pn^4

SMOFlipid®

(lipid injectable emulsion),
for intravenous use

Designed with *more* oil sources
for a balanced fatty acid profile

FRESENIUS KABI

Please see Brief Summary of Prescribing Information on pages 17-19.

Get to know SMOFlipid

FDA approved for pediatric patients in 2022[1]

Studied in more than 170 pediatric patients in 4 randomized active-controlled, double-blind, parallel-group controlled clinical trials[1]

Well-established safety and tolerability profile[1]

Administered to more than 7 million pediatric and adult patients worldwide*

Trusted lipid for the top 10 children's hospitals†*

Comprehensive compatibility and stability testing methodology and data*

Sustainably sourced fish oil*

*Data on file 4/1/25.
†As reported by US News & World Report: https://health.usnews.com/best-hospitals/pediatric-rankings

Explore the 4-oil difference

SMOFlipid is the only PN innovation for use in pediatric patients designed to nourish daily with a **proprietary blend of 4 oils.**[1]

30% Soybean oil:
Provides essential fatty acids

30% Medium-chain triglycerides (MCT):
A source of rapidly available energy[2]

25% Olive oil:
Supplies monounsaturated fatty acids

15% Fish oil:
A good source of omega-3 fatty acids, which include DHA and EPA[3]

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PN, parenteral nutrition.

Lipids and fatty acids

The omega-3 fatty acids DHA and EPA are considered important due to their physiological roles*[4,5]:

May be considered conditionally essential for growth and development[6,7]

DHA is highly enriched in specific phospholipids of the retina and nonmyelin membranes of the nervous system[8]

Important structural elements of cell membranes[5]

***The physiological roles of EPA and DHA have not been established in clinical studies (with SMOFlipid).**

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

DHA and ARA decline in the first week of life[9,10]

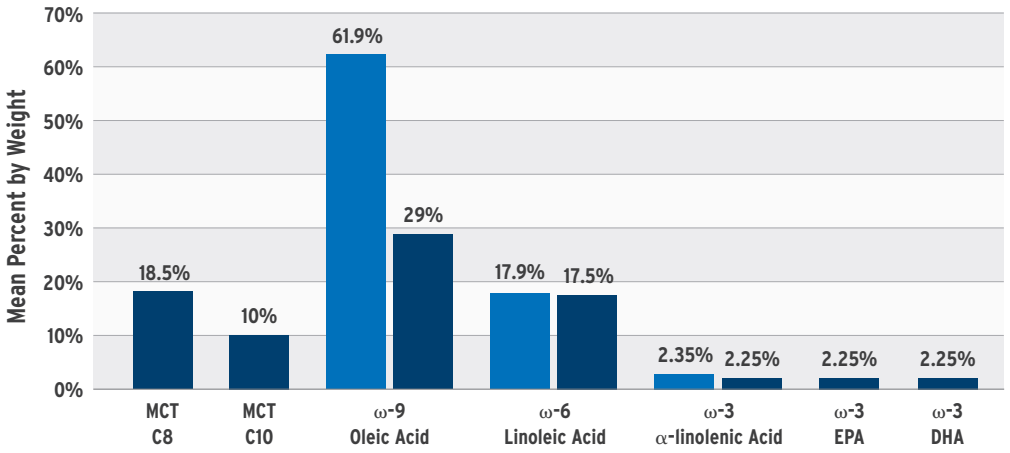
- DHA and ARA decline in the first week of life regardless of the lipid product, including SMOFlipid and good enteral nutrition, specifically breast milk[9,10]
- In-utero accretion of DHA and ARA occurs particularly in the retina and central nervous system[11]
- DHA and ARA stores decline in premature infants (missing the third trimester biomagnification)[12]
- DHA and ARA stores continue to decline in infants fed a SO ILE, despite adequate essential fatty acids[9,10]

Abbreviations: ARA, arachidonic acid; DHA, docosahexaenoic acid; ILE, lipid injectable emulsion; SO, soybean oil.

A composition comparison

SMOFlipid vs Clinolipid (Lipid Injectable Emulsion) for Intravenous Use

Fatty acid composition[1,13]



Clinolipid is a registered trademark of Baxter International Inc.

Fatty acids in ILEs are a necessary part of PN[9-12,14]

Infants need lipids as part of PN to[4,14]:

- Supply essential fatty acids, such as LA and ALA which are precursors to LCPUFAs that help prevent EFAD
  - LA is an omega-6 fatty acid and precursor to ARA, whereas ALA is an omega-3 fatty acid and precursor to DHA and EPA
  - DHA and ARA play a role in infant development
- SMOFlipid contains these fatty acids[1]

Abbreviations: ALA, alpha-linolenic acid; ARA, arachidonic acid; DHA, docosahexaenoic acid; EFAD, essential fatty acid deficiency; EPA, eicosapentaenoic acid; ILE, lipid injectable emulsion; LA, linoleic acid; LCPUFAs, long-chain polyunsaturated fatty acids; PN, parenteral nutrition.

Breast milk and fatty acids

Breast milk is rich in a variety of fatty acids.[15] When breast feeding is not an option, formulas with added fatty acids are used to mimic breast milk.[16] For infants unable to feed enterally, PN with a similar fatty acid profile could be considered.

When considering lipids as part of PN:

- Specific nutrients are important in pediatric PN, similar to pediatric-specific amino acids and vitamin mineral additives
- A variety of fatty acids including omega-3 fatty acids with DHA and EPA, as well as omega-6 and omega-9 fatty acids, resembles the fatty acid profile provided by breast milk or infant formula[17]

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PN, parenteral nutrition.

Fatty acid pattern of SMOFlipid vs human breast milk[17]

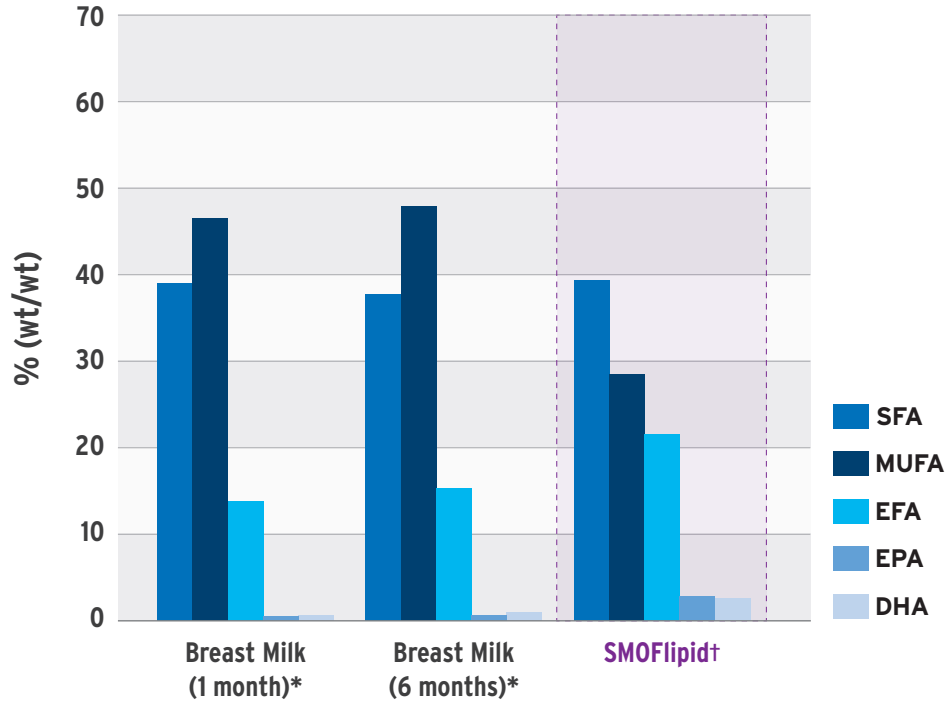


Figure adapted with permission from: Goulet O. *Nutrients*. 2024;16(3):440.[17]
Fatty acid pattern of lipid emulsions vs. human breast milk. Compiled from *Koletzko et al., 2016, †Goulet et al., 2010.

In this analysis, **SMOFlipid** had a fatty acid composition that is similar to breast milk.[17]

PNAC may develop less frequently in pediatric patients fed a 4-oil ILE vs 100% SO ILE[1]

In a randomized clinical trial among neonates and infants expected to be treated with PN for at least 28 days, **PNAC, a precursor to PNALD, developed less frequently in SMOFlipid-treated patients than in 100% SO lipid emulsion-treated patients.**[1]

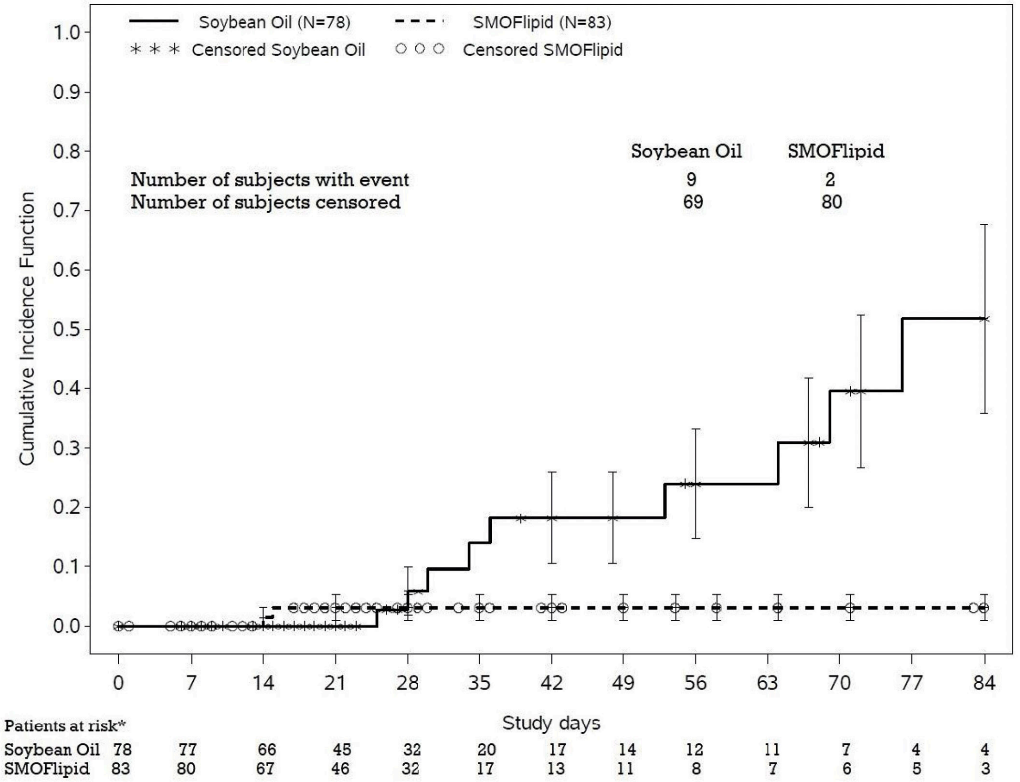
Pediatric Study 1 also compared the incidence of PNAC (DBIL >2 mg/dL with a second confirmed DBIL >2 mg/dL at least 7 days later) in both groups[1]:

- PNAC mostly occurred in patients who received treatment for more than 28 days
- 2.4% (2/83) of SMOFlipid-treated patients developed PNAC
- 11.5% (9/78) of SO lipid emulsion-treated patients developed PNAC

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.[1]

Abbreviations: DBIL, direct bilirubin; ILE, lipid injectable emulsion; PNAC, parenteral nutrition-associated cholestasis; PNALD, parenteral nutrition-associated liver disease; SO, soybean oil.

Estimated cumulative incidence of PNAC[1]



*There is increasing uncertainty in the estimate of the cumulative incidence as fewer patients are at risk.

Monitor liver tests in patients treated with SMOFlipid and consider discontinuation or dosage reduction if abnormalities occur.[1]

Abbreviations: PNAC, parenteral nutrition-associated cholestasis.

Intravenous lipid use in high-risk neonates requiring PN and associated hepatic outcomes*[18]

Study Purpose and Design:

- Evaluate effects of SMOFlipid vs. Intralipid® in neonates requiring PN ≥28 days
- Double-blind, randomized, controlled trial at 14 US study sites
- Randomization of 161 term and preterm neonates at high risk for IFALD
- Intervention: Intralipid (n=78), SMOFlipid (n=83), up to 3 g/kg/day as part of PN (mean lipid dose 2.0 ± 0.1 g/kg/day SMOFlipid, 2.6 ± 0.2 g/kg/day Intralipid)

Liver Results:

- Analysis showed a trend toward a lower risk of cholestasis in the SMOFlipid group (NS due to the low number of events)
- Significantly lower conjugated bilirubin concentration (P = 0.006) at the end of the initial treatment phase in the SMOFlipid group
- No new cases of confirmed cholestasis occurred after day 28 in the SMOFlipid group for up to 84 days

Study Limitations:

There was a low incidence of cholestasis in both treatment groups compared to historical data. Additionally, there was a low completion rate (40%) predominantly due to earlier weaning from PN. The use of SMOFlipid in patients with established cholestasis was not assessed.

> "Our data supports use of [SMOFlipid] a composite ILE with EPA and DHA from fish oil, for PN in high-risk neonates and infants at risk of IFALD such as those with impaired intestinal function or surgical conditions preventing use of enteral nutrition."[18]

Consider SMOFlipid as an alternative to Intralipid in high-risk neonates.

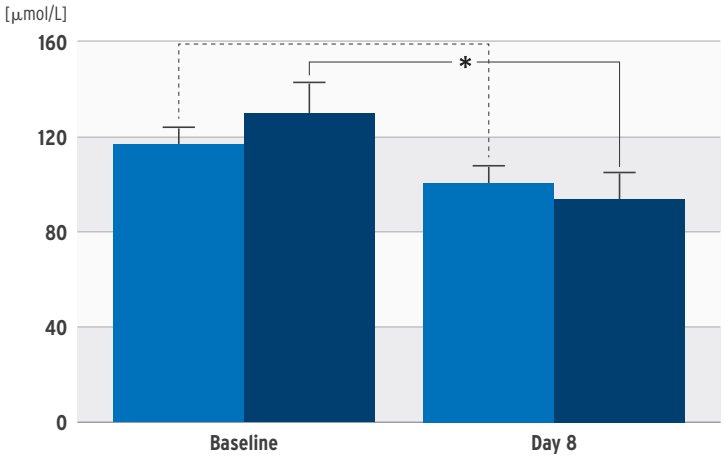
Parenteral Nutrition-Associated Liver Disease: Increased risk in patients who receive parenteral nutrition for greater than 2 weeks, especially preterm neonates. Monitor liver tests; if abnormalities occur, consider discontinuation or dosage reduction.[1]

***This trial was funded by Fresenius Kabi Deutschland GmbH upon requirement of a postmarketing study from the United States Food and Drug Administration.**

Abbreviations: DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IFALD, intestinal failure-associated liver disease; ILE, lipid injectable emulsion; NS, not significant; PN, parenteral nutrition.

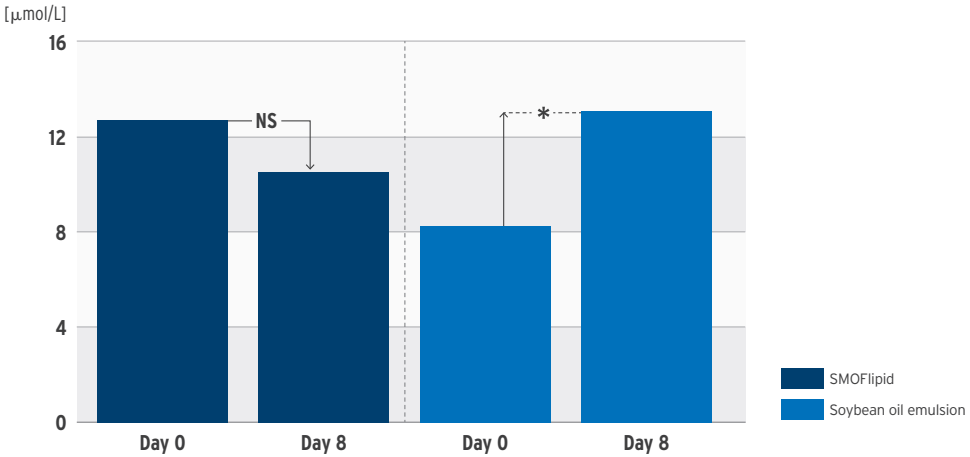
Impact on bilirubin in SMOFlipid clinical trials[19]

Decrease in **total bilirubin** concentration



Total bilirubin pre- and post-treatment (mean ± SEM)

Change in **direct bilirubin** concentration



Course of plasma concentrations of direct bilirubin after 8 days (mean ± SD)
NS, not significant.

*P < 0.05 between group difference of changes from baseline to last visit

Prospective, randomized, controlled, double-blind trial in 53 neonates (< 34 weeks' gestation); PN at least 7 days; test group: SMOFlipid, control group: soybean oil emulsion

Significantly higher decrease in total bilirubin concentration in the SMOFlipid-group.

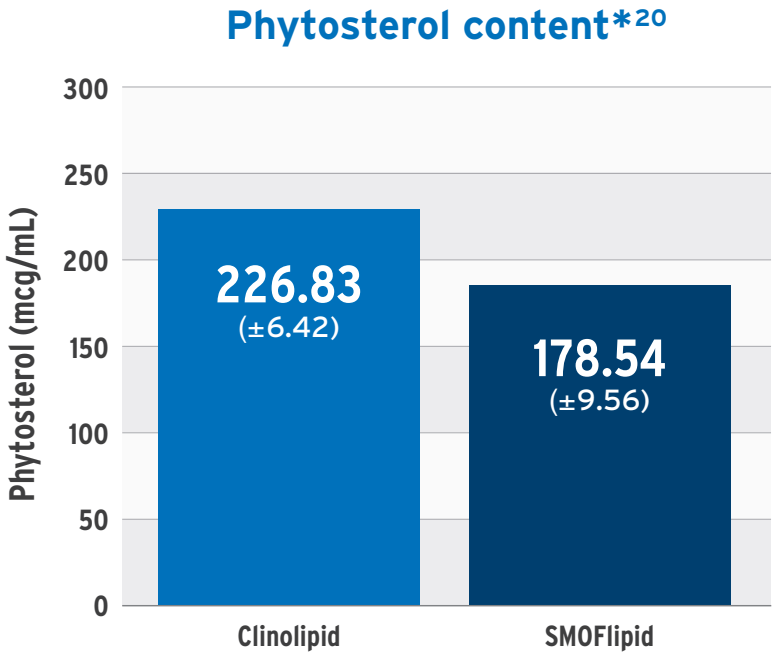
The change in direct bilirubin concentration from Day 0 to Day 8 for the SMOFlipid group compared to the change from Day 0 to Day 8 in the soybean oil emulsion group was significant between groups.

- One on-label submitted study showed no difference in total bilirubin between the two groups[9]

Parenteral Nutrition-Associated Liver Disease: Monitor liver tests; if abnormalities occur, consider discontinuation or dosage reduction.[1]

Abbreviations: PN, parenteral nutrition.

A composition comparison



In data from a study, **SMOFlipid** had lower levels of phytosterols than Clinolipid.[20]

*Data points are shown as mean values.
Clinolipid is a registered trademark of Baxter International Inc.

Parenteral nutrition-associated liver disease (PNALD): Increased risk in patients who receive PN for greater than 2 weeks, especially preterm neonates.[21] Monitor liver tests; if abnormalities occur, consider discontinuation or dosage reduction.[1]

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.[1]

Incidence of EFAD

SMOFlipid[1]

Treatment-emergent cases of moderate or severe EFAD (defined as the triene [Mead acid] to tetraene [ARA] ratio >0.2 and >0.4, respectively) **were not observed** in pediatric clinical trials of SMOFlipid **up to 28 days**.

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 for signs and symptoms of EFAD; monitor laboratory parameters.

Clinolipid[13]

One patient treated with Cinolipid **became at risk for EFAD (T:T ratio >0.2) after 14** days of treatment.

No cases of biochemical EFAD and no cases of clinical EFAD were observed; however, the median treatment duration in three of the four pediatric trials was 15 days or less.

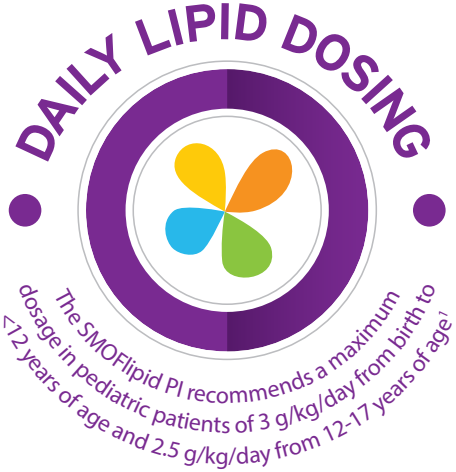
Clinolipid is a registered trademark of Baxter International Inc.

DISCLAIMER: FDA required postmarket studies on this outcome for both SMOFlipid and Clinolipid.

Abbreviations: ARA, arachidonic acid; EFAD, essential fatty acid deficiency; T:T, triene to tetraene.

SMOFlipid nourishes pediatric patients daily with a blend of 4 oil sources[1]

- The dosing of SMOFlipid varies in pediatrics and neonates; each patient group has its own specific dosing specifications
- The duration of infusion will vary depending on the clinical situation
- The administration flow rate is determined by dividing the volume of lipid by the duration of the infusion
- Protect the admixed PN solution from light
- Use a non-vented, non-DEHP 1.2 micron in-line filter set during administration



Pediatric Age Group	Initial Dose	Maximum Dose	Maximum Direct Infusion Rate
Birth to 2 years of age (including preterm and term neonates)	0.5 to 1 g/kg/day	3 g/kg/day	0.75 mL/kg/hour
2 to <12 years of age	1 to 2 g/kg/day	3 g/kg/day	0.75 mL/kg/hour
12 to 17 years of age	1 g/kg/day	2.5 g/kg/day	0.75 mL/kg/hour

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.[1]

Do not exceed the maximum infusion rate of 0.75 mL/kg/hour in pediatric patients.[1]

Clinical Decompensation with Rapid Infusion of Intravenous Lipid Emulsion in Neonates and Infants: Acute respiratory distress, metabolic acidosis, and death after rapid infusion of intravenous lipid emulsions have been reported.[1]

Abbreviations: PN, parenteral nutrition.

Explore the 4-oil difference[1]

- An alternative lipid for your pediatric patients requiring parenteral nutrition
- Provides a source of calories and essential fatty acids
- Nourishes your tiny patients with a one-of-a-kind blend of 4 oil sources

SMOFlipid contains ***more*** oil sources for a diverse blend

Learn more at **SMOFlipidPediatrics.com**

SMOFLIPID (lipid injectable emulsion), for intravenous use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This brief summary does not include all the information needed to use SMOFlipid safely and effectively. Please see full prescribing information for SMOFlipid (lipid injectable emulsion), for intravenous use at www.FreseniusKabiNutrition.com/SMOFlipidPI.

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.

DOSAGE AND ADMINISTRATION

The recommended daily dosage and initial and maximum infusion rates for pediatric and adult patients are provided in Table 1. Do not exceed the recommended maximum infusion rate in Table 1. The recommended duration of infusion for SMOFlipid will vary depending on the clinical situation. Adjust the administration flow rate by taking into account the dose being administered, the daily volume/intake, and the duration of the infusion.

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 for individual patient use. Use a non-vented, non-DEHP 1.2 micron in-line filter during administration. Protect the admixed PN solution from light.

Table 1: Recommended Pediatric and Adult Dosage and Infusion Rate

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

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

** Daily dosage should not exceed a maximum of 60% of total energy requirements

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

  Strictly adhere to the recommended total daily dosage; the hourly infusion rate should not exceed 0.75 mL/kg/hour.

  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.

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

- Parenteral Nutrition-Associated Liver Disease and Other Hepatobiliary Disorders.

  Risk of Parenteral Nutrition-Associated Liver Disease (PNALD): PNALD, or Intestinal failure-associated liver disease (IFALD), can present as cholestasis or hepatic stenosis 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.

  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 parenteral nutrition-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.

- 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, or 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.

- 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.
- Fat Overload Syndrome: This is a rare condition that has been reported with intravenous lipid 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.
- 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.
- 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.
- 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 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 impaired kidney function, including preterm infants, 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 may occur at even lower rates of administration.
- 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. However, cases of EFAD have been reported in adults 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 and poor growth) because these signs may emerge before laboratory evidence of EFAD is confirmed. 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.
- Monitoring/Laboratory Tests: Throughout treatment monitor serum triglycerides, 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 [LDH], bilirubin, and 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.

ADVERSE REACTIONS

Most common adverse drug reactions >1% of adult patients who received SMOFlipid 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.

Less common adverse reactions 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, pruritis, dizziness, rash, and thrombophlebitis.

The most common adverse drug reactions in >1% of pediatric patients who received SMOFlipid were anemia, vomiting, gamma-glutamyltransferase increased, nosocomial infection, cholestasis, pyrexia, C-reactive protein increased, hyperbilirubinemia, abdominal pain, bilirubin conjugated increased, diarrhea, tachycardia, thrombocytopenia, hyperglycemia, and sepsis.

Less common adverse reactions 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.

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

To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176, option 5, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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.

USE IN SPECIFIC POPULATIONS

- Pregnancy and Lactation: 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. 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.
- Pediatric Use: The safety and effectiveness of SMOFlipid have been established as a source of calories and essential fatty acids for parenteral nutrition 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. 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. The most common adverse reactions in SMOFlipid-treated pediatric patients were anemia, vomiting, gamma-glutamyltransferase increased, and nosocomial infection. 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. 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. 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. In the post marketing setting, clinical decompensation with rapid infusion of intravenous lipid emulsion in neonates and infants, sometimes fatal has been reported. Because of immature renal function, preterm infants receiving prolonged treatment with SMOFlipid may be at risk for aluminum toxicity.
- 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.

OVERDOSAGE

In the event of an overdose, serious adverse reactions may result. Stop the SMOFlipid infusion 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.

Sources: 1. SMOFlipid Prescribing Information, Fresenius Kabi USA, LLC. 2023. **2.** Deckelbaum RJ, Hamilton JA, Moser A, et al. Medium-chain versus long-chain triacylglycerol emulsion hydrolysis by lipoprotein lipase and hepatic lipase: implications for the mechanisms of lipase action. *Biochemistry*. 1990;29(5):1136-1142. **3.** Kalish BT, Fallon EM, Puder M. A tutorial on fatty acid biology. *JPEN J Parenter Enteral Nutr*. 2012;36(4):380-388. **4.** Agostoni C. Role of long-chain polyunsaturated fatty acids in the first year of life. *J Pediatr Gastroenterol Nutr*. 2008;47 Suppl 2:S41-S44. **5.** Cetin I, Koletzko B. Long-chain omega-3 fatty acid supply in pregnancy and lactation. *Curr Opin Clin Nutr Metab Care*. 2008;11(3):297-302. **6.** Bistrian BR. Clinical aspects of essential fatty acid metabolism: Jonathan Rhoads Lecture. *JPEN J Parenter Enteral Nutr*. 2003;27(3):168-175. **7.** Lapillonne A, Groh-Wargo S, Gonzalez CH, Uauy R. Lipid needs of preterm infants: updated recommendations. *J Pediatr*. 2013;162(3 Suppl):S37-S47. **8.** Institute of Medicine. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids. Washington, DC: The National Academies Press; 2005. Pg 439. **9.** Tomsits E, Pataki M, Tölgyesi A, Fekete G, Rischak K, Szollár L. Safety and efficacy of a lipid emulsion containing a mixture of soybean oil, medium-chain triglycerides, olive oil, and fish oil: a randomised, double-blind clinical trial in premature infants requiring parenteral nutrition. *J Pediatr Gastroenterol Nutr.* 2010;51(4):514-521. **10.** Robinson DT, Carlson SE, Murthy K, Frost B, Li S, Caplan M. Docosahexaenoic and arachidonic acid levels in extremely low birth weight infants with prolonged exposure to intravenous lipids. *J Pediatr*. 2013;162(1):56-61. **11.** Hadley KB, Ryan AS, Forsyth S, Gautier S, Salem N Jr. The Essentiality of Arachidonic Acid in Infant Development. *Nutrients*. 2016;8(4):216. Published 2016 Apr 12. **12.** Baack ML, Puumala SE, Messier SE, Pritchett DK, Harris WS. What is the relationship between gestational age and docosahexaenoic acid (DHA) and arachidonic acid (ARA) levels?. *Prostaglandins Leukot Essent Fatty Acids*. 2015;100:5-11. **13.** Clinolipid Prescribing Information, Baxter Healthcare. 2024. **14.** Fell GL, Nandivada P, Gura KM, Puder M. Intravenous Lipid Emulsions in Parenteral Nutrition. *Adv Nutr*. 2015;6(5):600-610. Published 2015 Sep 15. **15.** Ramiro-Cortijo D, Singh P, Liu Y, et al. Breast Milk Lipids and Fatty Acids in Regulating Neonatal Intestinal Development and Protecting against Intestinal Injury. *Nutrients*. 2020;12(2):534. Published 2020 Feb 19. **16.** Martin CR, Ling PR, Blackburn GL. Review of Infant Feeding: Key Features of Breast Milk and Infant Formula. *Nutrients*. 2016;8(5):279. Published 2016 May 11. **17.** Goulet O. An Overview of Parenteral Nutrition from Birth to Adolescence Based on a Composite Fish Oil Containing Lipid Emulsion and a Pediatric Amino Acid Solution. *Nutrients*. 2024;16(3):440. Published 2024 Feb 1. **18.** Abrams SA, Ernst KD, Weitkamp JH, et al. Safety and Efficacy of a Composite Lipid Emulsion with Fish Oil in Hospitalized Neonates and Infants Requiring Prolonged Parenteral Nutrition - A Randomized, Double-Blind, Multicenter, Controlled Trial. *J Nutr.* 2024;154(12):3615-3625. **19.** Rayyan M, Devlieger H, Jochum F, Allegaert K. Short-term use of parenteral nutrition with a lipid emulsion containing a mixture of soybean oil, olive oil, medium-chain triglycerides, and fish oil: a randomized double-blind study in preterm infants. *JPEN J Parenter Enteral Nutr*. 2012;36(1 Suppl):81S-94S. **20.** Harvey K, Xu Z, Walker C, et al. Parenteral lipid emulsions in guinea pigs differentially influence plasma and tissue levels of fatty acids, squalene, cholesterol, and phytosterols. *Lipids*. 2014;49(8):777-793. **21.** Lauriti G, Zani A, Aufieri R, et al. Incidence, prevention, and treatment of parenteral nutrition-associated cholestasis and intestinal failure-associated liver disease in infants and children: a systematic review. *JPEN J Parenter Enteral Nutr*. 2014;38(1):70-85.

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