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, USP), for intravenous use

Initial U.S. Approval: 2016

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----------
Smoflipid is indicated in adults as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.(1)

Limitations of Use
The omega-6: omega-3 fatty acid ratio and Medium Chain Triglycerides in Smoflipid have not been shown to improve clinical outcomes compared to other intravenous lipid emulsions. (1)

----------DOSAGE AND ADMINISTRATION----------
- For intravenous infusion only into a peripheral or central vein. (2.1)
- Recommended dosage depends on age, energy expenditure, clinical status, body weight, tolerance, ability to metabolize, and consideration of additional energy given to the patient. (2.5)
- The usual daily dosage in adults is 1 to 2 grams/kg per day and should not exceed 2.5 grams/kg per day (2.5)
- Smoflipid Pharmacy Bulk Package is only indicated for use in pharmacy admixture program for the preparation of three-in-one or total nutrition admixtures (TNAs) (2.3)
- Protect the admixed PN solution from light. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
Smoflipid is a lipid injectable emulsion with a lipid content of 0.2 grams/mL in 100 mL, 250 mL, 500 mL flexible containers and 1000 mL Pharmacy Bulk Package. (3)

----------CONTRAINDICATIONS----------
- Known hypersensitivity to fish, egg, soybean, or peanut protein, or to any of the active ingredients or excipients. (4)
- Severe hyperlipidemia or severe disorders of lipid metabolism with serum triglycerides > 1,000 mg/dL. (4, 5.8)

----------WARNINGS AND PRECAUTIONS----------
- Hypersensitivity Reactions: Monitor for signs or symptoms. Discontinue infusion if reactions occur. (5.2)
- Risk of Catheter-Related Infections, Fat Overload Syndrome, Hypertriglyceridemia, and Refeeding Syndrome: Monitor for signs and symptoms; monitor laboratory parameters. (5.3, 5.4, 5.5, 5.8)
- Aluminum Toxicity: Increased risk in patients with renal impairment, including preterm infants. (5.6, 8.4)
- Risk of Parenteral Nutrition-Associated Liver Disease: Increased risk in patients who receive parenteral nutrition for extended periods of time, especially preterm infants. Monitor liver function tests, if abnormalities occur consider discontinuation or dosage reduction. (5.7, 8.4)

----------ADVERSE REACTIONS----------
Most common adverse drug reactions (>1%) from clinical trials were nausea, vomiting, hyperglycemia, flatulence, pyrexia, abdominal pain, increased blood triglycerides, hypertension, sepsis, dyspepsia, urinary tract infection, anemia and device related 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----------
Coumarin and Coumarin Derivatives, Including Warfarin: Anticoagulant activity may be counteracted; monitor laboratory parameters. (7.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2020

FRESENIUS KABI

FULL PRESCRIBING INFORMATION: CONTENTS*
WARNING: DEATH IN PRETERM INFANTS

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

FULL PRESCRIBING INFORMATION

WARNING: DEATH IN PRETERM INFANTS
- **Deaths in preterm infants after infusion of intravenous lipid emulsions have been reported in the medical literature.**
- **Autopsy findings included intravascular fat accumulation in the lungs.**
- **Preterm infants and low-birth-weight infants have poor clearance of intravenous lipid emulsion and increased free fatty acid plasma levels following lipid emulsion infusion.**

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

1 INDICATIONS AND USAGE

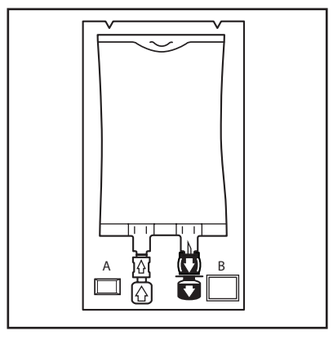
Smoflipid is indicated in adults as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.

Limitations of Use
The omega-6: omega-3 fatty acid ratio and Medium Chain Triglycerides in Smoflipid have not been shown to improve clinical outcomes compared to other intravenous lipid emulsions *[See Clinical Studies (14)]*.

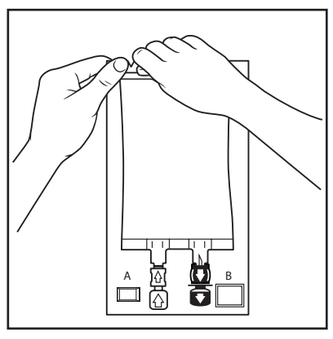
2 DOSAGE AND ADMINISTRATION

2.1 Administration Instructions
- Smoflipid is for central or peripheral intravenous infusion. When administered with dextrose and amino acids, the choice of a central or peripheral venous route should depend on the osmolarity of the final infusate. Solutions with osmolarity of ≥ 900 mOsm/L must be infused through a central vein.
- Use a 1.2 micron in-line filter.
- Use a dedicated line for parenteral nutrition (PN). 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.
- To prevent air embolism, use a non-vented infusion set or close the vent on a vented set, avoid multiple connections, do not connect flexible bags in series, 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 pump before the bag runs dry.
- Do not use administration sets and lines that contain di-2-ethylhexyl phthalate (DEHP). Administration sets that contain polyvinyl chloride (PVC) components have DEHP as a plasticizer
- Smoflipid 1000 mL is supplied as a Pharmacy Bulk Package *for admixing only* and is *not for direct infusion*. Prior to administration, transfer to a separate PN container *[see Dosage and Administration (2.3)]*.

2.2 Instructions for Use

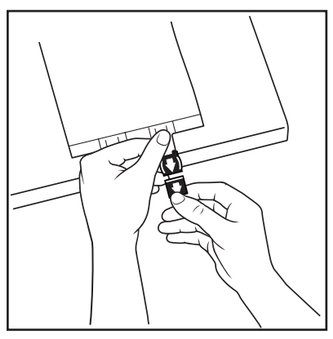


1. Inspect the integrity indicator (Oxalert®) (A) before removing the overpouch. Discard the product if the indicator is black.



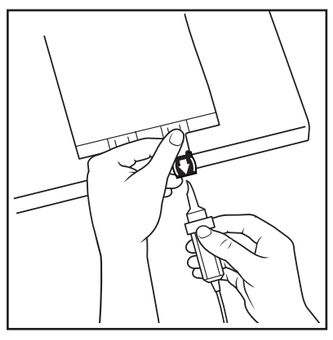
2. Place the bag on a clean, flat surface. Remove the overpouch by tearing at the notch and pulling down along the container. The Oxalert sachet (A) and the oxygen absorber (B) should be discarded.

   Inspect the bag and contents prior to administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect Smoflipid to ensure that the emulsion has not separated. The lipid emulsion should be a homogenous liquid with a milky appearance. Discard the bag if there appears to be a phase separation of the emulsion, or if any signs of discoloration, particulates, and/or leakage are observed.

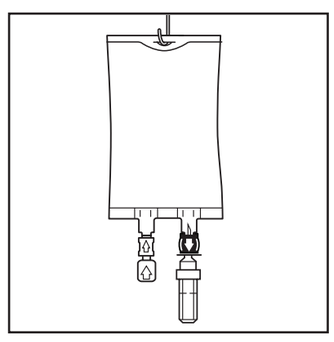


3. Break off the BLUE infusion port cap with the arrow pointing away from the bag.

NOTE: Choose a nonvented infusion set or close the air vent on a vented set. Follow the instructions for use for the infusion set. Use infusion sets (according to ISO Number 8536-4) with an external spike diameter of 5.5 to 5.7 mm. Use a 1.2 micron in-line filter during administration.



4. Hold the base of the infusion port. Insert the spike through the infusion port by rotating your wrist slightly until the spike is inserted.



5. Hang the bag using the hanger cut

   For Single Use Only
   Discard unused portion.

Smoflipid 100 mL, 250 mL and 500 mL Flexible Containers

- After removing the overpouch, infuse immediately. If not used immediately, the product should not be stored longer than 24 hours at 2° to 8°C (36° to 46°F). After removal from storage, infuse within 24 hours.

2.3 Preparation of Pharmacy Bulk Package
- Smoflipid 1000 mL Pharmacy Bulk Package is *for admixing use only. It is not for direct intravenous infusion*. Prior to administration, transfer to a separate PN container for individual patient use.
- Use the Pharmacy Bulk Package only in a suitable work area such as a laminar flow hood or an equivalent clean air compounding area.
- Do not pierce infusion port more than once.
- 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 up to 24 hours at 2° to 8°C (36° 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 (2.4)]*.

2.4 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.
- Smoflipid may be mixed with amino acid and dextrose injections to produce "all-in-one" PN admixtures. The following proper mixing sequence must be followed to minimize pH-related problems by ensuring that typically acidic dextrose injections are not mixed with lipid emulsions alone:
  1. Transfer dextrose injection to the PN container.
  2. Transfer amino acid injection.
  3. 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; shake bags gently after each addition.
- Do not inject additives directly into Smoflipid.
- Additions to the PN admixtures should be evaluated by a pharmacist for compatibility. Questions about compatibility may be directed to Fresenius Kabi USA, LLC at 1-800-551-7176. If it is deemed advisable to introduce additives, use strict aseptic techniques to avoid microbial contamination.
- 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.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect the admixture to ensure that:
  - precipitates have not formed during preparation of the admixture, and
  - the emulsion has not separated. Separation of the emulsion can be visibly identified by a yellowish streaking or the accumulation of yellowish droplets in the admixed emulsion.

  Discard the admixture if any of these are observed.
- The remaining contents of a partly used bag must be discarded.
- Infuse admixtures containing Smoflipid immediately. If not used immediately, store admixtures under refrigeration at 2° to 8°C (36° to 46°F) not to exceed 24 hours. Infusion must be complete within 24 hours after removal from refrigeration. Discard any remaining admixture.
- Protect the admixed PN solution from light.

2.5 Adult Dosing Information
- The dosing of Smoflipid depends on the patient's individual energy requirements influenced by age, body weight, tolerance, clinical status, and the ability to eliminate and metabolize 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.
- Smoflipid contains 0.163 to 0.225 mg/mL of all-rac-α-tocopherol. The daily US recommended dietary allowance (RDA) in adults for α-tocopherol (Vitamin E) is 15 mg. Take into account the amount of α-tocopherol in Smoflipid when determining the need for additional supplementation.

Recommended Adult Dosing
- The recommended dosage of Smoflipid for adult patients is 1 to 2 grams/kg per day and should not exceed 2.5 grams/kg per day.[1] The initial rate of infusion should be 0.5 mL/min 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 0.5 mL/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.
- Before starting the infusion, determine serum triglyceride levels to establish the baseline value. In patients with elevated triglyceride levels, initiate Smoflipid at a lower dosage and advance in smaller increments, monitoring the triglyceride levels with each adjustment *[see Warnings and Precautions (5.8, 5.9)]*.

3 DOSAGE FORMS AND STRENGTHS

Smoflipid is a lipid injectable emulsion with a lipid content of 0.2 g/mL available in 100 mL, 250 mL, 500 mL flexible containers and a 1000 mL Pharmacy Bulk Package (PBP).

4 CONTRAINDICATIONS

Use of Smoflipid is contraindicated in patients with:
- Known hypersensitivity to fish, egg, soybean, or peanut protein, or to any of the active ingredients or excipients, or
- Severe hyperlipidemia or severe disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglyceride concentrations > 1,000 mg/dL) *[see Warnings and Precautions (5.8)]*

5 WARNINGS AND PRECAUTIONS

5.1 Death in Preterm Infants
Deaths after infusion of soybean-based intravenous lipid emulsions have been reported in preterm infants. Autopsy findings included intravascular lipid accumulation in the lungs. Preterm and small-for-gestational-age infants have poor clearance of intravenous lipid emulsion and increased free fatty acid plasma levels following lipid emulsion infusion. The safe and effective use of Smoflipid in pediatric patients, including preterm infants, has not been established.

5.2 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 oil. Signs or symptoms of a hypersensitivity reaction may include: tachypnea, dyspnea, hypoxia, bronchospasm, tachycardia, hypotension, cyanosis, vomiting, nausea, headache, sweating, dizziness, altered mentation, flushing, rash, urticaria, erythema, pyrexia, or chills. If a hypersensitivity reaction occurs, stop infusion of Smoflipid immediately and undertake appropriate treatment and supportive measures.

5.3 Risk of Catheter-Related Infections
Lipid emulsions, such as Smoflipid, can support microbial growth and is an independent risk factor for the development of catheter-related bloodstream infections. The risk of infection is increased in patients with malnutrition-associated immunosuppression, long-term use and poor maintenance of intravenous catheters, or immunosuppressive effects of other concomitant conditions or drugs.
To decrease the risk of infectious complications, ensure aseptic techniques in catheter placement, catheter maintenance, and preparation and administration of Smoflipid. Monitor for signs and symptoms (fever and chills) of early infections, including laboratory test results that might indicate infection (including leukocytosis and hyperglycemia), and frequently checks of the parenteral access device and insertion site for edema, redness, and discharge.

5.4 Fat Overload Syndrome
Fat overload syndrome is a rare condition that has been reported with intravenous lipid emulsions. A reduced or limited ability to metabolize lipids accompanied by prolonged plasma clearance may result in a syndrome characterized by a sudden deterioration in the patient's condition including fever, anemia, leukopenia, thrombocytopenia, coagulation disorders, hyperlipidemia, liver fatty infiltration (hepatomegaly), deteriorating liver function, and central nervous system manifestations (e.g., coma). The cause of the fat overload syndrome is unclear. Although it has been most frequently observed when the recommended lipid dose was exceeded, cases have also been described where the lipid formulation was administered according to instructions. The syndrome is usually reversible when the infusion of the lipid emulsion is stopped.

5.5 Refeeding Syndrome
Refeeding severely undernourished patients with PN may result in the refeeding syndrome, characterized by the intracellular shift of potassium, phosphorus, and magnesium as the patient becomes anabolic. Thiamine deficiency and fluid retention may also develop. To prevent these complications, monitor severely undernourished patients and slowly increase their nutrient intakes.

5.6 Aluminum Toxicity
Smoflipid contains no more than 25 mcg/L of aluminum. However, with prolonged PN administration in patients with renal impairment, the aluminum levels in the patient may reach toxic levels. Preterm infants are at greater risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions, which contain aluminum.

Patients with renal impairment, including preterm infants, who receive parenteral levels of aluminum at greater than 4 to 5 mcg/kg/day accumulate aluminum to levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration of PN products.

5.7 Risk of Parenteral Nutrition-Associated Liver Disease
Parenteral nutrition-associated liver disease (PNALD) has been reported in patients who receive PN for extended periods of time, especially preterm infants, and can present as cholestasis or steatohepatitis. The exact etiology is unknown and is likely multifactorial. Intravenously administered phytosterols (plant sterols) contained in plant-derived lipid formulations have been associated with development of PNALD, although a causal relationship has not been established.

If Smoflipid-treated patients develop liver test abnormalities, consider discontinuation or dose reduction.

5.8 Hypertriglyceridemia
Impaired lipid metabolism with hypertriglyceridemia may occur in conditions such as inherited lipid disorders, obesity, diabetes mellitus, and metabolic syndrome.
To evaluate the patient's capacity to eliminate and metabolize the infused lipid emulsion, measure serum triglycerides before the start of infusion (baseline value), at the time of each increase in dosage, and regularly throughout treatment.
In adult patients with levels > 400 mg/dL, reduce the dose of Smoflipid and monitor serum triglyceride levels to avoid the clinical consequences associated with hypertriglyceridemia. Serum triglyceride levels > 1,000 mg/dL, have been associated with an increased risk of pancreatitis.

5.9 Monitoring/Laboratory Tests
Routine Monitoring
Monitor serum triglycerides *[see Warnings and Precautions (5.8)]*, fluid and electrolyte status, blood glucose, liver and kidney function, blood count including platelets, and coagulation parameters throughout treatment.

Essential Fatty Acids
Monitoring patients for signs and symptoms of essential fatty acid deficiency (EFAD) is recommended. Laboratory tests are available to determine serum fatty acids levels. Reference values should be consulted to help determine adequacy of essential fatty acid status. Increasing essential fatty acid intake (enterally or parenterally) is effective in treating and preventing EFAD.
In Smoflipid, the mean concentration of linoleic acid (an omega-6 essential fatty acid) is 35 mg/mL (range 28 to 50 mg/mL), and α-linolenic acid (an omega-3 essential fatty acid) is 4.5 mg/mL (range 3 to 7 mg/mL). There are insufficient long-term data to determine whether Smoflipid can supply essential fatty acids in adequate amounts in patients who may have increased requirements.

5.10 Interference with Laboratory Tests
Content of vitamin K may counteract anticoagulant activity *[see Drug Interactions (7.1)]*. The lipids contained in this emulsion may interfere with some laboratory blood tests (e.g., hemoglobin, lactate dehydrogenase [LDH], bilirubin, and oxygen saturation) if blood is sampled before lipids have cleared from the bloodstream. Lipids are normally cleared after a period of 5 to 6 hours once the lipid infusion is stopped.

6 ADVERSE REACTIONS

Adverse reactions described elsewhere in labeling:
- Death in Preterm Infants *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- Risk of Catheter-Related Infections *[see Warnings and Precautions (5.3)]*
- Fat Overload Syndrome *[see Warnings and Precautions (5.4)]*
- Refeeding Syndrome *[see Warnings and Precautions (5.5)]*
- Aluminum Toxicity *[see Warnings and Precautions (5.6)]*
- Risk of Parenteral Nutrition-Associated Liver Disease *[see Warnings and Precautions (5.7)]*
- Hypertriglyceridemia *[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.
The safety database for Smoflipid reflects exposure in 229 patients 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 were performed with Smoflipid as a component of PN delivered in a 3-chamber bag.
Adverse reactions occurring in at least 1% of patients who received Smoflipid are shown in Table 2.

Table 2:
Adverse Reactions in > 1% of 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 in ≤ 1% of 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.

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.

Infections and Infestations: infection
Respiratory, Thoracic and Mediastinal Disorders: dyspnea

7 DRUG INTERACTIONS

7.1 Coumarin and Coumarin Derivatives
No drug interaction studies have been performed with Smoflipid.
Soybean oil and olive oil have a natural content of vitamin K_1 that may counteract the anticoagulant activity of coumarin and coumarin derivatives including warfarin. Monitor laboratory parameters for anticoagulant activity in patients who are on both Smoflipid 20% and coumarin or coumarin derivatives.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
There are no available data on risks associated with Smoflipid when used in pregnant women. Animal reproduction studies have not been conducted with Smoflipid. It is not known whether Smoflipid can cause fetal harm when administered to a pregnant woman. Consider the benefits and risks of Smoflipid when prescribing to a pregnant woman. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations
Disease-associated maternal and/or embryo/fetal risk
Severe malnutrition in a pregnant woman is associated with preterm delivery, low birth weight, intrauterine growth restriction, congenital malformations, and perinatal mortality. Parenteral nutrition should be considered if the pregnant woman's nutritional requirements cannot be fulfilled by oral or enteral intake.

8.2 Lactation
Risk summary
No data are available regarding the presence of Smoflipid in human milk, the effects on the breast fed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Smoflipid, and any potential adverse effects on the breastfed infant from Smoflipid, or from the underlying maternal condition.

8.4 Pediatric Use
The safety and effectiveness of Smoflipid have not been established in pediatric patients. Deaths in preterm infants after infusion of intravenous lipid emulsion have been reported *[see Warnings and Precautions (5.1)]*. Because of immature renal function, preterm infants receiving prolonged treatment with Smoflipid may be at risk of aluminum toxicity *[see Warnings and Precautions (5.6)]*. Patients, including pediatric patients, may be at risk for PNALD *[see Warnings and Precautions (5.6)]*.

There are insufficient data from pediatric studies to establish that Smoflipid injection provides sufficient amounts of essential fatty acids (EFA) in pediatric patients. Pediatric patients may be particularly vulnerable to neurologic complications due to EFA deficiency if adequate amounts of EFA are not provided *[see Warnings and Precautions (5.9)]*. In clinical trials of a soybean oil-based intravenous lipid emulsion product, thrombocytopenia in neonates occurred (less than 1%). Smoflipid contains soybean oil (30% of total lipids).

8.5 Geriatric Use
Energy expenditure and requirements may be lower for older adults than younger patients. Of the 354 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.

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

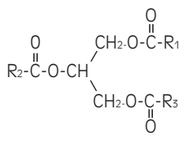
Monitor liver function parameters closely. Patients developing signs of hepatobiliary disorders should be assessed early by a clinician knowledgeable in liver diseases in order to identify causative and contributory factors, and possible therapeutic and prophylactic interventions.

10 OVERDOSAGE

In the event of an overdose, fat overload syndrome may occur *[see Warnings and Precautions (5.4)]*. Stop the Smoflipid infusion until triglyceride levels have normalized. The effects are usually reversible by stopping the lipid infusion. If medically appropriate, further intervention may be indicated. Lipids are not dialyzable from serum.

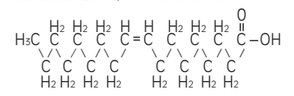
11 DESCRIPTION

Smoflipid is a sterile, nonpyrogenic, white, homogenous lipid emulsion for intravenous infusion. The lipid content of Smoflipid is 0.20 g/mL, and comprises a mixture of soybean oil, medium-chain triglycerides (MCTs), olive oil, and fish oil. The mean essential fatty acid content of Smoflipid is 35 mg/mL (range of 28 to 50 mg/mL) linoleic acid (omega-6) and 4.5 mg/mL (range of 3 to 7 mg/mL) α-linolenic acid (omega-3). 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*-α-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:

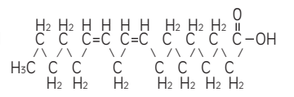


where $R_1CO–$, $R_2CO–$, and $R_3CO–$ are saturated and unsaturated fatty acid residues. The major components of the fatty acids in Smoflipid are oleic acid (23% to 35%), linoleic acid (14% to 25%), caprylic acid (13% to 24%), palmitic acid (7% to 12%), capric acid (5% to 15%), stearic acid (1.5% to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

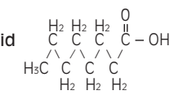
Oleic Acid
$C_{18}H_{34}O_2$



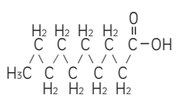
Linoleic Acid
$C_{18}H_{32}O_2$



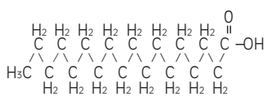
Caprylic Acid
$C_8H_{16}O_2$



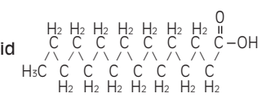
Capric Acid
$C_{10}H_{20}O_2$



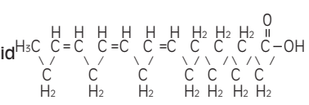
Stearic Acid
$C_{18}H_{36}O_2$



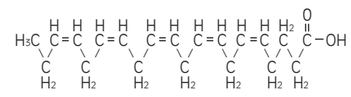
Palmitic Acid
$C_{16}H_{32}O_2$



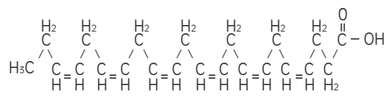
Linolenic Acid
$C_{18}H_{30}O_2$



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



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



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 administered intravenously 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, precursors for bioactive molecules (such as prostaglandins), and as regulators of gene expression.
Smoflipid causes an increase in heat production, decrease in respiratory quotient, and increase in oxygen consumption following its administration.

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

The efficacy of Smoflipid compared to soybean oil lipid emulsions was evaluated in three clinical trials. Of the 354 patients treated in these studies, (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 Study 1, Study 2, and Study 3 were not adequately designed to demonstrate 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. Nutritional efficacy was assessed by biomarkers of lipid metabolism, anthropometric indices (body weight, height, body mass index [BMI]), and/or biomarkers of protein metabolism (albumin) and mean changes in fatty acid parameters.

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.

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.

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.

15 REFERENCES

1. Mirtallo J, Canada T, Johnson D, Kumpf V, Petersen C, Sacks G, et al. Task Force for the Revision of Safe Practices for Parenteral Nutrition, Special Report: Safe practices for parenteral nutrition. *JPEN*. 2004:28 (6):S53-S55.

16 HOW SUPPLIED/STORAGE AND HANDLING

Smoflipid is a sterile lipid injectable emulsion with a lipid content of 0.2 grams/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 Bag
830307312	NDC 63323-820-12 Unit of 20	20 grams/100 mL (0.2 grams/mL)	NDC 63323-820-02 100 mL Bag
830570310	NDC 63323-820-74 Unit of 10	50 grams/250 mL (0.2 grams/mL)	NDC 63323-820-04 250 mL Bag
830820310	NDC 63323-820-50 Unit of 12	100 grams/500 mL (0.2 grams/mL)	NDC 63323-820-03 500 mL 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 flexible containers.

After removing the overpouch, infuse immediately. If not used immediately, storage should not be longer than 24 hours at 2° to 8°C (36° to 46°F). After removal from storage, infuse within 24 hours *[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 can be stored for up to 24 hours at 2° to 8°C (36° 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 (2.4)]*.

Admixtures

Infuse admixtures containing Smoflipid immediately. If not used immediately, admixtures should not be stored longer than 24 hours at 2° to 8°C (36° to 46°F). After removal from storage, infuse within 24 hours *[see Dosage and Administration (2.4)]*.

17 PATIENT COUNSELING INFORMATION

Inform patients, their families, or caregivers of the following risks of Smoflipid:
- Deaths in Preterm Infants *[see Warnings and Precautions (5.1)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.2)]*
- Risk of Catheter-Related Infections *[see Warnings and Precautions (5.3)]*
- Fat Overload Syndrome *[see Warnings and Precautions (5.4)]*
- Refeeding Syndrome *[see Warnings and Precautions (5.5)]*
- Aluminum Toxicity *[see Warnings and Precautions (5.6)]*
- Risk of Parenteral Nutrition-Associated Liver Disease *[see Warnings and Precautions (5.7)]*
- Hypertriglyceridemia *[see Warnings and Precautions (5.8)]*

Manufactured by:

FRESENIUS KABI

Uppsala, Sweden

451418C