

5.9 Monitoring/Laboratory Tests

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

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

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

Intralipid contains vitamin K that may counteract anticoagulant activity *[see Drug Interactions (7)]*.

6 ADVERSE REACTIONS

Adverse reactions described elsewhere in this Prescribing Information are:

- 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)]*

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 compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Intralipid or equivalent soybean oil lipid emulsions functioned as the comparator in trials of the 4-oil mixed lipid emulsion *[see Clinical Studies (14)]*. The adverse reactions from these studies are included to present the clinical experience with Intralipid.

The safety database for Intralipid or equivalent soybean oil lipid emulsion exposure in these studies includes 393 patients (230 adults, 163 pediatric) in 9 clinical trials. Adult patients were exposed for 5 days to 4 weeks in 5 clinical trials. Intralipid or equivalent soybean oil lipid emulsion was used as a component of PN which also included dextrose, amino acids, vitamins, and trace elements. Two of the 5 studies in adults were performed with Intralipid as a component of PN delivered in a 3-chamber bag.

effects on milk production. Available published literature includes fewer than five reported cases of breastfed infants exposed to various lipid emulsions via lactation, and these cases did not report adverse events. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Intralipid and any potential adverse effects of Intralipid on the breastfed infant, or from the underlying maternal condition.

8.4 Pediatric Use

Intralipid is contraindicated in pediatric patients with severe disorders of lipid metabolism *[see Contraindications (4)]*.

The safety and effectiveness of Intralipid have been established as a source of calories and essential fatty acids for PN in pediatric patients, including term and preterm neonates. Use of Intralipid in neonates is supported by evidence from short-term (i.e., 1- to 4- week) studies, and one study following neonates beyond 4 weeks *[see Clinical Studies (14.2)]*. Use of Intralipid in older pediatric patients is supported by evidence from short-term (i.e., <28 days) studies in pediatric patients 28 days to 12 years of age and additional evidence from studies in adults *[see Clinical Studies (14)]*. The most common adverse reactions in Intralipid-treated pediatric patients were anemia, vomiting, gamma-glutamyltransferase increased, and cholestasis. PNAC, a precursor to PNALD, developed more frequently in Intralipid-treated patients than in patients treated with a comparator 4-oil mixed lipid emulsion *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

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 neonates receiving prolonged treatment with Intralipid may be at risk for aluminum toxicity *[see Warnings and Precautions (5.8)]*.

8.5 Geriatric Use

Reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or drug therapy.

10 OVERDOSSAGE

In the event of an overdose, serious adverse reactions may result *[see Warnings and Precautions (5.1, 5.5)]*. Stop the infusion of Intralipid until triglyceride levels have normalized and symptoms have abated. The effects are usually reversible by stopping the lipid infusion. If medically appropriate, further intervention may be indicated. Lipids are not dialyzable from plasma.

Adult Study 3 was a double-blind randomized, active-controlled, parallel-group, single-center study in 32 adult patients who required TPN for 10 to 14 days. Patients were treated with either an equivalent soybean oil lipid emulsion to Intralipid or the comparator. The increase in mean triglyceride levels from baseline to the final assessment was similar in both the soybean oil lipid emulsion and the comparator groups.

14.2 Pediatric Clinical Studies

The efficacy of Intralipid compared to a 4-oil mixed lipid emulsion in pediatric patients of all age groups, including term and preterm neonates, was evaluated in 333 patients in 4 randomized active-controlled, double-blind, parallel-group controlled clinical studies. Although Pediatric Studies 1, 2, 3, and 4 were not designed for formal statistical comparisons between Intralipid and the comparator, they support Intralipid as a source of calories and essential fatty acids in pediatric patients. The 333 pediatric patients (163 Intralipid; 170 comparator) consisted of 296 patients who were <28 days old, 22 patients 29 days to <2 years old, and 15 patients 2 to <12 years old. Fifty percent of the pediatric patients were male and 87% were Caucasian. All patients received Intralipid or the comparator as part of a PN regimen. Nutritional efficacy in neonates was assessed by changes in anthropometric indices (body weight, height, head circumference). Nutritional efficacy in pediatric patients, 28 days to 12 years of age, was assessed by changes in triglyceride concentrations and fatty acid parameters.

Pediatric Study 1 enrolled 152 preterm and term neonates (birth up to 28 days) and 9 patients ranging in age from 29 to 153 days. Patients were treated with either Intralipid (n=78) or the comparator (n=83). A total of 119 patients (58 Intralipid; 61 comparator) received study treatment for ≥14 days. A total of 27 patients received Intralipid for ≥29 days; 5 patients received Intralipid for the maximum study duration of 78-84 days.

Pediatric Studies 2 and 3 enrolled 60 and 84 preterm neonates, respectively, who were treated with either Intralipid or the comparator (72 neonates in each group). The median treatment duration for Intralipid group was 9 days in Pediatric Study 2 and 6 days in Pediatric Study 3.

Pediatric Study 4 enrolled 13 patients 5 months to <2 years of age and 15 patients 2 to 11.5 years of age. Patients were treated with either Intralipid (n=13) or the comparator (n=15) with a median treatment duration of 27 days.

In Pediatric Studies 1, 2 and 3, which enrolled neonates, Intralipid-treated patients showed increases in the median body weight, height/length, and head circumference (which was measured in Studies 1 and 3) comparable to the comparator-treated patients. Mean triglyceride levels from baseline to the final assessment in Pediatric Studies 1, 2, and 3 were variable in these neonates, but overall differences between groups were not considered clinically relevant. Mean triglyceride levels in Pediatric Study 4 were variable but remained within the normal range.

Table 2: Adverse Reactions in >1% of Adult Patients Treated with Intralipid/soybean oil emulsion

Adverse Reaction	Number of Patients In Soybean Oil Lipid Emulsion Group (N=230)	Number of Patients In 4-Oil Mixed Lipid Emulsion Comparator Group (N=229)
Nausea	26 (11%)	20 (9%)
Vomiting	12 (5%)	15 (7%)
Pyrexia	11 (5%)	9 (4%)
Hypertension	9 (4%)	6 (3%)
Headache	7 (3%)	3 (1%)
Hyperglycemia	5 (2%)	12 (5%)
Abdominal pain	5 (2%)	8 (4%)
Flatulence	4 (2%)	10 (4%)
Blood triglycerides increased	4 (2%)	6 (3%)
Sepsis	4 (2%)	5 (2%)
Diarrhea	4 (2%)	3 (1%)
Pneumonia	4 (2%)	3 (1%)
Pruritus	4 (2%)	3 (1%)
Gamma-glutamyltransferase increased	4 (2%)	2 (1%)

Less common adverse reactions occurring in ≤1% of adult patients who received Intralipid or equivalent soybean oil lipid emulsion were dyspepsia, urinary tract infection, anemia, infection, dyspnea, cholestasis, dysgeusia, increased blood alkaline phosphatase, tachycardia, liver function test abnormalities, dizziness, rash, and thrombophlebitis.

The 163 patients treated with Intralipid in four pediatric trials consisted of 147 patients <28 days of age, 9 patients 28 days to <2 years of age, and 7 patients 2 to 7 years of age; the duration of exposure was 7 to 84 days. Fifty-six percent of the pediatric patients were female, and 85% were Caucasian. Most pediatric patients were preterm neonates with feeding intolerance or other conditions requiring short-term (<29 days) PN.

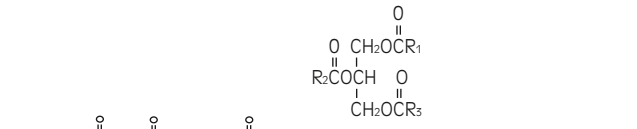
Table 3: Adverse Reactions in >1% of Pediatric Patients Treated with Intralipid

Adverse Reaction	Number of Patients In Intralipid Group (N=163)	Number of Patients In 4-Oil Mixed Lipid Emulsion Comparator Group (N=170)
Anemia	33 (20%)	30 (18%)
Vomiting	16 (10%)	16 (9%)
Gamma-glutamyltransferase increased	12 (7%)	10 (6%)
Cholestasis	10 (6%)	7 (4%)
Pyrexia	7 (4%)	7 (4%)
C-reactive protein increased	7 (4%)	6 (4%)
Hyperbilirubinemia	7 (4%)	5 (3%)
Bilirubin conjugated increased	7 (4%)	3 (2%)
Nosocomial infection	6 (4%)	10 (6%)
Blood alkaline phosphatase increased	6 (4%)	1 (1%)
Abdominal pain	5 (3%)	4 (2%)

11 DESCRIPTION

Intralipid is a sterile, non-pyrogenic, white, homogenous lipid emulsion for intravenous infusion as a source of calories and essential fatty acids. The lipid content of Intralipid is 0.2 g/mL and comprises soybean oil. The phosphate content is 15 mmol/L. The total energy content, including fat, phospholipids, and glycerin is 2,000 kcal/L.

Each 100 mL of Intralipid contains approximately 20 g soybean oil, 1.2 g egg yolk phospholipids, 2.25 g glycerin, water for injection, and sodium hydroxide for pH adjustment (pH 6 to 8.9). Intralipid has an osmolality of approximately 350 mOsmol/kg water (which represents an osmolality of 260 mOsmol/L). The soybean oil is a refined natural product consisting of a mixture of neutral triglycerides of predominantly unsaturated fatty acids with the following structure:



where R₁C-, R₂C- and R₃C- are saturated and unsaturated fatty acid residues.

The major component fatty acids in Intralipid are linoleic acid (44% to 62%), oleic acid (19% to 30%), palmitic acid (7% to 14%), alpha-linolenic acid (4% to 11%), and stearic acid (1.4% to 5.5%). These fatty acids have the following chemical and structural formulas:

Linoleic Acid C₁₈H₃₂O₂	
Oleic Acid C₁₈H₃₄O₂	
Palmitic Acid C₁₆H₃₂O₂	
α-Linolenic Acid C₁₈H₃₂O₂	
Stearic Acid C₁₈H₃₆O₂	

16 HOW SUPPLIED/STORAGE AND HANDLING

Intralipid 20% (lipid injectable emulsion, USP) is a sterile, homogeneous, milky, white lipid emulsion supplied in Flexible Containers as follows:

Product Code	Unit of Use	Unit of Sale
831800311	NDC 65219-531-01 One 100 mL freeflex ® bag	NDC 65219-531-10 Package of 10 freeflex ® bags
831818311	NDC 65219-533-01 One 250 mL freeflex ® bag	NDC 65219-533-25 Package of 10 freeflex ® bags
831826311	NDC 65219-535-01 One 500 mL freeflex ® bag	NDC 65219-535-50 Package of 12 freeflex ® bags
831842311	NDC 65219-539-01 One 1000 mL Pharmacy Bulk Package freeflex ® bag	NDC 65219-539-10 Package of 6 freeflex ® bags

Store below 25°C (77°F). Avoid excessive heat. Do not freeze. If accidentally frozen, discard container. Store in the overpouch until ready for use.

Intralipid 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 at 2°C to 8°C (36°F to 46°F) for no longer than 24 hours. After removal from storage, infuse within 12 hours when using a Y-connector or within 24 hours if used as part of an admixture *[see Dosage and Administration (2.2)]*.

Intralipid 1,000 mL Pharmacy Bulk Package

Use the Pharmacy Bulk Package immediately for admixing after removal from the overpouch. If not used immediately, the product should be stored for no longer than 24 hours at 2°C to 8°C (36°F to 46°F). After removal from storage, and once the closure is penetrated, use Pharmacy Bulk Package contents within 4 hours *[see Dosage and Administration (2.2)]*.

Admixtures

Infuse admixtures containing Intralipid immediately. If not used immediately, admixtures should be stored at 2°C to 8°C (36°F to 46°F) for no longer than 24 hours. After removal from storage, infuse within 24 hours *[see Dosage and Administration (2.2)]*. Protect the admixed PN solution from light *[see Dosage and Administration (2.2)]*.

Hematocrit decreased	5 (3%)	2 (1%)
Metabolic acidosis	5 (3%)	2 (1%)
Diarrhea	4 (3%)	3 (2%)
Tachycardia	4 (3%)	3 (2%)
Thrombocytopenia	4 (3%)	3 (2%)
Alanine aminotransferase increased	3 (2%)	1 (1%)
Aspartate aminotransferase increased	3 (2%)	0 (0%)
Parenteral nutrition-associated liver disease	3 (2%)	0 (0%)

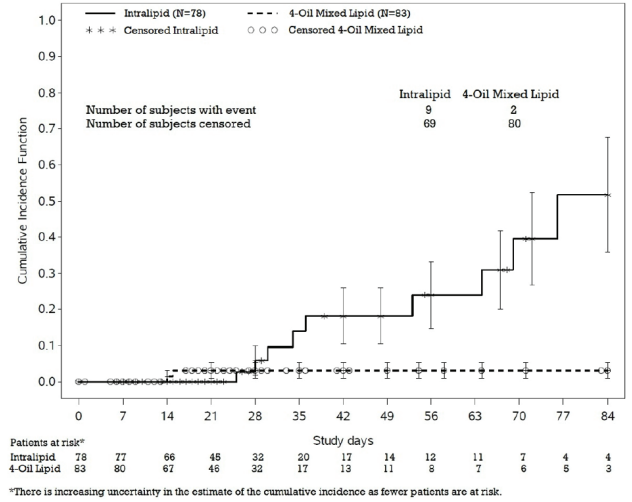
Less common adverse reactions occurring in ≤1% of pediatric patients who received intralipid were hyperglycemia, sepsis, increased blood triglycerides, infection, fluid overload, hypertension, hypertriglyceridemia, rash, and hyperlipidemia.

In a randomized active-controlled, double-blind, parallel-group, multi-center study that included 152 neonates and 9 patients ranging in age from 29 to 153 days who were expected to require PN for at least 28 days, PNAC, a precursor to PNALD, developed more frequently in Intralipid-treated patients than in patients treated with a comparator 4-oil mixed lipid emulsion.

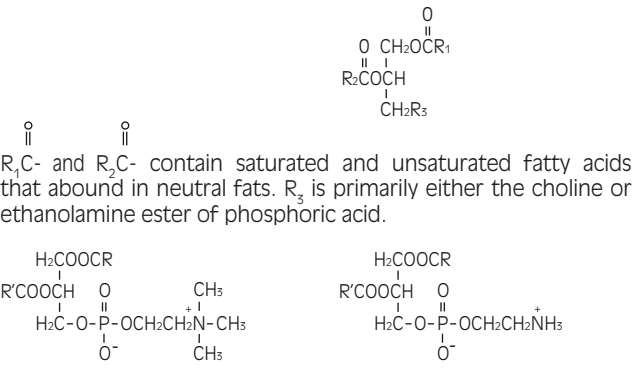
PNAC (defined as direct bilirubin >2 mg/dL with a second confirmed elevation >2 mg/dL at least 7 days later) occurred in 11.5% (9/78) in Intralipid-treated patients and 2.4% (2/83) of patients treated with a 4-oil mixed lipid emulsion. Most PNAC events occurred in patients who were treated for longer than 28 days.

The estimated cumulative incidence of PNAC is shown in the Kaplan-Meier cumulative incidence curve in Figure 1 *[see Pediatric Clinical Studies (14.2)]*.

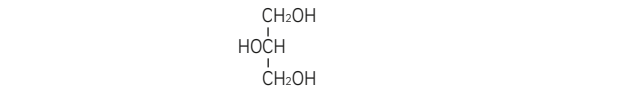
Figure 1: Cumulative Incidence Curve of Time to Parenteral Nutrition-Associated Cholestasis (PNAC) with Standard Error Bars



Purified egg phosphatides are a mixture of naturally occurring phospholipids which are isolated from the egg yolk. These phospholipids have the following general structure:



Glycerin is chemically designated C₃H₈O₃ and is a clear colorless, hygroscopic syrupy liquid. It has the following structural formula:



The container-solution unit is a closed system and is not dependent upon entry of external air during administration. The container is overwrapped to provide protection from the physical environment and to provide an additional oxygen and moisture barrier when necessary.

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

The container is not made with natural rubber latex, PVC, or DEHP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Intralipid provides a biologically utilizable source of calories and essential fatty acids.

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 also important for membrane structure and function, as precursors for bioactive molecules (such as prostaglandins), and as regulators of gene expression.

12.2 Pharmacodynamics

The pharmacodynamic effects of Intralipid have not been fully characterized.

17 PATIENT COUNSELING INFORMATION

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

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

Inform caregivers that acute respiratory distress and death may occur in neonates and infants after rapid infusion of intravenous lipid emulsions. If Intralipid is infused at home, instruct caregivers not to exceed the maximum infusion rate *[see Warnings and Precautions (5.1)]*.

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 Intralipid may cause hypersensitivity reactions, including anaphylaxis. If Intralipid is infused at home, instruct patients or caregivers to stop the infusion of Intralipid immediately and seek medical attention if they experience signs or symptoms of a hypersensitivity reaction, such as rapid or weak heartbeat, feeling faint, difficulty in breathing or swallowing, vomiting, nausea, headache, sweating, dizziness, hives, rash, itching, flushing, dizziness, fever, or chills *[see Warnings and Precautions (5.3)]*.

Infections

Inform patients and caregivers that patients who receive Intralipid are at risk of infection. If Intralipid is infused at home, instruct patients or caregivers to ensure aseptic techniques are used for the preparation and administration of Intralipid 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 Intralipid is infused at home, instruct patients or caregivers to stop the infusion of Intralipid 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 Intralipid may result in refeeding syndrome *[see Warnings and Precautions (5.6)]*.

Hypertriglyceridemia

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

Aluminum Toxicity

Inform patients and their caregivers that prolonged PN

6.2 Postmarketing Experience

The following adverse reactions from voluntary reports have been reported with Intralipid. Because many of these reactions were 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.

Cardiac disorders: palpitations
Gastrointestinal disorders: vomiting, nausea
General disorders and administration site conditions: chills, chest discomfort, pyrexia
Nervous system disorders: dizziness
Respiratory, thoracic, and mediastinal disorders: dyspnea
Immune system disorders: hypersensitivity reactions, including anaphylaxis *[see Contraindications (4), Warnings and Precautions (5.3)]*
Vascular disorders: phlebitis
Blood and lymphatic system disorders: hypercoagulability

7 DRUG INTERACTIONS

Soybean oil in Intralipid contains vitamin K₁ which may counteract the anticoagulant activity of vitamin K antagonists such as warfarin. In patients who receive concomitant Intralipid and warfarin, increase monitoring of laboratory parameters for anticoagulant activity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Administration of the recommended dose of Intralipid is not expected to cause major birth defects, miscarriage, or other adverse maternal or fetal outcomes. No animal reproduction studies have been conducted with Intralipid. There are risks to the fetus associated with severe malnutrition during pregnancy *[see Clinical Considerations]*.

The background risk of major birth defects and miscarriage for the indicated population(s) is 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 pregnant women is associated with preterm delivery, low birth weight, intrauterine growth restriction, congenital malformations, and perinatal mortality. Parenteral nutrition should be considered if the pregnant woman's nutritional requirements cannot be fulfilled by oral or enteral intake.

8.2 Lactation

Risk Summary

Administration of the recommended dose of Intralipid is not expected to cause harm to a breastfed infant. There are no data on the presence of Intralipid in human or animal milk or its

12.3 Pharmacokinetics

Intralipid provides fatty acids in the form of triglycerides which are hydrolyzed by lipoprotein lipase to release free fatty acids. Linoleic acid and alpha-linolenic acid are metabolized within a common biochemical pathway through a series of desaturation and elongation steps.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity, genetic toxicology, and animal fertility studies have not been performed with Intralipid.

14 CLINICAL STUDIES

Intralipid or equivalent soybean oil lipid emulsion functioned as the comparator for the 4-oil mixed lipid emulsion in the clinical studies described in sections 14.1 and 14.2. The trial results are included to present the clinical experience with Intralipid.

14.1 Adult Clinical Studies

The efficacy of Intralipid or equivalent soybean oil lipid emulsion compared to a 4-oil mixed lipid emulsion was evaluated in 3 clinical studies in adult patients. Nutritional efficacy in adult studies was assessed by changes in anthropometric indices (body weight, height, and body mass index [BMI]), changes in lipid and protein metabolism (albumin), and fatty acid parameters. Of the 354 adult patients (178 Intralipid; 176 comparator), 62% were male, 99% were Caucasian, and ages ranged from 19 to 96 years. All patients received Intralipid/equivalent soybean oil lipid emulsion or the comparator as part of a PN regimen. Although Adult Study 1, Adult Study 2, and Adult Study 3 were not designed for formal statistical comparisons between Intralipid/equivalent soybean oil lipid emulsion and the comparator, they support Intralipid as a source of calories and essential fatty acids in adults. The lipid dosage was variable in these studies and adjusted to the patient's nutritional requirements.

Adult Study 1 was a double-blind, randomized, active-controlled, parallel-group, multicenter study in patients who required PN for at least 28 days. Seventy-five patients were enrolled, and 73 patients were treated with either Intralipid or the comparator. Changes in mean triglyceride levels from baseline values to Week 4 were similar in both the Intralipid and comparator groups. Mean albumin levels demonstrated a comparable decrease in both groups. Mean changes in body weight (kg) and BMI (kg/m²) were similar in both the Intralipid and the comparator groups.

Adult Study 2 was a phase 3, randomized, double-blind, active-controlled, multicenter study. A total of 249 postoperative adult patients were randomized to receive either an equivalent soybean oil lipid emulsion to Intralipid or the comparator for at least 5 days as part of their total parenteral nutrition (TPN) regimen. From baseline to Day 6, mean triglyceride levels increased similarly in both the soybean oil lipid emulsion and the comparator groups.

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 Intralipid at home, then provide recommendations on how to inspect and prepare, add compatible additives (when appropriate), administer, and store Intralipid *[see Dosage and Administration (2.1, 2.2)]*. Inform patients or caregivers not to deviate from the administration instructions given by the healthcare provider.

Manufactured by:



Uppsala, Sweden

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www.fresenius-kabi.com/us
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