FRESENIUS KABI
caring for life

SMOFlipid®

Lipid Injectable Emulsion, USP 20%

An Advancement in Lipid Emulsion for Adults

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.**

Please see Brief Summary of Prescribing Information for SMOFlipid on page 10.

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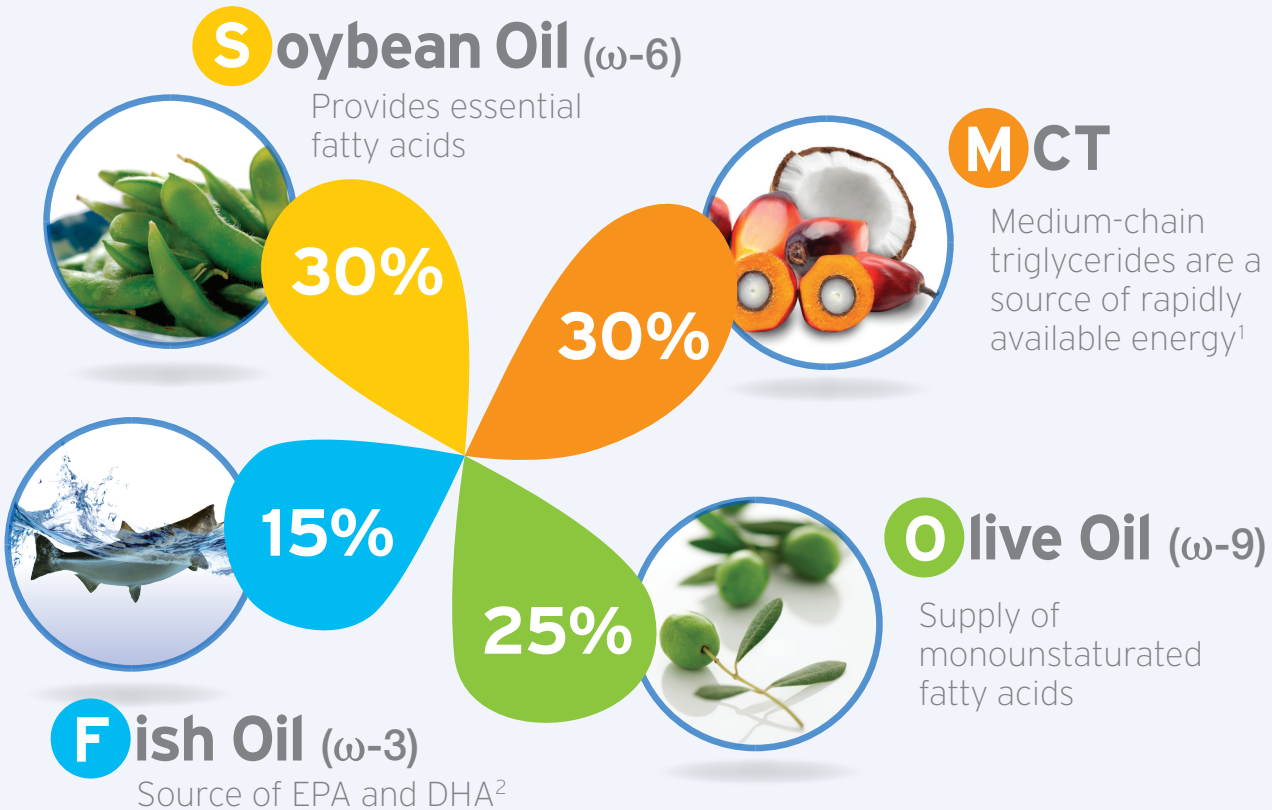
Lipid Injectable Emulsion, USP 20%

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 ω-6:ω-3 fatty acid ratio and Medium Chain Triglycerides in SMOFlipid have not been shown to improve clinical outcomes compared to other intravenous lipid emulsions

SMOFlipid® is a unique blend of 4 oil sources



α–tocopherol (approx.200 mg/L) is an important antioxidant that protects long-chain polyunsaturated fats from peroxidation.[3,4]

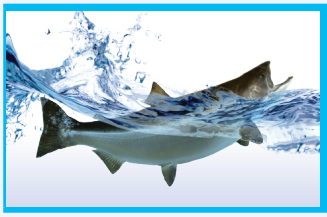
Please see Brief Summary of Prescribing Information, including **Boxed Warning**, for SMOFlipid on page 10.

Some characteristics of oil sources found in intravenous lipid emulsions (ILE)

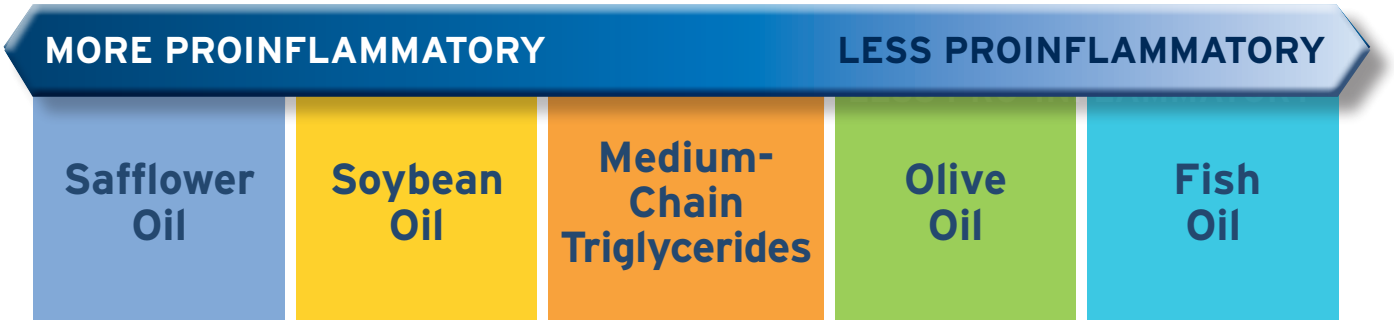
- Source of essential fatty acids
- Provides energy

- Source of rapidly available energy[1]
- Clears faster from the bloodstream than other fatty acids[5]

- Provides ω-9 fatty acids (MUFA)
- Contains small amounts of linoleic acid and α-linolenic acid
- Provides energy



- A source of ω-3 fatty acids (EPA and DHA)[2]
  - Considered conditionally essential fatty acids
- Provides energy



Graphic adapted from 6. Vanek VW, et al.

"Based on substantial biochemical and clinical evidence, alternative oil-based IVFEs may have less pro-inflammatory effects, less immune suppression, and more antioxidant effects than the standard soybean oil (SO) IVFEs and may potentially be a better alternative energy source. However, the evidence for the clinical use of these alternative IVFEs is still not clearly defined, particularly with regard to specific indications..."

Vanek VW, Seidner DL, Allen P, et al. *Nutrition Clinical Practice* 2012.[6]

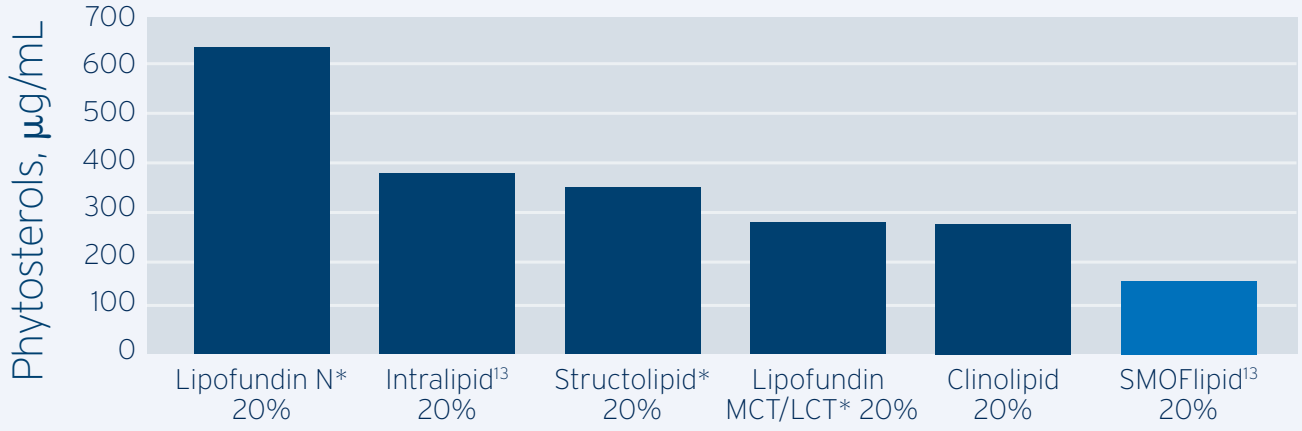
Composition of Current ILEs

	Intralipid®[7]	Nutrilipid®[8]	Clinolipid®[9]	SMOFlipid®[10]
	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 value or range % by weight)[6,7-10]				
α-Linolenic Acid (ω-3)	4-11	4-11	2.35	**2.25**
Eicosapentaenoic (EPA ω-3)	0	0	0	**1-3.5**
Docosahexaenoic (DHA ω-3)	0	0	0	**1-3.5**
Linoleic Acid (ω-6)	44-62	48-58	17.9	**17.5**
Oleic Acid (ω-9)	19-30	17-30	44.3-79.5	**23-35**
α-Tocopherol (mg/L)	38	ND	32	**163-225**

ND = No Data

Per mL, SMOFlipid® contains the lowest amount of phytosterols in commercially available lipid emulsions indicated for adults[11,12]

ILEs and Phytosterol Content



11. Xu Z, et al. *Nutrients.* 2012;4:904-921.
*Not approved in the U.S.

Please see Brief Summary of Prescribing Information, including **Boxed Warning**, for SMOFlipid on page 10.

Expert recommendation suggests an optimal ω-6:ω-3 ratio of 2:1 to 4:1 in intravenous lipid emulsions[14]

Lipid Emulsion	Ratio of ω-6:ω-3 Fatty Acids
Recommendations[14-17]	**4:1 to 2:1**
Soybean Oil Emulsion	**7:1**
MCT/LCT Emulsion	**7:1**
Olive Oil/Soybean Oil Emulsion	**9:1**
SMOFlipid®[10]	**2.5:1**

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

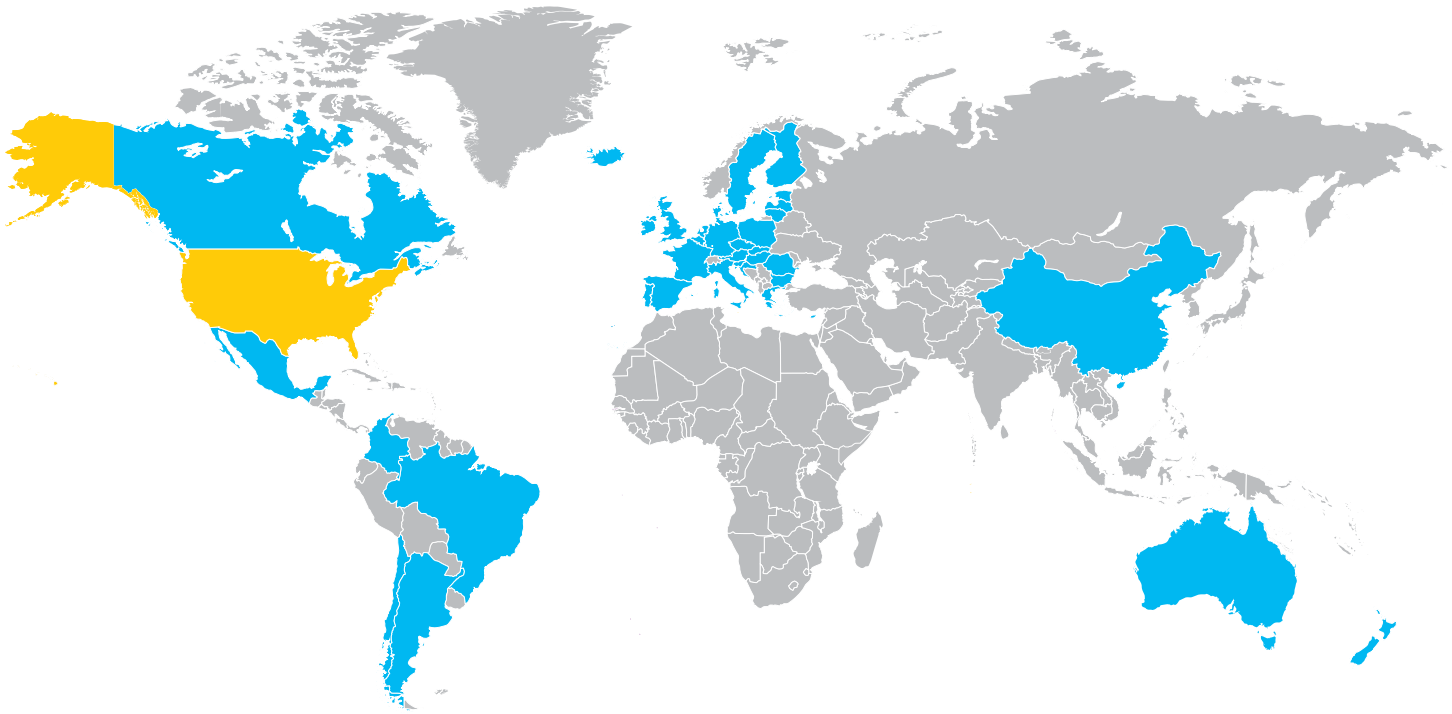
The ω-6:ω-3 fatty acid ratio in SMOFlipid has not been shown to improve clinical outcomes compared to other ILEs

EPA/DHA

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 over 6 million patients
- Studied in more than 20 clinical trials



Currently approved in 78 countries, including all of the European Union, Canada, and Australia.

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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."[6]

ASPEN/SCCM Critical Care Guidelines

"When alternative IVFE are available in the US, based on expert opinion, alternative IVFE 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 ω-6 fatty acids/ soybean oil emulsions should be considered."[20]

ESPEN guidelines for critically ill patients:

"Lipids should be an integral part of PN for energy to ensure essential fatty acid provision in long-term intensive care unit patients."[18]

"This may include fish oil-enriched and olive oil-based lipid emulsions."[18]

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."[21]

ESPEN Workshop on "Lipids in the ICU"

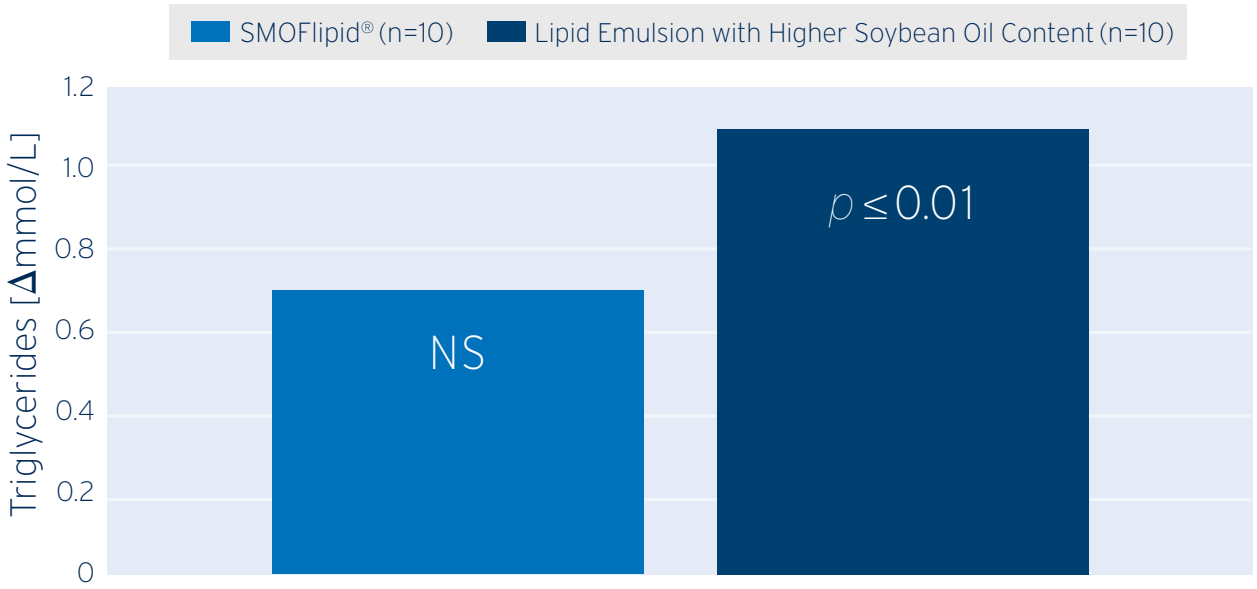
"In addition to its positive effects on inflammation and immune function, fish oil (FO)-enriched PN may help to preserve liver function in critically ill surgical patients"[22]

"If PN is required post-operatively in the ICU, 2nd or 3rd generation lipid emulsions may be administered, and in the case of surgical complications, FO-containing PN is recommended"[22]

"Whilst the evidence base is not conclusive, there appears to be a potential for FO-enriched nutrition, particularly administered perioperatively, to reduce the rate of complications and ICU and hospital stay in surgical ICU patients, as well as to improve complications such as IFALD associated with SO-based ILEs"[22]

Studies showed triglyceride levels increased less with SMOFlipid® compared to lipid emulsions with higher soybean oil content[23,24]

Triglyceride change after 5 days



NS=not significant

Chart adapted from Antébi H, et al. *JPEN J Parenter Enteral Nutr.* 2004;28(3):142-148.

STUDY TAKEAWAY

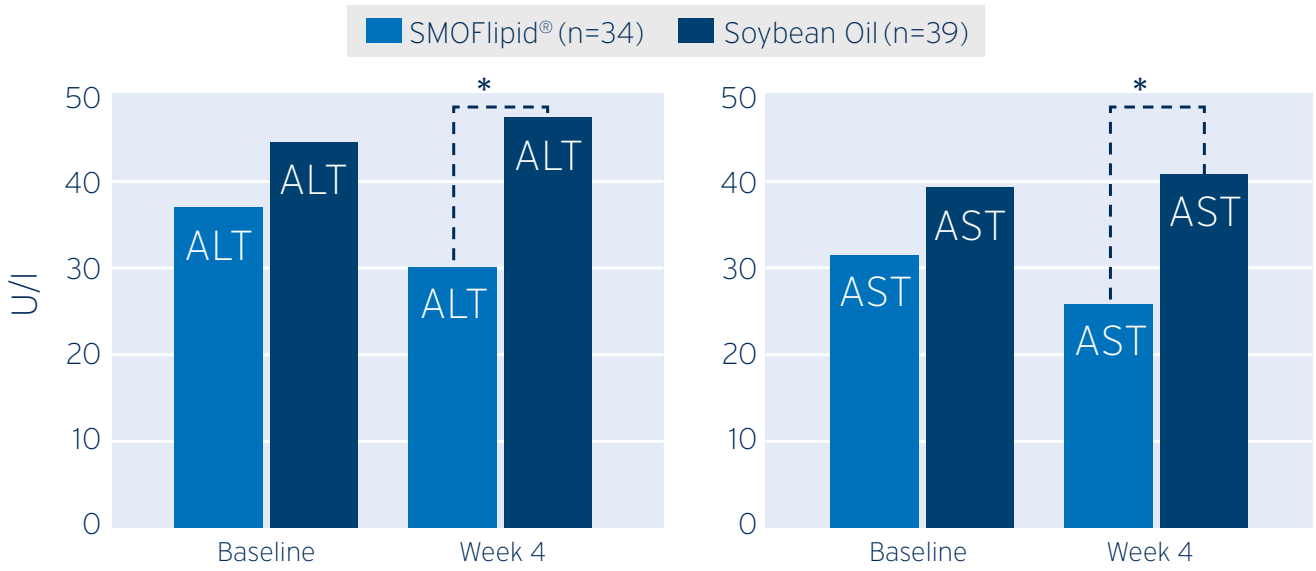
In postoperative surgical patients, SMOFlipid® demonstrated a lower triglyceride increase compared to those patients who received a lipid emulsion (1.5 g/kg/d ILE dose in both groups) with a higher soybean oil content.[23]

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.

Please see Brief Summary of Prescribing Information, including **Boxed Warning**, for SMOFlipid on page 10.

There was less of an elevation/increase in liver function tests in patients receiving SMOFlipid vs. 100% soybean oil emulsions[23,25]

Parameters of liver function at baseline and at week 4



*statistically significant difference between groups at week 4 ($p<0.05$)
Chart adapted from Klek S, et al. *Clin Nutr.* 2013;32(2):224-31.

ALT = alanine aminotransferase
AST = aspartate aminotransferase

STUDY TAKEAWAY

SMOFlipid® showed lower concentrations of liver enzymes (ALT, AST) 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.[25]

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

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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.smoflipid.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.

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 (also see BOXED WARNING)

- 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 ≤ 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, et al. Medium-chain versus long-chain triacylglycerol emulsion hydrolysis by lipoprotein lipase and hepatic lipase: implications for the mechanisms of lipase action. *Biochemistry (Mosc).* 1990;29(5):1136-1142.
2. Kalish BT, Fallon EM, Puder M. *JPEN J Parenter Enteral Nutr.* 2012;36:380-8.
3. Burrin DG, et al. Impact of new-generation lipid emulsions on cellular mechanisms of parenteral nutrition-associated liver disease. *Adv Nutr.* 2014;5(1):82-91.
4. Biesalski HK. Vitamin E requirements in parenteral nutrition. *Gastroenterology.* 2009;137(5 Suppl):S92-S104.
5. Bach AC, et al. Medium-chain triglycerides: an update. *Am J Clin Nutr.* 1982;36(5):950-962.
6. Vanek VW, et al. A.S.P.E.N. position paper: Clinical role for alternative intravenous fat emulsions. *Nutr Clin Pract.* 2012;27(2):150-192
7. Intralipid [prescribing information].
8. Nutrilipid [prescribing information].
9. Clinolipid [prescribing information].
10. SMOFlipid [prescribing information].
11. Xu Z, et al. *Nutrients.* 2012;4:904-921.
12. Harvey K, et al. *Lipids.* 2014;49:777-793.
13. Data on file.
14. Grimble R. *Clin Nutr Supp.* 2005;1:9-15.
15. Waitzberg DL, et al. *JPEN J Parenter Enteral Nutr.* 2006;30(4):351-367.
16. Mayer K, et al. *Curr Opin Clin Nutr Metab Care.* 2006;9(2):140-148. 5.
17. Grimm H, 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, et al. ESPEN Guidelines on Parenteral Nutrition: intensive care. *Clin Nutr.* 2009;28(4):387-400.
19. McClave SA, 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.). *JPEN J Parenter Enteral Nutr.* 2016;40(2):159-211.
20. Heyland DK, et al. Canadian Clinical Practice Guidelines 2013 and 2015. Critical Care Nutrition website. www.criticalcarenutrition. com. Accessed Oct 14, 2019.
21. Weimann A, et al. ESPEN guideline: Clinical nutrition in surgery. *Clin Nutr.* 2017;36:632-650.
22. Calder PC, et al. *Clin Nutr.* 2018 Feb;37(1):1-18.
23. Antébi H, 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.
24. 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.* 2018;doi: 10.1016/j. clnu.2018.12.010. [Epub ahead of print].
25. Klek S, 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.
26. Mertes N, et al. 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.
27. Ma CJ, et al. A double-blind randomized study comparing the efficacy and safety of a composite vs a conventional intravenous fat emulsion in postsurgical gastrointestinal tumor patients. *Nutr Clin Pract.* 2012;27(3):410-415.

SMOFlipid®

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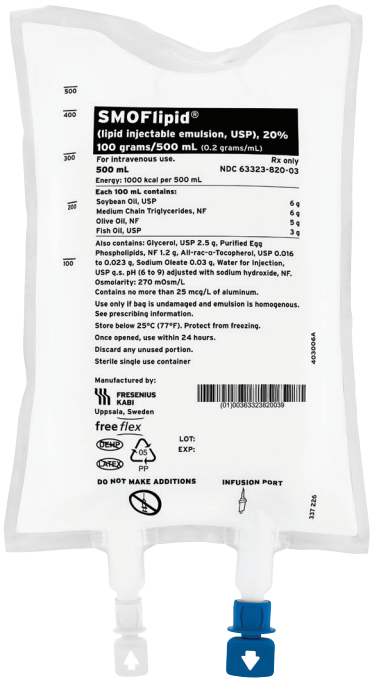

The **first** and **only** modern lipid emulsion in the U.S. that contains four oils

- Balanced lipid profile containing: soybean oil, medium-chain triglycerides, olive oil, and fish oil
- Provides energy and essential fatty acids for parenterally fed patients
- Safe and well tolerated[25-27]

freeflex®

Important Bag Features

- Non-PVC
- Non-DEHP
- Not made with natural rubber latex
- Made from multi-layer polyolefin

NDC Codes		
100 mL	63323-820-00	10 bags/box
250 mL	63323-820-74	10 bags/box
500 mL	63323-820-50	12 bags/box
NOW AVAILABLE 1000 mL Pharmacy Bulk Package	63323-820-10	6 bags/box

FOR MORE INFORMATION ABOUT SMOFLIPID®:

Website: www.smoflipid.com
To Order: 1.888.386.1300
Med Info phone: 1.800.551.7176 (option 4)
Med Info email: nutrition.medinfo.USA@fresenius-kabi.com

FRESENIUS KABI
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