HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SMOFLIPID safely and effectively. See full prescribing information for SMOFLIPID.

SMOFLIPID®

(lipid injectable emulsion), for intravenous use

Initial U.S. Approval: 2016

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	3/2022
Dosage and Administration (2.1, 2.2, 2.3)	3/2022
Warnings and Precautions (5.1, 5.2, 5.7, 5.9)	3/2022

----------INDICATIONS AND USAGE----------

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

----------DOSAGE AND ADMINISTRATION----------

- For intravenous infusion only into a central or peripheral vein. (2.1)
- SMOFlipid 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 PN solution from light. (2.2)
- 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. (2.3)
- The recommended daily dosage in adults is 1 to 2 g/kg/day and should not exceed 2.5 g/kg/day. (2.3)
- The recommended daily dosage in pediatric patients is:

Pediatric Age group	Initial Dose	Maximum Dose	Duration of infusion
Birth to 2 years of age (including preterm and term neonates)	0.5 to 1 g/kg/day Increase the dose by 0.5 to 1 g/kg/day	3 g/kg/day	20 to 24 hours for preterm and term neonates 12 to 24 hours for patients 1 month to 2 years
2 to <12 years of age	1 to 2 g/kg/day Increase the dose by 0.5 to 1 g/kg/day	3 g/kg/day	12 to 24 hours
12 to 17 years of age	1 to 2 g/kg/day	2.5 g/kg/day	12 to 24 hours

----------DOSAGE FORMS AND STRENGTHS----------

SMOFlipid is a sterile, homogenous lipid injectable emulsion supplied as 20 g of lipid/100 mL in 100 mL single-dose Flexible Container, 50 g of lipid/250 mL in 250 mL single-dose Flexible Container, 100 g of lipid/500 mL in 500 mL single-dose Flexible Container, and 200 g of lipid/1000 mL in 1000 mL Pharmacy Bulk Package. (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to fish, egg, soybean, peanut protein, or to 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----------

- 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. (5.1, 6.1, 8.4)
- Risk of Death in Preterm Infants due to Pulmonary Lipid Accumulation: Deaths in preterm infants after infusion of intravenous 100% soybean oil lipid emulsions have been reported in the literature. (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 adverse drug reactions (≥5%) from clinical trials in adults were nausea, vomiting, and hyperglycemia. Most common adverse drug reactions (≥5%) from clinical trials in pediatric patients were anemia, vomiting, increased gamma-glutamyltransferase, and nosocomial infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Vitamin K Antagonists (e.g., warfarin): Anticoagulant activity may be counteracted; increase monitoring of coagulation parameters. (7)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 3/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SMOFlipid is indicated in adult 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.

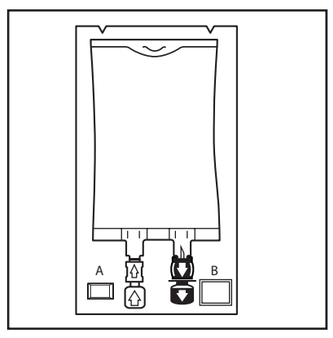
2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

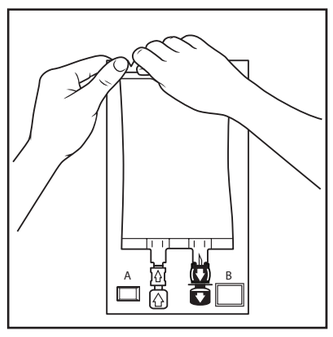
- SMOFlipid is prepared and administered by a healthcare provider in the inpatient setting. Patients and caregivers may prepare and administer SMOFlipid for home use after appropriate training by a trained healthcare provider.
- SMOFlipid is for central or peripheral intravenous infusion only.
- SMOFlipid admixtures with osmolarity
  - Greater than or equal to 900 mOsm/L must be infused through a central vein.
  - Less than 900 mOsm/L may be administered either through a central or peripheral vein.
- Use a 1.2 micron in-line filter during administration.
- Use a dedicated infusion line without any connections. Do not connect multiple medications in series.
- To prevent air embolism, use a nonvented infusion set or close the vent on a vented set and fully evacuate residual gas in the bag prior to administration.
- Do not pressurize the flexible bag to increase flow rates, and if administration is controlled by a pumping device, turn off the pump before the bag runs dry.
- Do not use infusion sets and lines that contain di-2-ethylhexyl phthalate (DEHP), including infusion sets that contain polyvinyl chloride (PVC) components, because they contain DEHP as a plasticizer.
- SMOFlipid can be infused concurrently into the same vein as dextrose-amino acid solutions (as part of PN) by a Y-connector located near the infusion site; flow rates of each solution should be controlled separately by infusion pumps.
- After connecting the infusion set, start infusion of SMOFlipid immediately. Complete the infusion within 12 hours when using a Y-connector and within 24 hours when used as part of an admixture.

2.2 Preparation Instructions

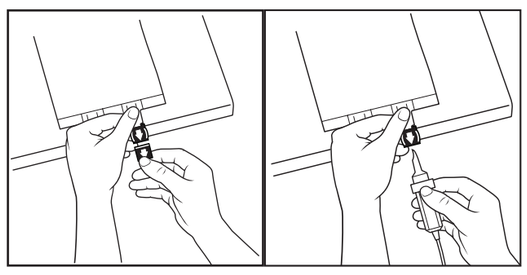
Use the following instructions to prepare single-dose SMOFlipid 100 mL, 250 mL, and 500 mL Flexible Containers for administration:



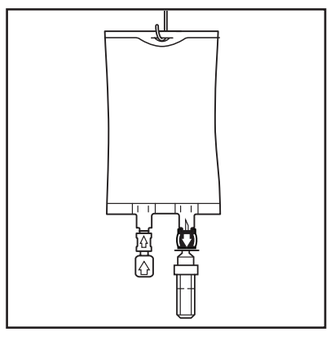
1. Inspect Bag
   - Inspect the integrity indicator (Oxalert®) (A) before removing the overpouch.
   - Discard the product if the indicator is black, overpouch is opened or damaged, emulsion color is not white, or seals of bag are broken.



2. Remove Overpouch
   - Place the bag on a clean, flat surface.
   - Tear overpouch at notch and pull down.
   - Discard the Oxalert sachet (A) and the oxygen absorber (B).
   - Visually inspect the bag and contents for particulate matter and discoloration prior to administration. The lipid emulsion should be a homogenous liquid with a milky white appearance. If the mixture is not white or the emulsion has separated (noted by discoloration, phase separation, or oily droplets), or if particulates and/or leakage are observed, discard the bag.



3. Spike Bag
   - Identify the infusion port (**blue** cap with the arrow pointing away from the bag).
   - Immediately before inserting the infusion set, break off the **blue** infusion port cap.
   - Use infusion sets according to ISO Number 8536-4 with an external spike diameter of 5.5 to 5.7 mm and use a nonvented infusion set or close the air-inlet on a vented set.
   - Use a 1.2 micron in-line filter for administration.
   - Hold the base of the infusion port.
   - Insert the spike through the infusion port by rotating your wrist slightly until the spike is inserted.
   - Do not pierce the infusion port more than once.



4. Hang the bag
   - On the hanger cut and start infusion.
   - Discard unused portion.

SMOFlipid 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 and within 24 hours when used as part of an admixture.

SMOFlipid 1000 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 blue infusion port using a suitable sterile transfer device or dispensing set. Discard any unused contents.
- Use the Pharmacy Bulk Package immediately for admixing after removal from overpouch. If not used immediately, the product can 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.

Admixing Instructions

- Prepare the admixture in PN containers using strict aseptic techniques to avoid microbial contamination.
- Do not add SMOFlipid to the PN container first; destabilization of the lipid may occur. The prime destabilizers of emulsions are excessive acidity (such as a pH <5) and inappropriate electrolyte content. Amino acid solutions exert buffering effects that protect the emulsion from destabilization. Give careful consideration to the addition of divalent cations (Ca^{++} and Mg^{++}), which have been shown to cause emulsion instability.
- Do not inject additives directly into SMOFlipid.
- SMOFlipid may be mixed with amino acid and dextrose injections to produce "all-in-one" PN admixtures. The mixing sequence below must be followed for manual compounding to minimize pH-related problems by ensuring that typically acidic dextrose injections are not mixed with lipid emulsions alone; shake bags gently after each addition.
  - Transfer dextrose injection to the PN container.
  - Transfer amino acid injection.
  - Transfer SMOFlipid.
- Simultaneous transfer of amino acid injection, dextrose injection, and SMOFlipid to the PN container is also permitted; follow automated compounding device instructions as indicated. Use gentle agitation during admixing to minimize localized concentration effects.
- Additions to the PN admixtures should be evaluated by a pharmacist for compatibility. Questions about compatibility may be directed to Fresenius Kabi USA, LLC.
- Inspect the admixture to ensure that precipitates have not formed during preparation of the admixture and the emulsion has not separated. Discard the admixture if any of the above are observed.
- Infuse admixtures containing SMOFlipid immediately. If not used immediately, store admixtures under refrigeration at 2°C to 8°C (36°F to 46°F) for no longer than 24 hours. Infusion must be complete within 24 hours after removal from refrigeration. Discard any remaining admixture.
- Protect the admixed PN solution from light.

2.3 Recommended Dosage and Administration

- The dosing of SMOFlipid depends on the patient's individual energy requirements influenced by age, body weight, tolerance, clinical status, and the ability to metabolize and eliminate lipids.
- When determining dose, energy supplied by dextrose and amino acids from PN, as well as energy from oral or enteral nutrition, has to be taken into account. Energy and lipid provided from lipid-based medications should also be taken into account (e.g., propofol).
- Prior to administration of SMOFlipid, correct severe fluid and electrolyte disorders and measure serum triglyceride levels to establish a baseline value. In patients with elevated triglyceride levels, initiate SMOFlipid at a lower dosage and titrate in smaller increments, monitoring the triglyceride levels with each adjustment *[see Warnings and Precautions (5.7)]*. SMOFlipid contains 0.162 to 0.225 mg/mL of all-rac-alpha-tocopherol. Take into account the amount of all-rac-alpha-tocopherol in SMOFlipid when determining the need for additional supplementation.

Recommended Adult Dosage

- The recommended dosage of SMOFlipid for adult patients is 1 to 2 g/kg/day and should not exceed 2.5 g/kg/day. The initial rate of infusion should be 0.1 g/minute for the first 15 to 30 minutes of infusion. If tolerated, gradually increase until reaching the required rate after 30 minutes. Maximum infusion rate should not exceed 0.1 g/kg/hour. The daily dose should also not exceed a maximum of 60% of total energy requirements *[see Overdosage (10)]*.
- The recommended duration of infusion for SMOFlipid is between 12 and 24 hours, depending on the clinical situation. The administration flow rate is determined by dividing the volume of lipid by the duration of the infusion.

Recommended Pediatric Dosage

- The recommend dosage of SMOFlipid for pediatric patients is shown in Table 1.
- The duration of infusion will vary depending on the clinical situation, but infuse SMOFlipid over a longer duration in neonates as shown in Table 1.
- Do not exceed an infusion rate of 0.15 g/kg/hour.
- The administration flow rate is determined by dividing the volume of lipid by the duration of the infusion.

Table 1: Recommended Pediatric Dosage

Pediatric Age group	Initial Dose	Maximum Dose	Duration of infusion
Birth to 2 years of age (including preterm and term neonates*)	0.5 to 1 g/kg/day Increase the dose by 0.5 to 1 g/kg/day	3 g/kg/day	20 to 24 hours for preterm and term neonates 12 to 24 hours for patients 1 month to 2 years
2 to <12 years of age	1 to 2 g/kg/day Increase the dose by 0.5 to 1 g/kg/day	3 g/kg/day	12 to 24 hours
12 to 17 years of age	1 to 2 g/kg/day	2.5 g/kg/day	12 to 24 hours

* 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).

3 DOSAGE FORMS AND STRENGTHS

SMOFlipid is a sterile, homogenous lipid injectable emulsion in Flexible Containers supplied as:

- 20 g of lipid/100 mL in 100 mL single-dose Flexible Container
- 50 g of lipid/250 mL in 250 mL single-dose Flexible Container
- 100 g of lipid/500 mL in 500 mL single-dose Flexible Container
- 200 g of lipid/1000 mL in 1000 mL Pharmacy Bulk Package

4 CONTRAINDICATIONS

Use of SMOFlipid is contraindicated in patients with:

- Known hypersensitivity to fish, egg, soybean, peanut protein, or to any of the active or inactive ingredients in SMOFlipid *(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 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 SMOFlipid, have been associated with development of PNALD.

In a randomized study of neonates and infants expected to be treated with PN for at least 28 days, parenteral nutrition-associated cholestasis (PNAC), a precursor to PNALD, developed less frequently in SMOFlipid-treated patients than in 100% soybean oil lipid emulsion-treated patients *[see Adverse Reactions (6.1), Use in Specific Populations (8.4)]*.

Monitor liver tests in patients treated with SMOFlipid 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 SMOFlipid. Patients developing signs of hepatobiliary disorders should be assessed early to determine whether these conditions are related to SMOFlipid use.

5.2 Death in Preterm Neonates

Deaths in preterm neonates after infusion of lipid injectable emulsions containing only soybean oil have been reported in the medical literature. Autopsy findings in these preterm neonates included intravascular lipid accumulation in the lungs. Preterm and small-for-gestational-age neonates have poor clearance of intravenous lipid emulsion and increased free fatty acid plasma levels following lipid emulsion infusion. This risk due to poor lipid clearance should be considered when administering intravenous lipid emulsions.

Monitor patients receiving SMOFlipid for signs and symptoms of pleural or pericardial effusion.

5.3 Hypersensitivity Reactions

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

5.4 Infections

Lipid emulsions, such as SMOFlipid, 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 SMOFlipid.

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 injectable emulsions 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 SMOFlipid. The syndrome is usually reversible when the infusion of the lipid emulsion is stopped.

5.6 Refeeding Syndrome

Administering PN to severely malnourished patients may result in refeeding syndrome, which is characterized by the intracellular shift of potassium, phosphorus, and magnesium as 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 SMOFlipid 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 SMOFlipid. In addition, patients with hypertriglyceridemia may have worsening of their hypertriglyceridemia with administration of SMOFlipid. 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 SMOFlipid infusion and monitor serum triglyceride levels to avoid clinical consequences of hypertriglyceridemia such as pancreatitis. In pediatric patients with hypertriglyceridemia, lower triglyceride levels (i.e., below 400 mg/dL) may be associated with adverse reactions. Monitor serum triglyceride levels to avoid potential complications with hypertriglyceridemia such as pancreatitis, lipid pneumonitis, and neurologic changes, including kernicterus.

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

SMOFlipid contains no more than 25 mcg/L of aluminum. Prolonged PN administration in patients with renal impairment may result in aluminum reaching toxic levels. Preterm neonates 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 neonates, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day can accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading in these patients may occur at even lower rates of administration.

5.9 Essential Fatty Acid Deficiency

Treatment-emergent cases of moderate or severe essential fatty acid deficiency (EFAD) (defined as the triene [Mead acid] to tetraene [arachidonic acid] ratio >0.2 and >0.4, respectively) were not observed in pediatric clinical trials of SMOFlipid up to 28 days *[see Adverse Reactions (6.1)]*.
However, cases of EFAD have been reported in adult and pediatric patients in the postmarketing period with the use of SMOFlipid. The median time to onset was greater than 28 days among cases that reported time to onset.

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 SMOFlipid to prevent EFAD *[see Dosage and Administration (2.3), Description (11)]*.

5.10 Monitoring/Laboratory Tests

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

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

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

6 ADVERSE REACTIONS

Adverse reactions described elsewhere in this Prescribing Information are:

- Parenteral Nutrition-Associated Liver Disease and Other Hepatobiliary Disorders *[see Warnings and Precautions (5.1)]*
- Death in Preterm Neonates *[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 compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety database for SMOFlipid includes exposure in 399 patients (229 adults; 170 pediatric) in 9 clinical trials. Adult patients were exposed for 5 days to 4 weeks in 5 clinical trials. The pooled population exposed to SMOFlipid was adult patients up to 89 years old (20 to 89 years of age), 43% female and 99% Caucasian. The most frequently reported medical histories in the SMOFlipid group were surgical and medical procedures (84%), neoplasms (57%), gastrointestinal disorders (53%), vascular disorders (37%), and infections and infestations (20%). SMOFlipid 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 SMOFlipid as a component of PN delivered in a 3-chamber bag.

Table 2: Adverse Reactions in > 1% of Adult Patients Treated with SMOFlipid

Adverse Reaction	Number of Patients in SMOFlipid Group (N=229)	Number of Patients in Comparator Group (N=230)
Nausea	20 (9%)	26 (11%)
Vomiting	15 (7%)	12 (5%)
Hyperglycemia	12 (5%)	5 (2%)
Flatulence	10 (4%)	4 (2%)
Pyrexia	9 (4%)	11 (5%)
Abdominal pain	8 (4%)	5 (2%)
Blood triglycerides increased	6 (3%)	4 (2%)
Hypertension	6 (3%)	9 (4%)
Sepsis	5 (2%)	4 (2%)
Dyspepsia	5 (2%)	1 (0%)
Urinary tract infection	4 (2%)	3 (1%)
Anemia	4 (2%)	2 (1%)
Device related infection	4 (2%)	2 (1%)

Less common adverse reactions occurring in ≤1% of adult patients who received SMOFlipid were dyspnea, leukocytosis, diarrhea, pneumonia, cholestasis, dysgeusia, increased blood alkaline phosphatase, increased gamma-glutamyltransferase, increased C-reactive protein, tachycardia, liver function test abnormalities, headache, pruritus, dizziness, rash and thrombophlebitis.

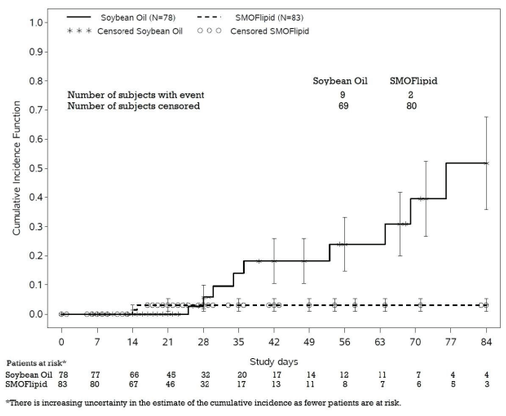
The 170 patients treated with SMOFlipid in four pediatric trials consisted of 149 patients <28 days of age, 13 patients 28 days to <2 years of age, and 8 patients 2 to 7 years of age; the duration of exposure was 7 to 84 days. Forty five percent of the pediatric patients were female, and 89% were Caucasian. Most pediatric patients were preterm neonates with feeding intolerance or other conditions requiring short-term (<29 days) PN.

The hepatic safety of SMOFlipid was evaluated in Pediatric Study 1, 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 (defined as direct bilirubin >2mg/dl with a second confirmed elevation >2mg/dl at least 7 days later) occurred in 2.4% (2/83) of SMOFlipid-treated patients and 11.5% (9/78) in soybean oil lipid emulsion-treated patients. 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 Clinical Trials (14)]*.

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



In the same trial, EFAD was determined by calculating the Holman index (the triene [Mead acid] to tetraene [arachidonic acid] ratio; T:T ratio). At the end of the first 28 days of treatment, 2.4% (2/83) SMOFlipid-treated patients and 2.6% (2/78) soybean oil lipid emulsion-treated patients had suspected EFAD (T:T ratio >0.05), and there were no cases of moderate (T:T ratio >0.2) or severe (T:T ratio >0.4) EFAD. There are insufficient data from this trial to determine the incidence of EFAD with duration of SMOFlipid treatment greater than 28 days because of substantial patient discontinuation from PN during the first 28 days.

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

Adverse Reaction	Number of Patients in SMOFlipid Group (N=170)	Number of Patients in Comparator Group (N=163)
Anemia	30 (18%)	33 (20%)
Vomiting	16 (9%)	16 (10%)
Gamma-glutamyltransferase increased	10 (6%)	12 (7%)
Nosocomial infection	10 (6%)	6 (4%)
Cholestasis	7 (4%)	10 (6%)
Pyrexia	7 (4%)	7 (4%)
C-reactive protein increased	6 (4%)	7 (4%)
Hyperbilirubinemia	5 (3%)	7 (4%)
Abdominal pain	4 (2%)	5 (3%)
Bilirubin conjugated increased	3 (2%)	7 (4%)
Diarrhea	3 (2%)	4 (3%)
Tachycardia	3 (2%)	4 (3%)
Thrombocytopenia	3 (2%)	4 (3%)
Hyperglycemia	3 (2%)	2 (1%)
Sepsis	3 (2%)	2 (1%)

Less common adverse reactions occurring in ≤1% of pediatric patients who received SMOFlipid were decreased hematocrit, metabolic acidosis, increased blood triglycerides, infection, increased blood alkaline phosphatase, increased alanine aminotransferase, fluid overload, hypertension, hypertriglyceridemia, and rash.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of SMOFlipid in countries where it is registered. 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 product exposure.

Cardiac disorders: palpitations
General disorders and administration site conditions: chills, chest pain, malaise
Hepatobiliary disorders: cholestasis
Infections and infestations: infection
Metabolism and nutrition disorders: fatty acid deficiency
Respiratory, thoracic and mediastinal disorders: dyspnea
Skin and subcutaneous tissue disorders: hyperhidrosis
Vascular disorders: phlebitis

7 DRUG INTERACTIONS

Soybean and olive oils in SMOFlipid contain vitamin K_1 which may counteract the anticoagulant activity of vitamin K antagonists such as warfarin. In patients who receive concomitant SMOFlipid 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 SMOFlipid is not expected to cause major birth defects, miscarriage, or other adverse maternal or fetal outcomes. No animal reproduction studies have been conducted with SMOFlipid. There are risks to the fetus associated with severe malnutrition during pregnancy *(see Clinical Considerations)*.

The estimated 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 SMOFlipid is not expected to cause harm to a breastfed infant. There are no data on the presence of SMOFlipid in human or animal milk or its 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 SMOFlipid and any potential adverse effects of SMOFlipid on the breastfed infant, or from the underlying maternal condition.

8.4 Pediatric Use

The safety and effectiveness of SMOFlipid have been established as a source of calories and essential fatty acids for PN when oral or enteral nutrition is not possible, insufficient, or contraindicated in pediatric patients, including term and preterm neonates. Use of SMOFlipid 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 SMOFlipid in older pediatric patients is supported by evidence from a short-term (i.e., <28 days) study 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 SMOFlipid-treated pediatric patients were anemia, vomiting, gamma-glutamyltransferase increased, and nosocomial infection *(see Adverse Reactions (6.1))*.

PNALD, also referred to as IFALD, has been reported in pediatric patients who received SMOFlipid for more than 2 weeks. PNAC (a precursor to PNALD) was reported less frequently in SMOFlipid-treated patients compared to soybean oil lipid emulsion-treated patients in Pediatric Study 1 *(see Warnings and Precautions (5.1) and Adverse Reactions (6.1))*. Although clinically significant cases of EFAD were not observed during short-term use in pediatric clinical studies, cases of EFAD have been reported with the use of SMOFlipid in the postmarketing setting *(see Warnings and Precautions (5.9), Adverse Reactions (6.1))*. Monitor pediatric patients for laboratory evidence of EFAD 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))*.

Deaths in preterm infants after infusion of lipid injectable emulsions containing only soybean oil have been reported in medical literature *(see Warnings and Precautions (5.2))*. Because of immature renal function, preterm infants receiving prolonged treatment with SMOFlipid may be at risk for aluminum toxicity *(see Warnings and Precautions (5.8))*.

8.5 Geriatric Use

Energy expenditure and requirements may be lower for older adults than younger patients. Of the 354 adult patients in clinical studies of SMOFlipid, 35% were >65 years of age and 10% were >75 years of age. No overall differences in the safety and efficacy of SMOFlipid were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity in some older patients cannot be ruled out.

10 OVERDOSAGE

In the event of an overdose, fat overload syndrome may occur *(see Warnings and Precautions (5.5))*. Stop the infusion of SMOFlipid 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.

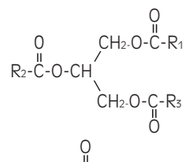
11 DESCRIPTION

SMOFlipid is a sterile, nonpyrogenic, white, homogenous lipid emulsion for intravenous infusion. The lipid content of SMOFlipid is 0.2 g/mL, and comprises a mixture of soybean oil, MCTs, olive oil, and fish oil. The mean concentration of linoleic acid (an omega-6 essential fatty acid) is 35 mg/mL (range of 28 to 50 mg/mL), and alpha-linolenic acid (an omega-3 essential fatty acid) is 4.5 mg/mL (range of 3 to 7 mg/mL). The phosphate content is 15 mmol/L.

The total energy content, including fat, phospholipids, and glycerol is 2,000 kcal/L.

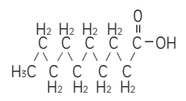
Each 100 mL of SMOFlipid contains approximately 6 g soybean oil, 6 g MCT, 5 g olive oil, 3 g fish oil, 1.2 g egg phospholipids, 2.5 g glycerin, 16.3 to 22.5 mg all-rac-alpha-tocopherol, 0.03 g sodium oleate, water for injection, and sodium hydroxide for pH adjustment (pH 6 to 9).
SMOFlipid has an osmolality of approximately 380 mOsm/kg water (which represents an osmolarity of 270 mOsm/L).

The oils included in SMOFlipid consist of a mixture of triglycerides of predominantly unsaturated fatty acids with the following structure:

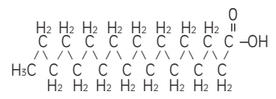


where $R_1CO–$, $R_2CO–$, and $R_3CO–$ are saturated and unsaturated fatty acid residues. The major components of the fatty acids in SMOFlipid are oleic acid (23% to 35%), linoleic acid (14% to 25%), caprylic acid (13% to 24%), palmitic acid (7% to 12%), capric acid (5% to 15%), stearic acid (1.5% to 4%), alpha-linolenic acid (1.5% to 3.5%), eicosapentaenoic acid (EPA; 1% to 3.5%), and docosahexaenoic acid (DHA; 1% to 3.5%).

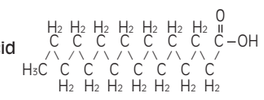
Capric Acid $C_{10}H_{20}O_2$



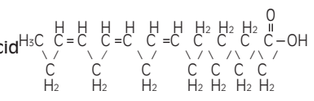
Stearic Acid $C_{18}H_{36}O_2$



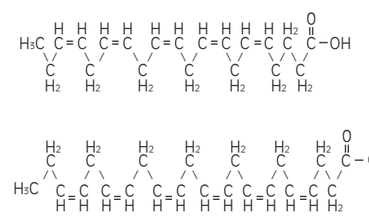
Palmitic Acid $C_{16}H_{32}O_2$



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

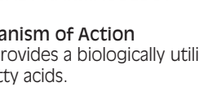


EPA $C_{20}H_{30}O_2$

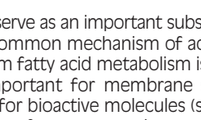


DHA $C_{22}H_{32}O_2$

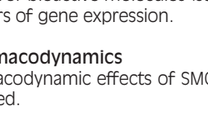
Oleic Acid $C_{18}H_{34}O_2$



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



Caprylic Acid $C_8H_{16}O_2$



SMOFlipid 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

SMOFlipid 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 SMOFlipid have not been fully characterized.

12.3 Pharmacokinetics

SMOFlipid provides fatty acids in the form of triglycerides which are hydrolyzed by lipoprotein lipase to release free fatty acids. Alpha-linolenic acid and linoleic acid are metabolized within a common biochemical pathway through a series of desaturation and elongation steps. Downstream products of alpha-linolenic acid are EPA and DHA, and linoleic acid is converted to arachidonic acid.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

No mutagenic effects were observed in the following in vitro studies with SMOFlipid: bacterial gene mutation assay in *Salmonella typhimurium*, chromosomal aberration assay in human lymphocytes, and hypoxanthine phosphoribosyl transferase (HPRT) gene mutation assay in V79 cells.

In an in vivo bone marrow cytogenic study in rats, no mutagenic effect was observed.

14 CLINICAL STUDIES

14.1 Adult Clinical Studies

The efficacy of SMOFlipid compared to soybean oil lipid emulsions 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 (176 SMOFlipid; 178 comparator), 62% were male, 99% were Caucasian, and ages ranged from 19 to 96 years. All patients received SMOFlipid or the comparator as part of a PN regimen. Although Adult Study 1, Adult Study 2, and Adult Study 3 were not adequately designed to demonstrate the noninferiority of SMOFlipid to the soybean oil comparator, they support SMOFlipid 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 SMOFlipid or a soybean oil lipid emulsion. Changes in mean triglyceride levels from baseline values to Week 4 were similar in both the SMOFlipid and comparator groups. Mean albumin levels demonstrated a comparable decrease in both groups. Mean changes in body weight (kg) and BMI (kg/m^2) were similar in both the SMOFlipid and comparator group.

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 SMOFlipid or a soybean oil intravenous lipid emulsion 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 SMOFlipid and comparator groups.

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 SMOFlipid or a soybean oil lipid emulsion. The increase in mean triglyceride levels from baseline to the final assessment was similar in both the SMOFlipid and comparator groups.

14.2 Pediatric Clinical Studies

The efficacy of SMOFlipid compared to soybean oil lipid emulsions in pediatric patients of all age groups, including term and preterm neonates, was evaluated in 333 pediatric patients in 4 randomized active-controlled, double-blind, parallel-group controlled clinical studies. Although Pediatric Studies 1, 2, 3, and 4 were not adequately designed to demonstrate the noninferiority of SMOFlipid to the soybean oil comparator, they support SMOFlipid as a source of calories and essential fatty acids in pediatric patients. The 333 pediatric patients (170 SMOFlipid; 163 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 SMOFlipid 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 SMOFlipid (n=83) or a soybean oil lipid emulsion (n=78). A total of 119 patients (61 SMOFlipid; 58 comparator) received study treatment for ≥14 days. A total of 25 patients received SMOFlipid for ≥29 days; 5 patients received SMOFlipid 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 SMOFlipid or a soybean oil lipid emulsion (72 neonates in each group). The median treatment duration for SMOFlipid group was 12 days in Pediatric Study 2 and 7 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 SMOFlipid (n=15) or a soybean oil lipid emulsion (n=13) with a median treatment duration of 27 days.

In Pediatric Studies 1, 2 and 3, which enrolled neonates, SMOFlipid-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 soybean oil lipid emulsion-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.

16 HOW SUPPLIED/STORAGE AND HANDLING

SMOFlipid is a sterile lipid injectable emulsion with a lipid content of 0.2 gram/mL available in Flexible Containers in the following sizes:

Product Code	Unit of Sale	Strength	Each
830307310	NDC 63323-820-00 Unit of 10	20 grams/100 mL (0.2 grams/mL)	NDC 63323-820-01 100 mL single-dose Bag
830307312	NDC 63323-820-12 Unit of 20	20 grams/100 mL (0.2 grams/mL)	NDC 63323-820-02 100 mL single-dose Bag
830570310	NDC 63323-820-74 Unit of 10	50 grams/250 mL (0.2 grams/mL)	NDC 63323-820-04 250 mL single-dose Bag
830820310	NDC 63323-820-50 Unit of 12	100 grams/500 mL (0.2 grams/mL)	NDC 63323-820-03 500 mL single-dose Bag
830920310	NDC 63323-820-10 Unit of 6	200 grams/1000 mL (0.2 grams/mL)	NDC 63323-820-05 1000 mL Pharmacy Bulk Package Bag

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

SMOFlipid 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))*.

SMOFlipid 1000 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 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 SMOFlipid 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))*.

17 PATIENT COUNSELING INFORMATION

When initiating SMOFlipid 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 (5.1))*.

Death in Preterm Neonates
Inform patients and caregivers that deaths in preterm infants after infusion of lipid injectable emulsions containing only soybean oil have been reported in the medical literature *(see Warnings and Precautions (5.2))*.

Hypersensitivity Reactions
Inform patients and caregivers that SMOFlipid may cause hypersensitivity reactions. If using SMOFlipid at home, instruct patients or caregivers if a hypersensitivity reaction occurs, stop the infusion of SMOFlipid immediately and seek medical attention *(see Warnings and Precautions (5.3))*.

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

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

Aluminum Toxicity
Inform patients and their 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))*.

Essential Fatty Acid Deficiency
Inform patients and caregivers that cases of EFAD with the use of SMOFlipid have been reported in adults and pediatric patients in the postmarketing period *(see Warnings and Precautions (5.9))*.

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

Manufactured by:

FRESENIUS KABI

Uppsala, Sweden
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