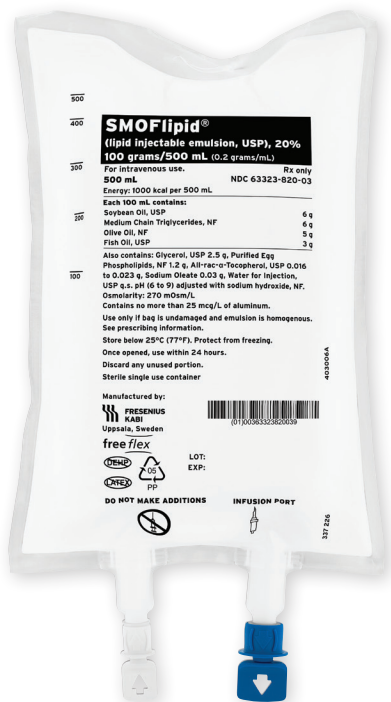


SMOFlipid[®]

Lipid Injectable Emulsion, USP 20%



The **FIRST** and **only**
4-oil lipid emulsion
for adults in the U.S.

Fresenius Kabi USA **Nutrition**

SMOFlipid is indicated in adults as a source of calories and essential fatty acids for PN 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.

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

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.



SMOFlipid is a unique blend
of 4 oil sources



Soybean oil 30% (omega-6)
Provides essential fatty acids.



Medium-chain triglycerides (MCT) 30%
A source of rapidly available energy.¹



Olive oil 25% (omega-9)
Supplies monounsaturated fatty acids.



Fish oil 15% (omega-3)
A source of EPA and DHA.²



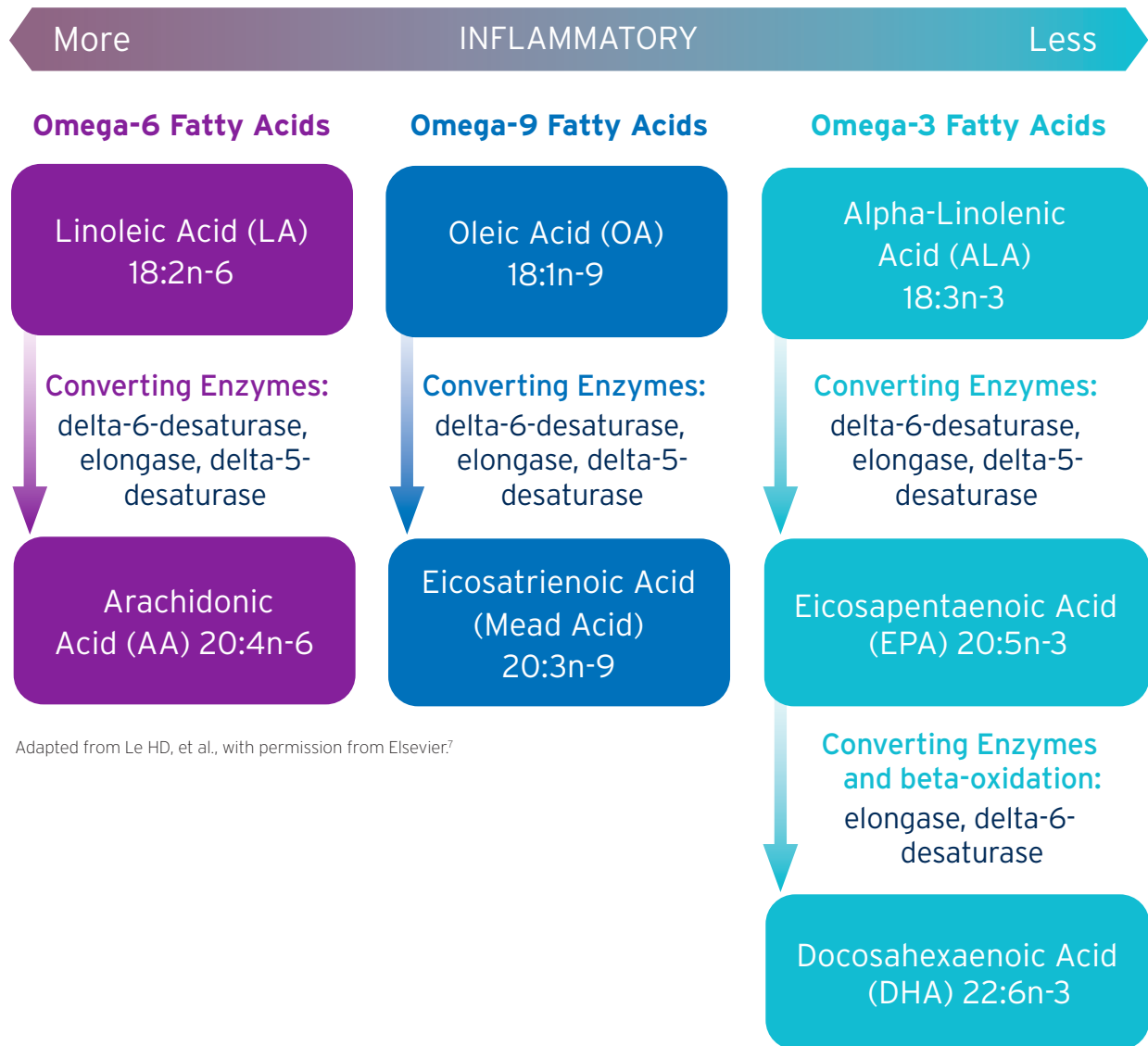
Alpha-tocopherol (approx. 200 mg/L) is an important antioxidant
that protects long-chain polyunsaturated fats from peroxidation.^{3,4}

Demonstrated safety
and tolerability^{5,6} in
more than

7 million
patients worldwide.*

*Internal data.

Fatty acid pathways and impact on inflammation⁷



“

Based on substantial biochemical and clinical evidence, alternative oil-based intravenous fat emulsions (IVFEs) may have less proinflammatory effects, less immune suppression, and more antioxidant effects than the standard soybean oil IVFEs and may potentially be a better alternative energy source.⁸

”



Composition of current ILEs

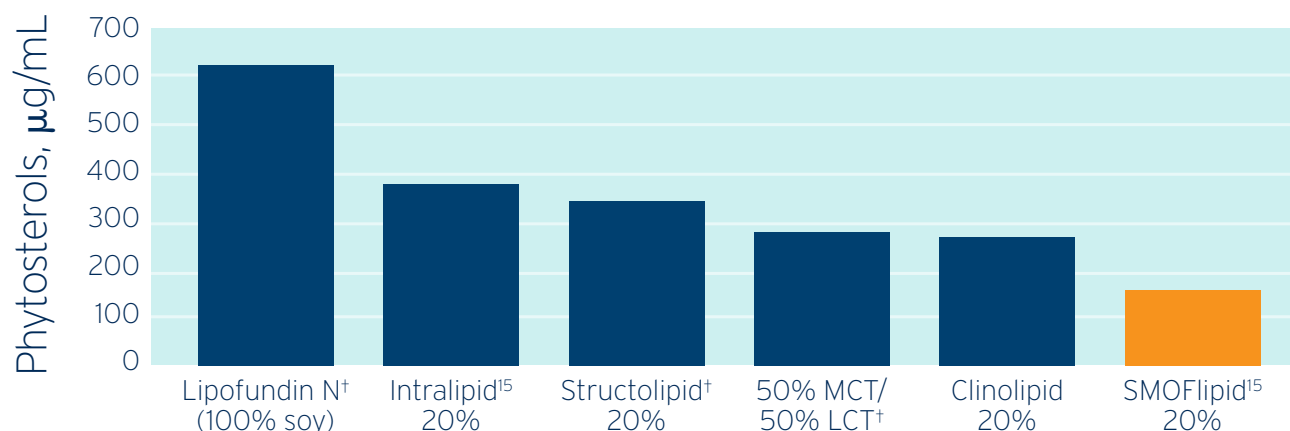
Intralipid® ⁹	Nutrilipid® ¹⁰	Clinolipid® ¹¹	SMOFlipid ¹²
Soybean Oil 100%	Soybean Oil 100%	Soybean Oil 20% Olive Oil 80%	Soybean Oil 30% MCT 30% Olive Oil 25% Fish Oil 15%

Fat Composition (% , mean values)				
Alpha-linolenic (omega-3)	7.5	7.5	2.4	2.5
Eicosapentaenoic (EPA omega-3)	0	0	0	2.3
Docosahexaenoic (DHA omega-3)	0	0	0	2.3
Linoleic (omega-6)	53	53	17.9	19.5
Oleic (omega-9)	24.5	23.5	61.9	29
Alpha-tocopherol (mg/L)	N/A	N/A	32	~200
Phytosterol Content mcg/mL	381 ± 28.9*	ND	226.83 ± 6.42 274.38 ± 2.60 ¹³	165 ± 10.4*

*Internal data.

Per mL, SMOFlipid contains the lowest amount of phytosterols in commercially available lipid emulsions indicated for adults^{13,14}

ILEs and Phytosterol Content



⁺Not approved in the U.S.

Expert recommendation suggests a potential benefit of a balanced omega-6:omega-3 ratio in ILE¹⁶

Lipid Emulsion	Ratio of omega-6:omega-3 Fatty Acids
Soybean oil emulsion	7:1
MCT/LCT emulsion	7:1
Olive oil/Soybean oil emulsion	9:1
SMOFlipid¹²	2.5:1

MCT=medium-chain triglyceride; LCT=long-chain triglyceride

The omega-6:omega-3 fatty acid ratio in SMOFlipid has not been shown to improve clinical outcomes compared to other ILEs.¹²



EPA/DHA

- SMOFlipid has been shown to improve EPA and DHA levels in adult patients^{5,17}
 - ESPEN states, "Addition of EPA and DHA to lipid emulsions has demonstrable effects on cell membranes and inflammatory processes." (Grade B)¹⁸

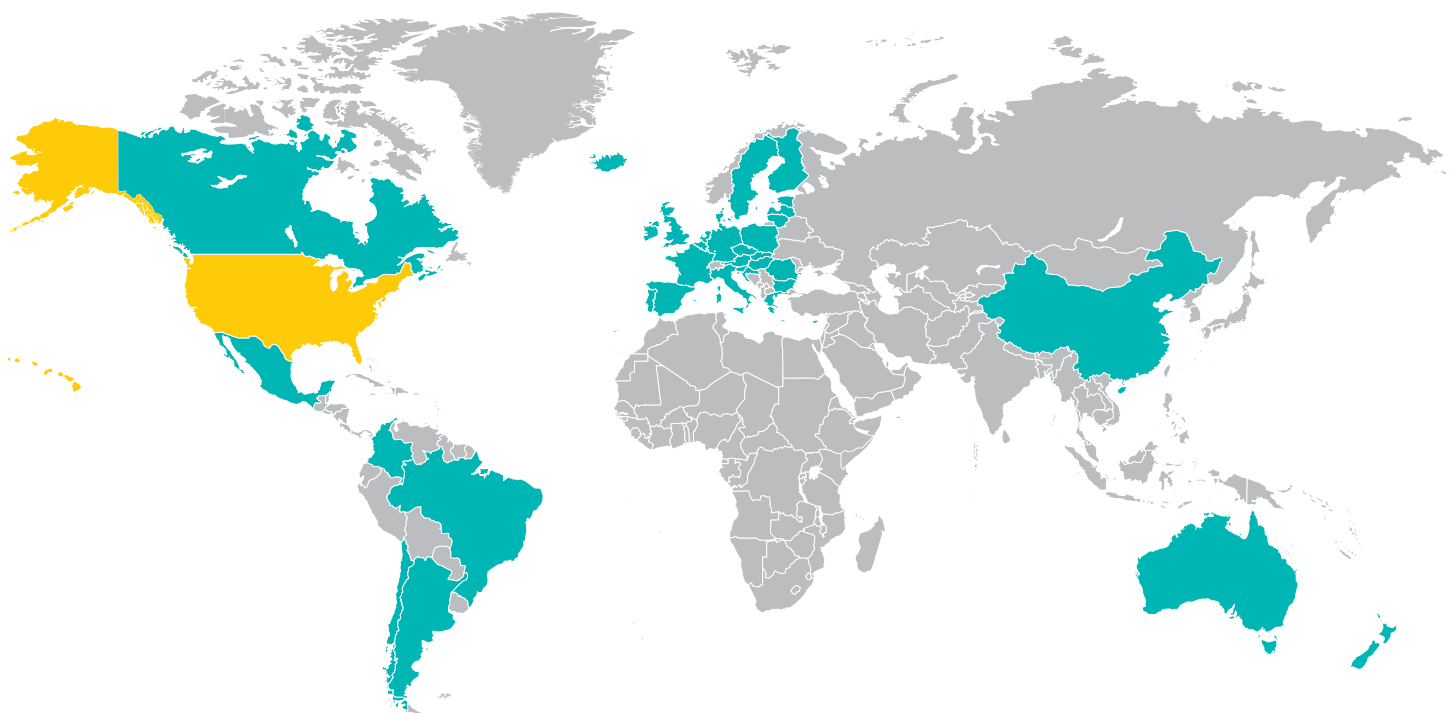


SMOFlipid is globally recognized

Over a 10-year history of use

Worldwide use in more than
7 million patients*

Studied in more than
20 clinical trials



Currently approved in over 75 countries, including all of the European Union, Canada, and Australia.

*Data on file.

SMOFlipid[®]
Lipid Injectable Emulsion, USP 20%

Clinical guidelines and expert recommendations regarding the use of alternative intravenous lipid emulsions (ILEs)



American Society for Parenteral and Enteral Nutrition (ASPEN) position paper:

"Alternative oil-based IVFEs are safe and effective alternatives to soybean oil IVFEs for a source of energy and essential FAs and may have potential biochemical and/or clinical benefits."⁸

ASPEN/SCCM Critical Care Guidelines

"When alternative IVFEs are available in the US, based on expert opinion, alternative IVFEs should be considered in the critically ill patient who is an appropriate candidate for PN."¹⁹

Canadian Critical Care Nutrition guidelines:

"When PN with IV lipids is indicated, IV lipids that reduce the load of omega-6 fatty acids/soybean oil emulsions should be considered."²⁰

ESPEN guidelines for critically ill patients:

"The administration of intravenous lipid emulsions should be generally a part of PN."²¹

ESPEN guidelines for surgical patients:

"Post-op PN including omega-3-fatty acids should be considered only in patients who cannot be adequately fed enterally and, therefore, require parenteral nutrition."²²

Lipids in Parenteral Nutrition International Summit (2018):

"In our view, there is sufficient scientific evidence to justify the indication of fish-oil containing ILEs as part of PN in critically ill, adult surgical patients requiring PN (100% agreement)."²³

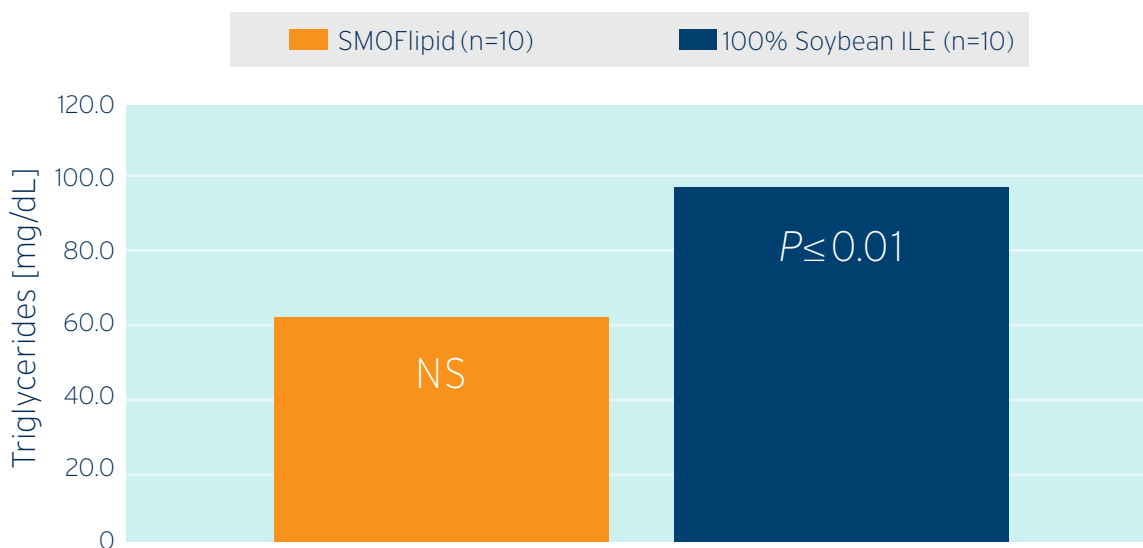
"In high-risk, critically ill, adult patients (eg, sepsis, ARDS, PICS), we recommend using fish-oil containing ILEs as part of PN (82% agreement)."²³

"In high-risk, critically ill, adult patients (eg, sepsis, ARDS, PICS), we recommend including fish-oil containing ILEs as part of PN in the first week of PN (94% agreement)."²³



Studies showed triglyceride levels increased less with SMOFlipid compared to lipid emulsions with higher soybean oil content^{24,25}

Triglyceride Change After 5 Days



NS=not significant
Chart adapted from Antébi H, et al.²⁴

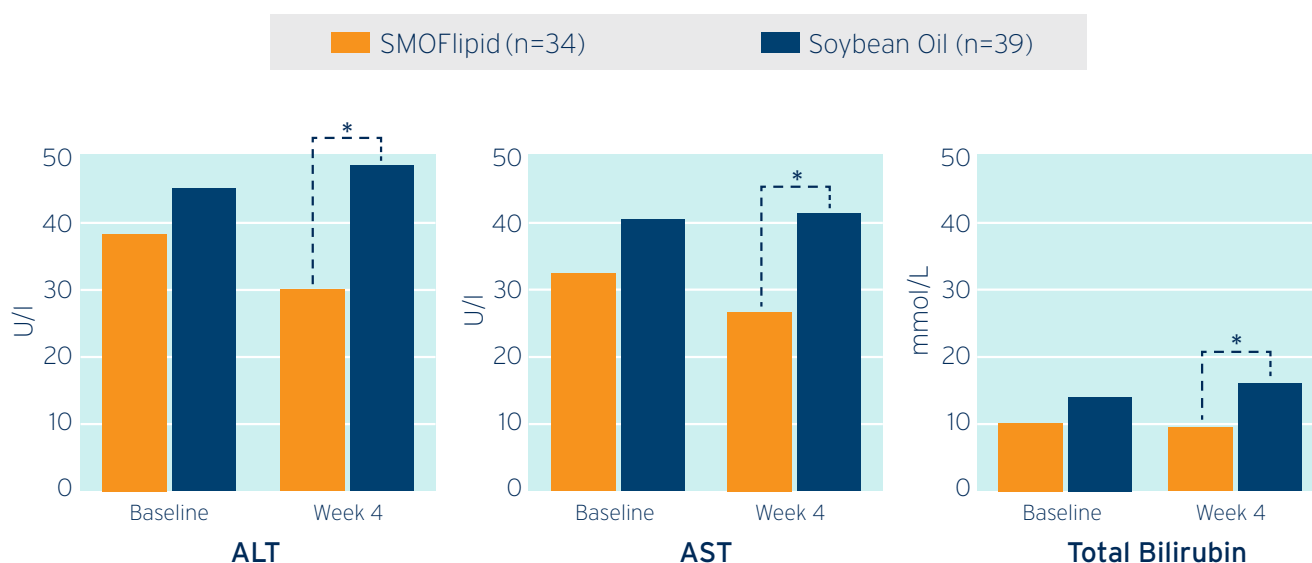
STUDY TAKEAWAY

In this randomized controlled trial including postoperative surgical ICU patients (n=20), SMOFlipid demonstrated a lower triglyceride increase compared to those patients who received a lipid emulsion (1.5 g/kg/d ILE dose in both groups) with a higher soybean oil content.²⁴

Monitor serum triglycerides before and during treatment with SMOFlipid. Company-sponsored studies showed that mean triglyceride levels from baseline values to week 4 were similar in both the SMOFlipid and comparator groups.

There was less of an elevation/increase in liver function tests in patients receiving SMOFlipid vs. 100% soybean oil emulsions^{5,24}

Parameters of Liver Function at Baseline and at Week 4



STUDY TAKEAWAY

In this randomized controlled trial, SMOFlipid showed lower concentrations of liver enzymes (ALT, AST, total bilirubin) compared to soybean oil lipid emulsions (1.3 g/kg/d ILE dose in both groups), indicating an improvement in the patient's liver function.⁵

Monitor liver function. If SMOFlipid-treated patients develop liver enzyme abnormalities, consider discontinuation or dose reduction.

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, including Boxed Warning for SMOFlipid (lipid injectable emulsion), for intravenous use at www.FreseniusKabiNutrition.com.

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.**

INDICATIONS AND USAGE

SMOFlipid is indicated in adults as a source of calories and essential fatty acids for parenteral nutrition (PN) 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.

DOSAGE AND ADMINISTRATION

The recommended daily dosage in adults is 1 to 2 grams/kg per day and should not exceed 2.5 grams/kg per day. 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. Protect the admixed PN solution from light.

CONTRAINDICATIONS

Known hypersensitivity to fish, egg, soybean, or peanut protein, or to any of the active ingredients or excipients.

Severe hyperlipidemia or severe disorders of lipid metabolism with serum triglycerides $>1,000$ mg/dL.

WARNINGS AND PRECAUTIONS

- **Death in Preterm Infants:** (see BLACK BOX WARNING)
- **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.
- **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.
- **Fat Overload Syndrome:** This 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, fatty liver infiltration (hepatomegaly), deteriorating liver function, and central nervous system manifestations (e.g., coma).
- **Refeeding Syndrome:** Reintroducing calories and protein to 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.
- **Aluminum Toxicity:** SMOFlipid contains no more than 25 mcg/L of aluminum. During 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 intakes of aluminum at greater than 4 to 5 mcg/kg/day can 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.

- **Risk of Parenteral Nutrition-Associated Liver Disease (PNALD):** 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.
- **Hypertriglyceridemia:** Impaired lipid metabolism with hypertriglyceridemia may occur in conditions such as inherited lipid disorders, obesity, diabetes mellitus, and metabolic syndrome.
- **Monitoring/Laboratory Tests:** Routinely monitor serum triglycerides, fluid and electrolyte status, blood glucose, liver and kidney function, blood count including platelets, and coagulation parameters throughout treatment. Monitoring patients for signs and symptoms of essential fatty acid deficiency (EFAD) is recommended.
- **Interference with Laboratory Tests:** Content of vitamin K may counteract anticoagulant activity. 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.

ADVERSE REACTIONS

Most common adverse drug reactions $>1\%$ of 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 $\leq 1\%$ 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, pruritis, dizziness, rash and thrombophlebitis.

The following adverse reactions have been identified during post-approval use of SMOFlipid in countries where it is registered. Infections and Infestations: infection. Respiratory, Thoracic and Mediastinal Disorders: dyspnea.

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

Coumarin and Coumarin Derivatives, Including Warfarin: Anticoagulant activity may be counteracted; monitor laboratory parameters.

USE IN SPECIFIC POPULATIONS

- **Pregnancy and Lactation:** There are no available data on risks associated with SMOFlipid when used in pregnant or lactating women.
- **Pediatric Use:** The safety and effectiveness of SMOFlipid have not been established in pediatric patients.
- **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 PN, including cholestasis, hepatic steatosis, fibrosis and cirrhosis (PN associated liver disease), possibly leading to hepatic failure.

OVERDOSAGE

In the event of an overdose, fat overload syndrome may occur. 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.

References: 1. 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. 2. Kalish BT, Fallon EM, Puder M. A tutorial on fatty acid biology. *JPEN J Parenter Enteral Nutr*. 2012;36(4):380-388. 3. Burrin DG, Ng K, Stoll B, Sáenz De Pipaón M. Impact of new-generation lipid emulsions on cellular mechanisms of parenteral nutrition-associated liver disease. *Adv Nutr*. 2014;5(1):82-91. Published 2014 Jan 1. 4. Biesalski HK. Vitamin E requirements in parenteral nutrition. *Gastroenterology*. 2009;137(5 Suppl):S92-S104. 5. Klek S, Chambrier C, Singer P, et al. Four-week parenteral nutrition using a third generation lipid emulsion (SMOFlipid)—a double-blind, randomised, multicentre study in adults. *Clin Nutr*. 2013;32(2):224-231. 6. Mertes N, Grimm H, Fürst P, Stehle P. Safety and efficacy of a new parenteral lipid emulsion (SMOFlipid) in surgical patients: a randomized, double-blind, multicenter study. *Ann Nutr Metab*. 2006;50(3):253-259. 7. Le HD, Meisel JA, de Meijer VE, Gura KM, Puder M. The essentiality of arachidonic acid and docosahexaenoic acid. *Prostaglandins Leukot Essent Fatty Acids*. 2009;81(2-3):165-170. 8. Vanek VW, Seidner DL, Allen P, et al. A.S.P.E.N. position paper: Clinical role for alternative intravenous fat emulsions. *Nutr Clin Pract*. 2012;27(2):150-192. 9. Intralipid 20% Prescribing Information, Fresenius Kabi USA, LLC. 2015. 10. Nutrilipid Prescribing Information, B. Braun Medical Inc. 2014. 11. Clinolipid Prescribing Information, Baxter. 2013. 12. SMOFlipid Prescribing Information, Fresenius Kabi USA, LLC. 2020. 13. Xu Z, Harvey KA, Pavlina T, et al. Steroidal Compounds in Commercial Parenteral Lipid Emulsions. *Nutrients*. 2012;4(8):904-921. 14. 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. 15. Data on file. 16. Grimbé R. Fatty acid profile of modern lipid emulsions: Scientific considerations for creating the ideal composition. *Clin Nutr Suppl*. 2005;1(3):9-15. 17. Grimm H, Mertes N, Goeters C, et al. Improved fatty acid and leukotriene pattern with a novel lipid emulsion in surgical patients. *Eur J Nutr*. 2006;45(1):55-60. 18. Singer P, Berger MM, Van den Berghe G, et al. ESPEN Guidelines on Parenteral Nutrition: intensive care. *Clin Nutr*. 2009;28(4):387-400. 19. McClave SA, Taylor BE, Martindale RG, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) [published correction appears in *JPEN J Parenter Enteral Nutr*. 2016 Nov;40(8):1200]. *JPEN J Parenter Enteral Nutr*. 2016;40(2):159-211. 20. Canadian Clinical Practice Guidelines. 9.2 Composition of Parenteral Nutrition: Type of Lipids. 2013,2015 Recommendations. <https://www.criticalcarenutrition.com/docs/CPGs%202015/9.2%202015.pdf>. Accessed October 14, 2021. 21. Singer P, Blaser AR, Berger MM, et al. ESPEN guideline on clinical nutrition in the intensive care unit. *Clin Nutr*. 2019;38(1):48-79. 22. Weimann A, Braga M, Carli F, et al. ESPEN guideline: Clinical nutrition in surgery. *Clin Nutr*. 2017;36(3):623-650. 23. Martindale RG, Berlana D, Boullata JI, et al. Summary of Proceedings and Expert Consensus Statements From the International Summit "Lipids in Parenteral Nutrition". *JPEN J Parenter Enteral Nutr*. 2020;44 Suppl 1:S7-S20. 24. Antébi H, Mansoor O, Ferrier C, et al. Liver function and plasma antioxidant status in intensive care unit patients requiring total parenteral nutrition: comparison of 2 fat emulsions. *JPEN J Parenter Enteral Nutr*. 2004;28(3):142-148. 25. Donoghue V, Schleicher GK, Spruyt MGL, et al. Four-oil intravenous lipid emulsion effect on plasma fatty acid composition, inflammatory markers and clinical outcomes in acutely ill patients: A randomised control trial (Foil fact). *Clin Nutr*. 2019;38(6):2583-2591.



Lipid Injectable Emulsion, USP 20%

When it comes to innovations
that nourish, there's only **1 SMOF**



- S**upply of monounsaturated fatty acids
- M**ix of fatty acids may have less pro-inflammatory properties⁸
- O**mega-3 fatty acids from fish oil include EPA and DHA
- F**irst and only 4-oil lipid emulsion

free flex[®]

Important Bag Features	NDC Codes		
• Non-PVC • Non-DEHP • Not made with natural rubber latex • Recyclable material (made from multi-layer polyolefin)	100 mL	63323-820-00	10 bags/box
	250 mL	63323-820-74	10 bags/box
	500 mL	63323-820-50	12 bags/box
	1000 mL Pharmacy Bulk Package	63323-820-10	6 bags/box

FOR MORE INFORMATION ABOUT SMOFLIPID:

Website: www.FreseniusKabiNutrition.com/products/SMOFlipid

To Order: 1.888.386.1300

For coding/billing info: www.kabicare.us or call 1.833.Kabicare (1.833.522.4227)

Medical Information phone: 1.800.551.7176 (option 4)

Medical Information email: Nutrition.MedInfo.USA@fresenius-kabi.com