

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204508Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

CLINOLIPID (Lipid Injectable Emulsion) for intravenous use
Initial U.S. Approval: 1975

WARNING: DEATH IN PRETERM INFANTS

See full prescribing information for complete boxed warning

- Deaths in preterm infants have been reported in literature. (5.1, 8.4)
- Autopsy findings included intravascular fat accumulation in the lungs. (5.1, 8.4)
- Preterm and low birth weight infants have poor clearance of intravenous lipid emulsion and increased free fatty acid plasma levels following lipid emulsion infusion. (5.1, 8.4)

INDICATIONS AND USAGE

CLINOLIPID injection is a lipid emulsion indicated in adults for parenteral nutrition providing a source of calories and essential fatty acids when oral or enteral nutrition is not possible, insufficient, or contraindicated. (1)

DOSAGE AND ADMINISTRATION

CLINOLIPID injection is intended for intravenous infusion. The recommended dose depends on energy expenditure, clinical status, body weight, tolerance, ability to metabolize and consideration of additional energy given to the patient. The usual daily lipid dosage in adults is 1 to 1.5 g/kg/day and should not exceed 2.5 g/kg/day. (2)

DOSAGE FORMS AND STRENGTHS

CLINOLIPID 20% is a lipid injectable emulsion for intravenous infusion. The lipid content is 0.20 g/mL. (3)

CONTRAINDICATIONS

- Known hypersensitivity to egg and soybean proteins, the lipid emulsion and/or excipients. (4)
- Severe hyperlipidemia or severe disorders of lipid metabolism. (4)

WARNINGS AND PRECAUTIONS

- Preterm infants have poor clearance of intravenous lipid emulsion. (5.1)
- Monitor for signs or symptoms of hypersensitivity reactions. (5.2)
- Monitor for signs and symptoms of infection, fat overload, and refeeding complications. (5.3, 5.4, 5.5)
- Frequent clinical and laboratory determinations are necessary. (5.6)

ADVERSE REACTIONS

The most common (5%) adverse drug reactions from clinical trials were nausea and vomiting, hyperlipidemia, hyperglycemia, hypoproteinemia and abnormal liver function tests. (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)

USE IN SPECIFIC POPULATIONS

- Hepatic Impaired: Use with caution in patients with preexisting liver disease or liver insufficiency. (8.5)

See 17 for PATIENT COUNSELING INFORMATION

Revised: October 2013

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66 **FULL PRESCRIBING INFORMATION**

67
68 **WARNING: DEATH IN PRETERM INFANTS**

69
70 **Deaths in preterm infants after infusion of intravenous lipid emulsions have been reported in the**
71 **medical literature.**

72 **Autopsy findings included intravascular fat accumulation in the lungs.**

73 **Preterm infants and low birth weight infants have poor clearance of intravenous lipid emulsion and**
74 **increased free fatty acid plasma levels following lipid emulsion infusion.**

75 *[See Warnings and Precautions (5.1) and Use in Specific Populations (8.4)]*

76 **1 INDICATIONS AND USAGE**

77 CLINOLIPID injection is indicated in adults for providing a source of calories and essential fatty acids for
78 parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.

79 Limitations of Use

80 CLINOLIPID injection is not indicated for use in pediatric patients because there is insufficient data to
81 demonstrate that CLINOLIPID injection provides sufficient amounts of essential fatty acids in this
82 population. *[See Use in Specific Populations (8.4)]*

83 The omega-3: omega-6 fatty acid ratio in CLINOLIPID injection has not been shown to improve clinical
84 outcomes compared to other intravenous lipid emulsions. *[See Clinical Studies (14)]*

85 **2 DOSAGE AND ADMINISTRATION**

86 **2.1 Use of an Inline Filter**

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

93 **2.2 Important Administration Instructions**

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

98 After opening the bag, use the contents immediately and do not store for a subsequent infusion.

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

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

103 Air embolism can result if residual gas in the bag is not fully evacuated prior to administration if the flexible
104 bag is pressurized to increase flow rates.

105 Use of a vented intravenous administration set with the vent in the open position could result in air
106 embolism.

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

110 When infused alone, CLINOLIPID injection can be administered via central or peripheral vein. When
111 administered with dextrose and amino acids, the choice of a central or peripheral venous route should
112 depending on the osmolarity of the final infusate.

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

114 **2.3 Mixing Guidelines**

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

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

118 Do not use the EXACTAMIX Inlet H938173 with an EXACTAMIX compounder to transfer CLINOLIPID
119 injection. This inlet spike has been associated with dislodgement of the administration port membrane into
120 the CLINOLIPID injection bag.

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

- 123 1. Transfer Dextrose Injection to the Total Parenteral Nutrition Admixture Container
- 124 2. Transfer Amino Acid Injection
- 125 3. Transfer Lipid Emulsion
- 126

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

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

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

137 **2.4 Dosing Considerations**

138 The dosing of CLINOLIPID injection depends on energy expenditure, the patient's clinical status, body
139 weight, tolerance, and ability to metabolize CLINOLIPID injection, as well as additional energy given
140 orally/enterally to the patient. For complete parenteral nutrition, concomitant supplementation with amino
141 acids, carbohydrates, electrolytes, vitamins, and trace elements is necessary.

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

147 Adjust the administration flow rate by taking into account the dose being administered, the daily volume
148 intake, and the duration of the infusion [*see Overdosage (10)*].

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

152 The maximum daily dose of CLINOLIPID injection should be based on individual total nutritional
153 requirements and patient tolerance. The usual lipid dosage is 1 to 1.5 g/kg/day (equal to 5 to 7.5 mL/kg/day
154 of CLINOLIPID 20%)¹. The daily dose should not exceed 2.5 g/kg/day. The initial infusion rate should not
155 exceed 0.1 g (equal to 0.5 mL) per minute for the first 15 to 30 minutes. If tolerated, gradually increase
156 until reaching the required rate after 30 minutes.

157 **3 DOSAGE FORMS AND STRENGTHS**

158 CLINOLIPID injection is a lipid emulsion for intravenous infusion. The lipid content is 0.20 g/mL.

159 **4 CONTRAINDICATIONS**

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

- 161 • Known hypersensitivity to egg or soybean proteins or to any of the ingredients, including excipients.
- 162 • Severe hyperlipidemia (serum triglyceride concentrations above 1000 mg/dL) or severe disorders of
163 lipid metabolism characterized by hypertriglyceridemia.

164 **5 WARNINGS AND PRECAUTIONS**

165 **5.1 Death in Preterm Infants**

166 Deaths in preterm infants after infusion of intravenous lipid emulsions have been reported. Autopsy findings
167 included intravascular lipid accumulation in the lungs.

168 Preterm and small for gestational age infants have poor clearance of intravenous lipid emulsion and
169 increased free fatty acid plasma levels following lipid emulsion infusion.

170 The safe and effective use of CLINOLIPID injection in pediatric patients, including preterm infants, has not
171 been established. CLINOLIPID injection is not indicated for and not recommended for use in pediatric
172 patients.

173 **5.2 Hypersensitivity Reactions**

174 Stop infusion immediately and treat patient accordingly if signs or symptoms of a hypersensitivity or
175 allergic reaction develop. Signs or symptoms may include: tachypnea, dyspnea, hypoxia, bronchospasm,
176 tachycardia, hypotension, cyanosis, vomiting, nausea, headache, sweating, dizziness, altered mentation,
177 flushing, rash, urticaria, erythema, pyrexia and chills.

178 **5.3 Infections**

179 Patients who require parenteral nutrition are at high risk of infections due to malnutrition and their
180 underlying disease state.

181 Infection and sepsis may occur as a result of the use of intravenous catheters to administer parenteral
182 nutrition, poor maintenance of catheters, or immunosuppressive effects of illness, drugs, and parenteral
183 formulations.

184 Decrease the risk of septic complications with heightened emphasis on aseptic technique in catheter
185 placement and maintenance, as well as aseptic technique in the preparation of the nutritional formula.

186 Carefully monitor for signs and symptoms (including fever and chills) of early infections, including
187 laboratory test results (including leukocytosis and hyperglycemia) and frequent checks of the parenteral
188 access device.

189 **5.4 Fat Overload Syndrome**

190 Fat overload syndrome is a rare condition that has been reported with intravenous lipid formulations. A
191 reduced or limited ability to metabolize the lipids contained in CLINOLIPID injection accompanied by
192 prolonged plasma clearance may result in a syndrome characterized by a sudden deterioration in the
193 patient's condition accompanied by fever, anemia, leukopenia, thrombocytopenia, coagulation disorders,
194 hyperlipidemia, liver fatty infiltration (hepatomegaly), deteriorating liver function, and central nervous
195 system manifestations (e.g., coma). The cause of the fat overload syndrome is unclear. The syndrome is
196 usually reversible when the infusion of the lipid emulsion is stopped. Although it has been most frequently

197 observed when the recommended lipid dose was exceeded, cases have also been described where the lipid
198 formulation was administered according to instructions.

199 **5.5 Refeeding Syndrome**

200 Refeeding severely undernourished patients with parenteral nutrition may result in the refeeding syndrome,
201 characterized by the intracellular shift of potassium, phosphorus, and magnesium as the patient becomes
202 anabolic. Thiamine deficiency and fluid retention may also develop. Carefully monitor severely
203 undernourished patients and slowly increase their nutrient intakes, while avoiding overfeeding, to prevent
204 these complications.

205 **5.6 Monitoring/Laboratory Tests**

206 Routine Monitoring

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

208 Monitor serum triglycerides, fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney
209 function, and blood count, including platelets and coagulation parameters, throughout treatment.

210 Essential Fatty Acids

211 Monitoring patients for signs and symptoms of essential fatty acid deficiency (EFAD) is recommended.
212 Laboratory tests are available to determine serum fatty acids levels. Reference values should be consulted
213 to help determine adequacy of essential fatty acid status. Increasing essential fatty acid intake (enterally or
214 parenterally) is effective in treating and preventing EFAD.

215 In CLINOLIPID injection, the mean composition of linoleic acid (an omega-6 essential fatty acid) is 35.8
216 mg/mL (range 27.6 - 44.0 mg/mL) and α -linolenic acid (an omega-3 essential fatty acid) is 4.7 mg/mL
217 (range 1.0 - 8.4 mg/mL). There are insufficient long-term data to determine whether CLINOLIPID 20% can
218 supply essential fatty acids in adequate amounts in patients who may have increased requirements.

219 **5.7 Interference with Laboratory Tests**

220 Content of Vitamin K may counteract anticoagulant activity [*see Drug Interactions (7)*].

221 The lipids contained in this emulsion may interfere with the results of certain laboratory tests if the blood
222 sample is taken before the lipids are eliminated from the serum (these are generally eliminated after a period
223 of 5 to 6 hours without receiving lipids).

224 **5.8 Aluminum Toxicity**

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

226 The aluminum contained in CLINOLIPID injection may reach toxic levels with prolonged administration in
227 patients with impaired kidney function. Preterm infants are at greater risk because their kidneys are
228 immature, and they require large amounts of calcium and phosphate solutions that contain aluminum.

229 Patients with impaired kidney function, including preterm infants, who receive parenteral levels of
230 aluminum at greater than 4 to 5 mcg/kg/day, accumulate aluminum at levels associated with central nervous
231 system and bone toxicity. Tissue loading may occur at even lower rates of administration of total parenteral
232 nutrition products.

233 **5.9 Risk of Parenteral Nutrition Associated Liver Disease**

234 Parenteral Nutrition Associated Liver Disease (PNALD) has been reported in patients who receive
235 parenteral nutrition for extended periods of time, especially preterm infants, and can present as cholestasis
236 or steatohepatitis¹. The exact etiology is unknown and is likely multifactorial. Intravenously administered
237 phytosterols (plant sterols) contained in plant-derived lipid formulations have been associated with
238 development of PNALD although a causal relationship has not been clearly established. If CLINOLIPID
239 injection treated patients develop liver test abnormalities consider discontinuation or dose reduction.

240 **5.10 Hypertriglyceridemia**

241 Reduce dose of CLINOLIPID injection and monitor serum triglyceride levels in patients with serum
242 triglyceride concentrations above 400 mg/dL to avoid the clinical consequences associated with
243 hypertriglyceridemia. Serum triglyceride levels above 1000 mg/dL have been associated with an increased
244 risk of pancreatitis.

245 **6 ADVERSE REACTIONS**

246 **6.1 Clinical Trials Experience**

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

250 The CLINOLIPID injection trials had small sample sizes and patients had a variety of underlying medical
251 conditions both between different trials and within the individual trials. Patients had gastrointestinal
252 diseases/dysfunction or were recovering from gastrointestinal or other surgeries, trauma, burns, or were
253 afflicted by other chronic illness. The largest trial (Study 1, 48 subjects) enrolled patients with many
254 different underlying diagnoses. The rates of treatment emergent adverse reactions can therefore not be
255 directly compared to rates observed in the clinical trials of other related products and may not reflect the
256 rates observed in clinical practice.

257 Commonly observed adverse reactions in 261 adult patients who received CLINOLIPID injection were
258 nausea and vomiting, hyperlipidemia, hyperglycemia, hypoproteinemia and abnormal liver function tests
259 and occurred in 2-10 % of patients. In Study 1 the most common adverse reactions were infectious
260 complications (urinary tract infection, septicemia, and fever of unknown origin), treatment emergent
261 abnormalities on liver/gallbladder ultrasound and abnormalities of serum chemistries, principally, hepatic
262 function tests. Adverse reactions in Study 2 were similar.

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

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

269 **6.2 Post-marketing Experience**

270 The following adverse reactions have been identified during use of CLINOLIPID injection, and listed by
271 MedDRA System Organ Class, then by Preferred Term in order of severity. Because these reactions are
272 reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their
273 frequency or establish a causal relationship to drug exposure.

274 GASTROINTESTINAL DISORDERS: Diarrhea

275 SKIN AND SUBCUTANEOUS TISSUE DISORDERS: Pruritus

276 INVESTIGATIONS: International normalized ratio (INR) Decreased*

277 *(In anticoagulated patients, CLINOLIPID injection may lower the INR)

278

279 **7 DRUG INTERACTIONS**

280 No drug interaction studies have been performed with CLINOLIPID injection.

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

283 **8 USE IN SPECIFIC POPULATIONS**

284 **8.1 Pregnancy**

285 Pregnancy Category C

286 *Risk Summary*

287 There are no adequate and/or well-controlled studies with CLINOLIPID injection in pregnant women.
288 Animal reproduction studies have not been conducted with CLINOLIPID injection. It is also not known
289 whether CLINOLIPID injection can cause fetal harm when administered to a pregnant woman or can affect
290 reproduction capacity. CLINOLIPID injection should be given to a pregnant woman only if clearly needed.
291 It is not known whether the administration of CLINOLIPID injection 20% to pregnant women provides
292 adequate essential fatty acids to the developing fetus.

293 **8.3 Nursing Mothers**

294 It is not known whether CLINOLIPID injection is present in human milk. Because many drugs are present
295 in human milk, exercise caution when CLINOLIPID injection is administered to a nursing woman.

296 **8.4 Pediatric Use**

297 The safety and effectiveness of CLINOLIPID injection have not been established in pediatric patients.
298 CLINOLIPID injection is not indicated for use in pediatric patients. Pediatric studies did not establish that
299 CLINOLIPID injection provides sufficient amounts of essential fatty acids (EFA) in pediatric patients.
300 Pediatric patients may be particularly vulnerable to neurologic complications due to EFA deficiency if
301 adequate amounts of EFA are not provided.

302 Deaths in preterm infants after infusion of intravenous lipid emulsion have been reported [*See Warnings*
303 *and Precautions (5.1)*]. Patients, particularly preterm infants, are at risk for aluminum toxicity [*See*
304 *Warnings and Precautions (5.8)*]. Patients, including pediatric patients, may be at risk for PNALD [*See*
305 *Warnings and Precautions (5.9)*]. In clinical trials of a pure soybean oil based intravenous lipid emulsion
306 product, thrombocytopenia in neonates occurred (<1%).

307 **8.5 Geriatric Use**

308 Of the total number of subjects in clinical studies of CLINOLIPID injection, 21% were 65 and over, while
309 10% were 75 and over. No overall differences in safety or effectiveness were observed between these
310 subjects and younger subjects, and other reported clinical experience has not identified differences in
311 responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot
312 be ruled out.

313 **8.6 Hepatic Impairment**

314 Parenteral nutrition should be used with caution in patients with hepatic impairment. Hepatobiliary
315 disorders are known to develop in some patients without preexisting liver disease who receive parenteral
316 nutrition, including cholestasis, hepatic steatosis, fibrosis and cirrhosis (parenteral nutrition associated liver
317 disease), possibly leading to hepatic failure. Cholecystitis and cholelithiasis have also been observed. The
318 etiology of these disorders is thought to be multifactorial and may differ between patients.

319 Monitor liver function parameters closely. Patients developing signs of hepatobiliary disorders should be
320 assessed early by a clinician knowledgeable in liver diseases in order to identify causative and contributory
321 factors, and possible therapeutic and prophylactic interventions.

322 **10 OVERDOSAGE**

323 In the event of overdose, fat overload syndrome may result [*see Warnings and Precautions (5.4)*]. Stop the
324 infusion to allow lipids to clear from serum. The effects are usually reversible after the lipid infusion is
325 stopped. If medically appropriate, further intervention may be indicated. The lipid administered and fatty
326 acids produced are not dialyzable.

327 **11 DESCRIPTION**

328 CLINOLIPID Lipid Injectable Emulsion, USP is a sterile, non-pyrogenic lipid emulsion for intravenous
329 infusion. CLINOLIPID injection is a lipid emulsion containing a mixture of refined olive oil and refined
330 soybean oil in an approximate ratio of 4:1 (olive:soy). The lipid content is 0.20 g/mL. In CLINOLIPID

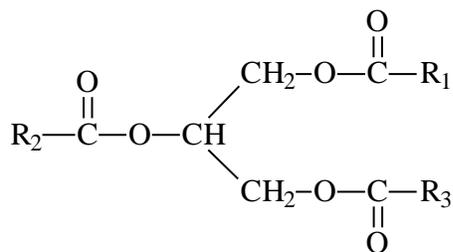
331 injection, the mean composition of linoleic acid (an omega-6 essential fatty acid) is 35.8 mg/mL (range
332 27.6 - 44.0 mg/mL) and α -linolenic acid (an omega-3 essential fatty acid) is 4.7 mg/mL (range 1.0 - 8.4
333 mg/mL). The phospholipids provide 470 milligrams or 15 mmol of phosphorus per liter.

334

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

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

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

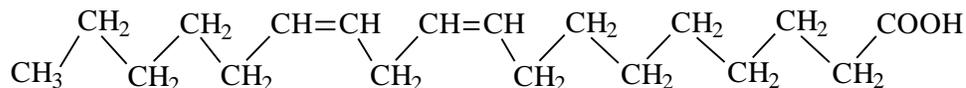


341

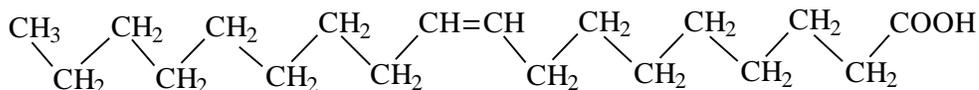
342 Where $\text{R}_1\overset{\text{O}}{\parallel}\text{CO}-$, $\text{R}_2\overset{\text{O}}{\parallel}\text{CO}-$, and $\text{R}_3\overset{\text{O}}{\parallel}\text{CO}-$ are the saturated and unsaturated fatty residues.

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

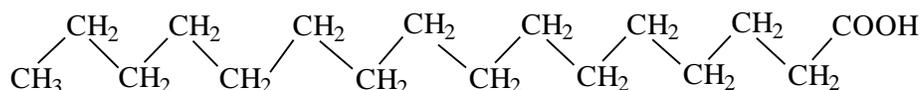
Linoleic acid
 $C_{18}H_{32}O_2$



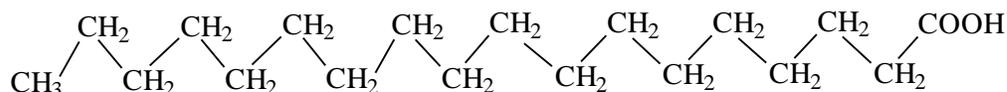
Oleic acid
 $C_{18}H_{34}O_2$



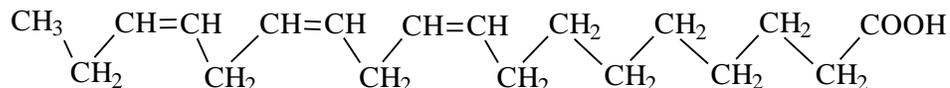
Palmitic acid
 $C_{16}H_{32}O_2$



Stearic acid
 $C_{18}H_{36}O_2$



Linolenic acid
 $C_{18}H_{30}O_2$



346

347 CLINOLIPID 20% has an osmolality of approximately 340 mOsmol/kg water (which represents an
348 osmolality of 260 mOsmol/liter of emulsion)

349 Drug product contains no more than 25 mcg/L of aluminum.

350 12 CLINICAL PHARMACOLOGY

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

353 12.1 Mechanism of Action

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

358 12.2 Pharmacodynamics

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

361 12.3 Pharmacokinetics

362 Metabolism and excretion

363 The fatty acids, phospholipids, and glycerol found in lipid emulsions are metabolized by cells to carbon
364 dioxide and water. The metabolism of these substances results in the generation of energy in the form of

365 adenosine triphosphate (ATP). Some fatty acids are stored in the body in fat tissue, cell membranes, or as
366 intracellular triglycerides. There is constant turn-over of these tissues, with the result that the lipid
367 components are eventually metabolized to carbon dioxide and water. Carbon dioxide is expired through the
368 lungs. Water is excreted through the kidneys or lost through evaporation/expiration through the skin, lungs,
369 and other tissue surfaces. Some lipids (i.e., phospholipids, cholesterol, and bile acids) are excreted through
370 the biliary system.

371 **13 NONCLINICAL TOXICOLOGY**

372 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility.** Studies with CLINOLIPID injection have
373 not been performed to evaluate the carcinogenic potential, mutagenic potential, or effects on fertility.

374 **13.2 Animal Toxicology and/or Pharmacology.** CLINOLIPID injection was evaluated in toxicity studies
375 conducted in rats and dogs for up to 3 months. The principle signs of toxicity noted in the 3-month studies
376 were:

- 377 • Slight hemolytic anemia at 12 g/kg/day in rats and at 6 g/kg/day in dogs. These doses in rats and
378 dogs are 4.8 and 2.4 times higher, respectively, than the recommended adult dose (2.5 g/kg/day) of
379 CLINOLIPID injection.
- 380 • Dose-dependent decrease in urea levels in rats at 6 and 12 g/kg/day dose levels and in dogs at 3, 4.5
381 and 6 g/kg/day dose levels associated with decreased feed consumption.
- 382 • Hypercholesterolemia in dogs at 3, 4.5 and 6 g/kg/day dose levels.
- 383 • Hepatic pathology of lipid and pigmentary overload in male and female rats at 3, 6 and 12 g/kg/day
384 dose levels and brownish-yellow pigmentation in vacuolated Kupffer cells in male and female dogs
385 at 3, 4.5 and 6 g/kg/day dose levels with hepatocyte vacuolation in male dogs at 6 g/kg/day and
386 female dogs at 4.5 and 6 g/kg/day dose levels.
- 387 • Splenic pigmentation and vacuolization in rats at 3, 6 and 12 g/kg/day dose levels, and dogs in 4.5
388 and 6 g/kg/day dose levels.

389
390 At doses of 3 g/kg/day, slight lipid and pigmentary overload of the liver and vacuolization of Kupffer cells
391 were observed in rats and dogs. At a dose of 12 g/kg/day in rats, hepatocellular vacuolation, granulomatous
392 inflammation of the liver, hepatocellular necrosis and hemosiderosis of the liver and lipid deposits and
393 splenic hemosiderosis, were observed. In dogs, at a dose of 6 g/kg/day, brownish-yellow pigmentation in the
394 Kupffer cells of liver and spleen, hyperplasia of vacuolated Kupffer cells, hepatocyte vacuolization, a slight
395 increase in the number of lipid storage cells (Ito cells) in the liver and macrophage vacuolization of the
396 spleen were observed.

397 **14 CLINICAL STUDIES**

398 Two clinical trials (Study 1 and Study 2) in adults compared CLINOLIPID injection to a pure soybean oil
399 based intravenous lipid emulsion. Although Study 1 and Study 2 were not adequately designed to
400 demonstrate noninferiority of CLINOLIPID injection to the soybean oil comparator, they support

401 CLINOLIPID injection as a source of calories and essential fatty acids in adults. The lipid dosage was
402 variable in Studies 1 and 2 and adjusted to the patient's nutritional requirements.

403 Study 1 was a randomized, open-label, multicenter study. Forty eight (48) patients, aged 17 to 75 years,
404 requiring ≥ 15 days (mean 22 days) exclusive parenteral nutrition (TPN) were enrolled and randomized to
405 either CLINOLIPID injection or a pure soybean oil based intravenous lipid emulsion. Nutritional efficacy
406 was assessed by anthropometric indices (body weight, arm circumference, skin-fold thickness), biomarkers
407 of protein metabolism (total protein, albumin) and lipid metabolism. Anthropometric criteria (body weight,
408 arm circumference, and skin fold thickness) were comparable for both groups. Mean total serum protein and
409 albumin increased similarly in both groups.

410 Study 2 was a randomized, open label multicenter study that enrolled 22 patients aged 32-81 years who
411 required long-term parenteral nutrition. Twelve patients received CLINOLIPID injection for a mean of 202
412 days (range 24-408 days) and 10 patients received the comparator lipid for a mean of 145 days (range 29-
413 394 days). The two groups had similar outcomes for weight, weight loss, mid-arm circumference and triceps
414 skinfold thickness.

415 **15 REFERENCES**

416 1. Mirtallo J, Canada T, Johnson D, Kumpf V, Petersen C, Sacks G, et al. Task Force for the Revision of
417 Safe Practices for Parenteral Nutrition, Special Report: safe practices for parenteral nutrition. *JPEN J*
418 *Parenter Enteral Nutr* 2004, 28(6 Suppl)

419
420 2. Clayton P T, Whitfield P, Iyer K. The Role of Phytosterols in the Pathogenesis of Liver Complications of
421 Pediatric Parenteral Nutrition, *Nutrition*, Volume 14, Issue 1, January 1998, Pages 158-164
422

423 **16 HOW SUPPLIED/STORAGE AND HANDLING**

424 CLINOLIPID Lipid Injectable Emulsion, USP is supplied in 1000 mL CLARITY polyolefin bag as follows:

425 EADB9524 NDC 0338-9540-04 1000 mL 1 Bag

426 EADB9524 NDC 0338-9540-08 1000 mL/bag 6 Pack

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

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

432 **17 PATIENT COUNSELING INFORMATION**

433 To ensure the safe and effective use of CLINOLIPID injection, this information should be discussed with
434 the patient.

435 **Inform patients of the following:**

- 436 • Deaths in preterm infants after infusion of intravenous lipid emulsions such as CLINOLIPID
437 injection have been reported.
- 438 • CLINOLIPID injection is given by infusion through a central or peripheral vein.
- 439 • Laboratory monitoring throughout treatment may be necessary.
- 440 • Allergic reactions to the lipid emulsion may occur.
- 441 • Risk of infection and sepsis associated with formulations administered intravenously.
- 442 • Fat overload syndrome can be caused by accumulation of fat in tissues, which may result in adverse
443 effects.
- 444 • CLINOLIPID injection may cause adverse reactions such as nausea and vomiting, excess fat (lipids)
445 in the blood, high blood sugar, low levels of protein in the blood and abnormal liver function tests.
- 446

447 **Should patients self-administer CLINOLIPID injection at home, patients should also be instructed to:**

- 448 • Do not deviate from the administration instructions given by the health provider.
- 449 • Inspect the bag visually for particulate matter and if the lipid emulsion is an evenly distributed liquid
450 with a milky appearance with no visible oil droplets at the surface prior to administration.
- 451 • Ensure that there is an in-line filter in place prior to and during administration.
- 452 • Inform their physicians about any changes in prescription or over-the-counter medications and
453 supplements.
- 454 • Have periodic laboratory tests and routinely follow up with their healthcare provider.
- 455 • Any remaining product from partially used bag must be discarded.
- 456 • Contact their healthcare provider should any signs of injection site infection, inflammation extending
457 from the injection site, or new-onset allergic reaction appear.
- 458

459 **Baxter Healthcare Corporation**

460 Deerfield, IL 60015 USA

461

462 Baxter, Clarity, Exactamix and Clinolipid are trademarks of Baxter International Inc.

EADB9524 Clinolipid (Lipid Injectable Emulsion, USP) 20% 200 grams/1000 mL (0.2 grams/mL) 6 pack x 1000 mL

Store at 20 to 25°C (68 to 77°F). Excursion permitted to 15 to 30°C (59 to 86°F). Protect from freezing. Avoid excessive heat. Store in overpouch until ready to use.

Rx only
Baxter Healthcare Corporation
Deerfield IL 60015



(01)55413760466731(17)999999(10)XXXXXXXXXXXX



(17)999999(10)XXXXXXXXXXXX



(01)00000033895408

Exp.: 99/9999 Lot: XXXXXXXXXXXXXXXX S.L.XXX 88.22.04.548_XXX

EADB9524 Clinolipid (Lipid Injectable Emulsion, USP) 20% 200 grams/1000 mL (0.2 grams/mL) 6 pack x 1000 mL

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(01)55413760466731(17)999999(10)XXXXXXXXXXXX



(17)999999(10)XXXXXXXXXXXX



(01)00000033895408

Exp.: 99/9999 Lot: XXXXXXXXXXXXXXXX S.L.XXX 88.22.04.548_XXX

EADB9524 1000 mL
NDC 0338-9540-04 **1000**

Baxter **900**

Clinolipid **800**

(Lipid Injectable Emulsion, USP) 20%
200 grams/1000 mL (0.2 grams/mL) **700**

Intravenous use only **600**

1000 mL sterile single dose container **500**
Energy Content 2000 kcal/L

Each 100 mL 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, Water for Injection USP and Sodium Hydroxide NF for pH adjustment pH 6.0–9.0 Osmolarity 260 mOsmol/L (calc) **400**

Cautions Use only if the color of the oxygen indicator is within allowable range Do not use unless emulsion has homogeneous milky appearance **300**

Do not add supplemental medications Must not be used in series connections **200**

Usual Dosage See package insert

Store at 20 to 25°C (68 to 77°F)
Excursion permitted to 15 to 30°C (59 to 86°F) **100**

See USP Controlled Room Temperature
Protect from freezing **50**

Do not use beyond 24 hours once opened;
discard unused portion after 24 hours

Rx Only approx volume (mL)

Baxter Healthcare Corporation

BE-35-02-606

EXP
XXXXXXX



LOT
XXXXXXX

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/s/

DONNA J GRIEBEL
10/03/2013