenous lipid emulsion in neonates and infants, sometimes fatal, has been reported [see Warnings and Precautions (5.1)]. Because of immature renal function, preterm infants receiving prolonged treatment with CLINOLIPID may be at risk for aluminum toxicity [see Warnings and Precautions(5.8)].

8.5 Geriatric Use

Of the total number of subjects in clinical studies of CLINOLIPID, 21% were 65 and over, while 10% were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

In the event of overdose, serious adverse reactions may result [see Warnings and Precautions (5.1, 5.5)]. Stop the infusion to allow lipids to clear from serum. The effects are usually reversible after the lipid infusion is stopped. If medically appropriate, further intervention may be indicated. The lipid administered and fatty acids produced are not dialyzable.

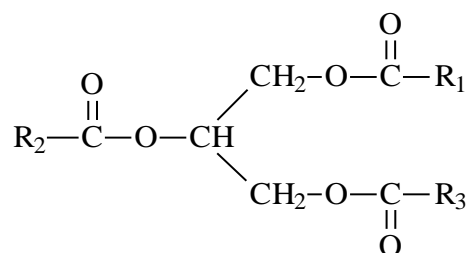
11 DESCRIPTION

CLINOLIPID lipid injectable emulsion, USP is a sterile, non-pyrogenic, homogenous, white, milky lipid emulsion for intravenous infusion. The lipid content of CLINOLIPID is 0.2 g/mL and comprises a mixture of refined olive oil and refined soybean oil in an approximate ratio of 4:1 (olive:soy). The mean concentration of linoleic acid (an omega-6 essential fatty acid) is 35.8 mg/mL (range 27.6 to 44.0 mg/mL) and α -linolenic acid (an omega-3 essential fatty acid) is 4.7 mg/mL (range 1.0 to 8.4 mg/mL). The phospholipids provide 470 milligrams or 15 mmol of phosphorus per liter.

The total energy content, including fat, phospholipids and glycerin is 2000 kcal/L.

Each 100 mL of CLINOLIPID 20% contains approximately 16 g of Olive Oil NF and 4 g of Soybean Oil USP, 1.2 g Egg Phospholipids NF, 2.25 g Glycerin USP, 0.03 g Sodium Oleate, and Water for Injection USP. Sodium Hydroxide NF for pH adjustment, pH: 6.0 to 9.0.

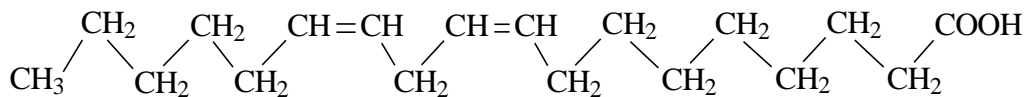
The olive and soybean oils are refined natural products consisting of a mixture of neutral triglycerides of predominantly unsaturated fatty acids with the following structure:



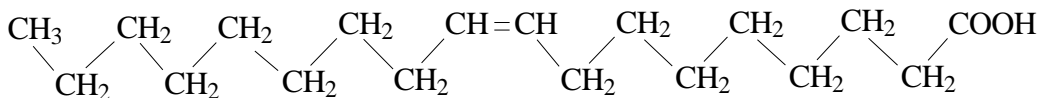
Where $\overset{\text{O}}{\parallel}\text{R}_1\text{CO}-$, $\overset{\text{O}}{\parallel}\text{R}_2\text{CO}-$, and $\overset{\text{O}}{\parallel}\text{R}_3\text{CO}-$ are the saturated and unsaturated fatty residues.

The major component fatty acids are linoleic (13.8 to 22.0%), oleic (44.3 to 79.5%), palmitic (7.6 to 19.3%), linolenic (0.5 to 4.2%), palmitoleic (0.0 to 3.2%) and stearic (0.7 to 5.0%). These fatty acids have the following chemical and structural formulas:

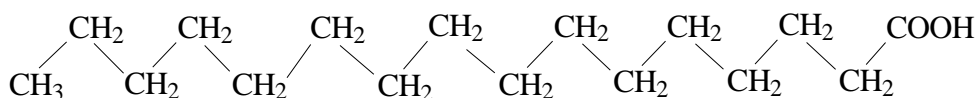
Linoleic acid
C₁₈H₃₂O₂



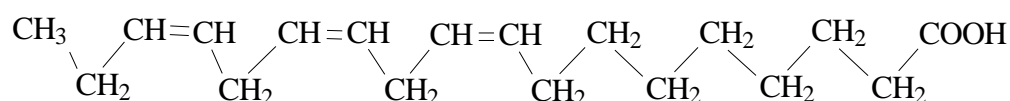
Oleic acid
C₁₈H₃₄O₂



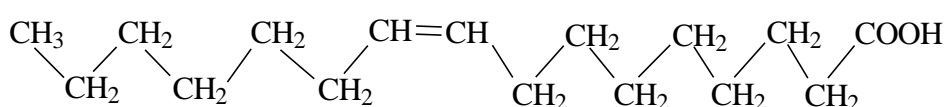
Palmitic acid
C₁₆H₃₂O₂



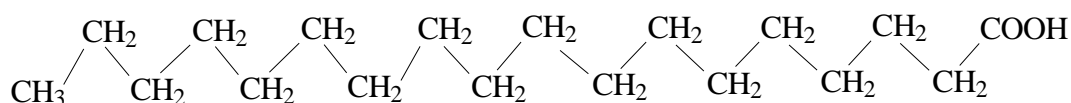
Linolenic acid
C₁₈H₃₀O₂



Palmitoleic acid
C₁₆H₃₀O₂



Stearic acid
C₁₈H₃₆O₂



CLINOLIPID has an osmolality of approximately 340 mOsmol/kg water (which represents an osmolarity of 260 mOsmol/liter of emulsion).

CLINOLIPID contains no more than 25 mcg/L of aluminum.

12 CLINICAL PHARMACOLOGY

CLINOLIPID administered intravenously provides biologically utilizable source of calories and essential fatty acids.

12.1 Mechanism of Action

Fatty acids serve as an important substrate for energy production. The most common mechanism of action for energy production derived from fatty acid metabolism is beta oxidation. Fatty acids are important for membrane structure and function, precursors for bioactive molecules (such as prostaglandins), and as regulators of gene expression.

12.2 Pharmacodynamics

Infused essential fatty acids are synthesized into higher derivative fatty acids. Olive oil contains significant amounts of alpha-tocopherol that contributes to Vitamin E status.

12.3 Pharmacokinetics

Metabolism and Excretion

The fatty acids, phospholipids, and glycerol found in lipid emulsions are metabolized by cells to carbon dioxide and water. The metabolism of these substances results in the generation of energy in the form of adenosine triphosphate (ATP). Some fatty acids are stored in the body in fat tissue, cell membranes, or as intracellular triglycerides. There is constant turn-over of these tissues, with the result that the lipid components are eventually metabolized to carbon dioxide and water. Carbon dioxide is expired through the lungs. Water is excreted through the kidneys or lost through evaporation/expiration through the skin, lungs, and other tissue surfaces. Some lipids (i.e., phospholipids, cholesterol, and bile acids) are excreted through the biliary system.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies with CLINOLIPID have not been performed to evaluate the carcinogenic potential, mutagenic potential, or effects on fertility.

13.2 Animal Toxicology and/or Pharmacology

CLINOLIPID was evaluated in toxicity studies conducted in rats and dogs for up to 3 months. The principal signs of toxicity noted in the 3-month studies were:

- Slight hemolytic anemia at 12 g/kg/day in rats and at 6 g/kg/day in dogs. These doses in rats and dogs are 4 and 2 times higher, respectively, than the maximum recommended pediatric dose (3 g/kg/day) of CLINOLIPID.
- Dose-dependent decrease in urea levels in rats at 6 and 12 g/kg/day dose levels and in dogs at 3, 4.5 and 6 g/kg/day dose levels associated with decreased feed consumption.
- Hypercholesterolemia in dogs at 3, 4.5 and 6 g/kg/day dose levels.
- Hepatic pathology of lipid and pigmentary overload in male and female rats at 3, 6 and 12 g/kg/day dose levels and brownish-yellow pigmentation in vacuolated Kupffer cells in male and female dogs at 3, 4.5 and 6 g/kg/day dose levels with hepatocyte vacuolation in male dogs at 6 g/kg/day and female dogs at 4.5 and 6 g/kg/day dose levels.
- Splenic pigmentation and vacuolization in rats at 3, 6 and 12 g/kg/day dose levels, and dogs in 4.5 and 6 g/kg/day dose levels.

At doses of 3 g/kg/day, slight lipid and pigmentary overload of the liver and vacuolization of Kupffer cells were observed in rats and dogs. At a dose of 12 g/kg/day in rats, hepatocellular vacuolation, granulomatous inflammation of the liver, hepatocellular necrosis and hemosiderosis of the liver and lipid deposits and splenic hemosiderosis, were observed. In dogs, at a dose of 6 g/kg/day, brownish-yellow pigmentation in the

Kupffer cells of liver and spleen, hyperplasia of vacuolated Kupffer cells, hepatocyte vacuolization, a slight increase in the number of lipid storage cells (Ito cells) in the liver and macrophage vacuolization of the spleen were observed.

14 CLINICAL STUDIES

14.1 Adult Clinical Studies

Two clinical trials (Study 1 and Study 2) in adults compared CLINOLIPID to a soybean oil-based intravenous lipid emulsion. Although Study 1 and Study 2 were not adequately designed to demonstrate noninferiority of CLINOLIPID to the soybean oil comparator, they support CLINOLIPID as a source of calories and essential fatty acids in adults. The lipid dosage was variable in Studies 1 and 2 and adjusted to the patient's nutritional requirements.

Study 1 was a randomized, open-label, multicenter study. Forty-eight patients, aged 17 to 75 years, requiring total parenteral nutrition (TPN) for ≥ 15 days (mean 22 days) were enrolled and randomized to either CLINOLIPID or a soybean oil-based intravenous lipid emulsion. Nutritional efficacy was assessed by anthropometric indices (body weight, arm circumference, skin-fold thickness), biomarkers of protein metabolism (total protein, albumin) and lipid metabolism. Anthropometric criteria (body weight, arm circumference, and skin fold thickness) were comparable for both groups. Mean total serum protein and albumin increased similarly in both groups.

Study 2 was a randomized, open label multicenter study that enrolled 22 patients aged 32-81 years who required long-term parenteral nutrition. Twelve patients received CLINOLIPID for a mean of 202 days (range 24 to 408 days) and 10 patients received the comparator lipid for a mean of 145 days (range 29-394 days). The two groups had similar outcomes for weight, weight loss, mid-arm circumference and triceps skinfold thickness.

14.2 Pediatric Clinical Studies

The efficacy of CLINOLIPID compared to soybean oil-based lipid emulsions was evaluated in 179 pediatric patients in four randomized, active-controlled, parallel-group clinical studies. Three studies (161 patients) were double-blinded. Although the four pediatric clinical studies were not adequately designed to demonstrate the noninferiority of CLINOLIPID to the soybean oil comparator, they support CLINOLIPID as a source of calories and essential fatty acids in pediatric patients, including term and preterm neonates. The 179 pediatric patients (89 treated with CLINOLIPID; 90 with comparator) consisted of 140 patients who were less than 1 month of age, 23 patients one month to less than two years old, and 16 patients two to less than 18 years old. Nutritional efficacy in pediatric patients, including preterm infants, was assessed by evaluating growth parameters, protein biomarkers, changes in triglyceride and cholesterol concentrations, and fatty acid parameters.

Study 3 (NCT 04555044) randomized 102 patients (101 analyzed) to receive either CLINOLIPID (n = 50) or a soybean oil-based lipid emulsion (n = 51) as part of PN in the hospital setting. Baseline characteristics and outcomes during the study were similar in the two groups. The majority of study patients (n=94, 93%) were preterm neonates born at less than 37 weeks of gestation. The median age at enrollment in this study

was day one of life and the median gestational age of neonates was 29 weeks. Eighty-five patients (84%) were very low birth weight, including 53 patients (52%) with a birth weight of 1000-1499 grams and 32 patients (32%) with a birthweight of less than 1000 g. Forty-one patients (41%) were Black, 42 (42%) were White, and 8 (8%) were Hispanic or Latino.

In both study groups, the mean daily dose administered was approximately 2.3 g/kg/day (SD 0.8 g/kg/day), and the median duration of treatment was 8 days (range: 3 – 60 days; interquartile range [IQR]: 8 – 10 days). The primary endpoint was at risk of developing EFAD, defined as triene:tetraene (T:T) ratio >0.4, which did not occur during the study in either treatment group. Secondary endpoints included incidence of parenteral nutrition-associated cholestasis (PNAC) defined as direct bilirubin \geq 2 mg/dL with no other etiology identified. One patient in the CLINOLIPID group (2%) and two patients in the comparator group (3.9%) developed PNAC during the study. Median increases in body weight, length/height, and head circumference were similar between CLINOLIPID and the soybean oil comparator group.

Study 4 randomized 45 preterm neonates of which 42 were treated and analyzed for safety, 33 (n=18 on CLINOLIPID and n=15 on soybean oil lipid emulsion) completed the 7-day treatment period and were analyzed for efficacy. The study evaluated weight, fatty acid profiles, triglyceride and cholesterol levels, and protein biomarkers. Two (6%) of patients had birth weight less than 1000 grams and 14 patients (42%) weighed between 1000 and 1500 grams at birth. The mean (range) daily dose of Clinolipid was 1.5 g/kg/day (0.7 – 1.7), and median (range) treatment duration period was 7 (2 – 7) days. Complete blood counts, total bilirubin, cholesterol, triglycerides, and weight of CLINOLIPID-treated patients were similar to those treated with soybean oil lipid emulsion.

Study 5 randomized 18 pediatric patients (16 analyzed) between two and 57 months of age (median 6.3 months) who were treated with either CLINOLIPID (n = 7) or soybean oil lipid emulsion (n = 9). In both groups, the mean (SD) daily dose of lipid emulsion was 2.9 (0.4) g/kg/day and median treatment duration was 15 days (range: 1 – 29 days, IQR: 15 – 17 days). There were no meaningful differences between the groups at day 15 in weight gain, complete blood count, total bilirubin, total protein, cholesterol, or triglycerides. No patient in the study had evidence of biochemical EFAD (T:T ratio >0.4).

Study 6 evaluated the long-term safety and efficacy of CLINOLIPID in 18 pediatric patients between one and nine years of age (median, 2.5 years) who had been treated with 50% medium-chain triglycerides/50% soybean oil lipid emulsion for 30 days, and were randomized to either CLINOLIPID (n = 9) or a soybean oil lipid emulsion (n = 9) three to five days per week. Patients had received PN for a mean of 34 months prior to study entry and treatment groups had comparable fatty acid profiles, lipids, albumin, total bilirubin, and parenteral nutrition intake during the run-in period. The average daily lipid dose in the treatment period was 1.9 g/kg/day (range: 1.4 – 3 g/kg/day) in CLINOLIPID group and 1.7 g/kg/day (range: 0.9 – 2.3 g/kg/day) for the soybean oil group. The median treatment duration for CLINOLIPID was 56 days (range: 56 – 63 days; IQR: 56 – 61 days). There were no meaningful differences between treatment groups in height, weight, and albumin levels. No patient in the study had evidence of biochemical EFAD (T:T ratio > 0.4).

16 HOW SUPPLIED/STORAGE AND HANDLING

CLINOLIPID is a sterile, white, milky homogenous lipid injectable emulsion supplied in CLARITY polyolefin Flexible Containers as follows:

Strengths	Container Size	Product Code	NDC Number (1 Bag)	NDC Number (Shelf Pack)
20% (20 g/100 mL) (0.2 g/mL)	100 mL	EADB9520	0338-9540-01 (single-dose Flexible Container)	0338-9540-05 (15 pack)
20% (50 g/250 mL) (0.2 g/mL)	250 mL	EADB9521	0338-9540-02 (single-dose Flexible Container)	0338-9540-06 (10 pack)
20% (100 g/500 mL) (0.2 g/mL)	500 mL	EADB9523	0338-9540-03 (single-dose Flexible Container)	0338-9540-07 (12 pack)
20% (200 g/1,000 mL) (0.2 g/mL)	1,000 mL	EADB9524	0338-9540-04 (Pharmacy Bulk Package bag)	0338-9540-08 (6 pack)

The CLARITY Container is a lipid-compatible plastic container (PL 2401-1). The bag is packaged in an oxygen barrier overpouch, which contains an oxygen absorber / oxygen indicator sachet.

CLINOLIPID should be stored at 20°C to 25°C (68°F to 77°F). Excursion permitted between 15°C to 30 °C (59°F to 86°F). See USP Controlled Room Temperature. Protect from freezing. Avoid excessive heat. Store in overpouch until ready to use.

CLINOLIPID 100 mL, 250 mL and 500 mL single-dose Flexible Containers:

After removing the overpouch, infuse immediately. If not used immediately, the product should be stored for no longer than 24 hours at not more than 25°C (77°F) [*See Dosage and Administration (2.2)*].

CLINOLIPID 1,000 mL Pharmacy Bulk Package:

Use the pharmacy bulk package immediately for admixing after removal from overpouch. If not used immediately, the product should be stored for no longer than 24 hours at not more than 25°C (77°F) [*see Dosage and Administration (2.2)*].

17 PATIENT COUNSELING INFORMATION

When initiating CLINOLIPID administration, discuss the following information with the patient or caregiver:

Parenteral Nutrition-Associated Liver Disease and Other Hepatobiliary Disorders

Inform patients and caregivers that use of parenteral nutrition may result in parenteral nutrition-associated liver disease and/or other hepatobiliary disorders [*see Warnings and Precautions (5.2)*].

Hypersensitivity Reactions

Inform patients and caregivers that CLINOLIPID may cause hypersensitivity reactions. If CLINOLIPID is infused at home, instruct patients or caregivers to stop the infusion of CLINOLIPID immediately and seek medical attention if a hypersensitivity reaction occurs [*see Warnings and Precautions (5.3)*].

Infections

Inform patients and caregivers that patients who receive CLINOLIPID are at risk of infection. If CLINOLIPID is infused at home, instruct patients or caregivers to ensure aseptic techniques are used for the preparation and administration of CLINOLIPID and to monitor for signs and symptoms of infection [*see Warnings and Precautions (5.4)*].

Fat Overload Syndrome

Inform patients and caregivers that fat overload syndrome has been reported with the use of intravenous lipid emulsions. If CLINOLIPID is infused at home, instruct patients or caregivers to stop CLINOLIPID if signs or symptoms of fat overload syndrome occur [*see Warnings and Precautions (5.5)*].

Refeeding Syndrome

If the patient is severely malnourished, inform patients and caregivers that administering parenteral nutrition including CLINOLIPID may result in refeeding syndrome [*see Warnings and Precautions (5.6)*].

Hypertriglyceridemia

Inform patients and caregivers about the risks of hypertriglyceridemia with CLINOLIPID use [*see Warnings and Precautions (5.7)*].

Aluminum Toxicity

Inform patients and caregivers that prolonged PN administration in patients with renal impairment, including preterm neonates, may result in aluminum reaching toxic levels associated with central nervous system and bone toxicity [*see Warnings and Precautions (5.8)*].

Preparation and Administration Instructions

If it is acceptable for a patient or caregiver to administer CLINOLIPID at home, then provide recommendations on how to prepare, add compatible additives (when appropriate), administer, and store CLINOLIPID [*see Dosage and Administration (2.1, 2.2)*].

Baxter Healthcare Corporation

Deerfield, IL 60015 USA

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