FRESENIUS KABI
caring for life

Fresenius Kabi USA **Nutrition**

Explore our **innovations that nourish** children of all ages

As the market leader in lipid injectable emulsions (ILEs)[1] and pioneer in alternative ILEs, our products provide a source of calories and fatty acids for kids from preterm neonates to toddlers to teenagers.[2,3]

SMOFlipid®
Lipid Injectable Emulsion, USP 20%

Omegaven®
(fish oil triglycerides) injectable emulsion

Nourish with a unique blend of lipids

The same product you've trusted for adults is approved for children aged 17 and under who require parenteral nutrition (PN), including the most vulnerable preterm babies.[2]

SMOFlipid is the only ILE in the U.S. that delivers a blend of 4 oils to pediatric patients[2]

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

Medium-chain triglycerides (MCT) 30%
A source of rapidly available energy.[4]

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

Fish oil 15%
(omega-3)
A source of EPA and DHA.[5]

SMOFlipid has demonstrated safety and tolerability[6,7] in more than **7 million patients worldwide**.[1]

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.

We're proud to support marine conservation by ensuring that the fish oil in our products is sustainably sourced.

Recommended pediatric dosing and administration for SMOFlipid[2]

- Dosing awareness is critical and based on patient age, weight, and nutrition needs
- The dosing of SMOFlipid varies in pediatrics, neonates, and adults; each patient group has its own unique dosing specifications
- The duration of infusion will vary depending on the clinical situation; however, infuse SMOFlipid over a longer duration in neonates as shown in the table below
- Do not exceed an infusion rate of 0.15 g/kg/hour
- The administration flow rate is determined by dividing the volume of lipid by the duration of the infusion
- 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	Duration of Infusion
Birth to 2 years of age (including preterm and term neonates)	0.5 to 1 g/kg/day Increase the dose by 0.5 to 1 g/kg/day	3 g/kg/day	20 to 24 hours for preterm and term neonates 12 to 24 hours for patients 1 month to 2 years
2 to <12 years of age	1 to 2 g/kg/day Increase the dose by 0.5 to 1 g/kg/day	3 g/kg/day	12 to 24 hours
12 to 17 years of age	1 to 2 g/kg/day	2.5 g/kg/day	12 to 24 hours

The safety and efficacy of SMOFlipid compared to soybean oil in pediatric patients of all groups, including term and preterm neonates, was evaluated in 333 pediatric patients in four randomized, active-controlled, double-blind, parallel-group controlled clinical studies.[2]

Contraindications: Known hypersensitivity to fish, egg, soybean, or peanut protein, 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).

Omegaven®
(fish oil triglycerides) injectable emulsion

Nurture with omega-3-rich fish oil

Omegaven is the only 100% fish oil ILE for pediatric patients with parenteral nutrition-associated cholestasis (PNAC) in the U.S.[3]

- Omegaven is a source of calories and fatty acids in pediatric patients with PNAC[3]
- Patients receiving Omegaven achieved age-appropriate growth[3]
- Omegaven-treated patients experienced improvement in liver function parameters[3]

Limitations of use: Omegaven is not indicated for the prevention of PNAC. It has not been demonstrated that Omegaven prevents PNAC in parenteral nutrition (PN)-dependent patients.

It has not been demonstrated that the clinical outcomes observed in patients treated with Omegaven are a result of the omega-6: omega-3 fatty acid ratio of the product.

What is **PNAC**?

Commonly known as intestinal failure-associated liver disease (IFALD) or parenteral nutrition-associated liver disease (PNALD).[8]

Most commonly defined as direct or conjugated bilirubin (DBIL) >2 mg/dL in patients who receive PN >2 weeks.[9-12]

Premature infants are at **greater risk for PNAC** because of an immature liver and intestines

- Premature infants physically incapable of absorbing adequate nutrients from normal feeding require PN[13]
- If the liver is not fully developed at birth, enterohepatic cycling is impaired, which results in cholestasis[14-17]
- Infants with intestinal failure, including congenital malformations, short bowel syndrome (SBS), intestinal infections such as necrotizing enterocolitis (NEC), or inflammatory bowel diseases often require long-term PN[9,10,15-17]
- **The average incidence rate of PNAC in neonates and infants is 29.9%[10]**

Development of PNAC is associated with increased morbidity and mortality and can progress to liver fibrosis, hepatic failure, and death.[18]

Certain conditions may **increase the risk** of PNAC

- Prematurity[10,19]
- Lack of enteral feeding[18]
- Low birth weight[10]
- Bacterial overgrowth[10,19]
- Genetic causes[10]
- Anatomic factors[10]
- Recurrent sepsis[18]
- Enzyme deficiencies[10]
- Factors relevant to PN[10]
- Susceptibility to cholestatic injury[10]
- Necrotizing enterocolitis (NEC)[19]

An alteration in DBIL is the earliest laboratory test that can indicate liver injury that is associated with PN.[17]

Appropriate initiation of Omegaven is key

Dosing[3]

- Initiate Omegaven dosing as soon as direct or conjugated bilirubin (DBil) levels are 2 mg/dL or greater in pediatric patients who are expected to be PN-dependent for at least 2 weeks.

Recommended Daily Dose/ Maximum Dose	Infusion Rate
1 g/kg/day	• Initial rate of infusion not to exceed 0.05 mL/minute for the first 15 to 30 minutes
	• If tolerated, gradually increase to the required rate after 30 minutes
	• Maximum infusion rate not to exceed 1.5 mL/kg/hour, corresponding to 0.15 g/kg/hour

Duration[3]

Administer Omegaven until direct or conjugated bilirubin levels are less than 2 mg/dL or until the patient no longer requires PN.

- Patients in our clinical trials conducted at Boston Children's Hospital and Texas Children's Hospital received Omegaven for a median of 2.7 months and up to 8 years.

Contraindications: Known hypersensitivity to fish or egg protein or to any of the active ingredients or excipients. Severe hemorrhagic disorders due to a potential effect on platelet aggregation. Severe hyperlipidemia or severe disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglyceride concentrations greater than 1,000 mg/dL).

Nourish with **SMOFlipid®** or **nurture** with **Omegaven®**?

- Consider SMOFlipid as your first choice for PN in pediatric patients requiring calories and essential fatty acids when oral or enteral nutrition is not possible, insufficient, or contraindicated
- Choose Omegaven as an option for pediatric patients diagnosed with PNAC*

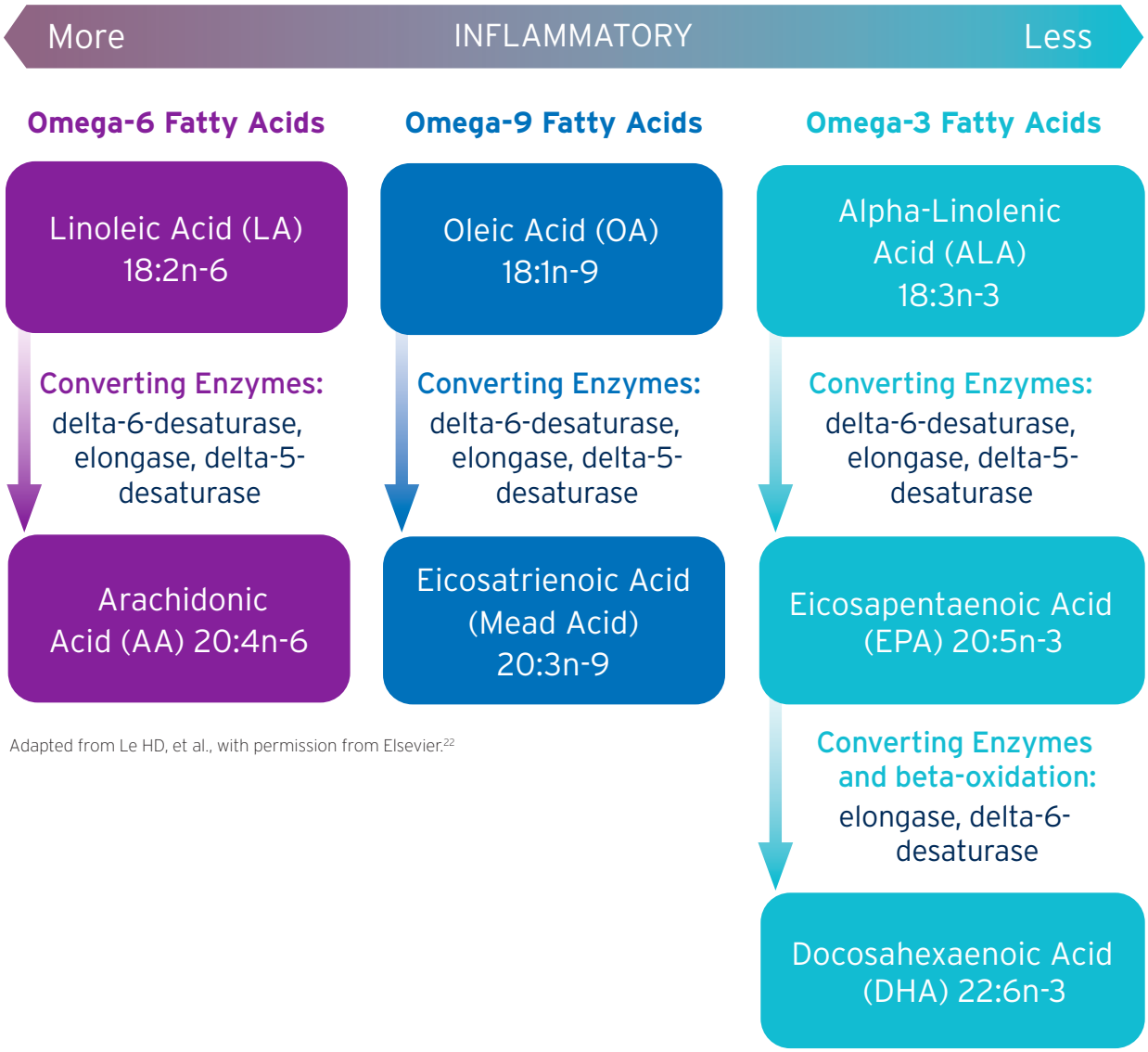
*See limitations of use for Omegaven on page 4 and 10.

ILE Composition Comparison

	Intralipid®[20] 20% Emulsion	Nutrilipid®[21] 20% Emulsion	SMOFlipid[2] 20% Emulsion	Omegaven[3] 10% Emulsion
Manufacturer	Fresenius Kabi/ Baxter*	B Braun	Fresenius Kabi	Fresenius Kabi
Oil Source	Soybean Oil	Soybean Oil	Soybean Oil 30% MCT 30% Olive Oil 25% Fish Oil 15%	Fish Oil
Indication	Adults & Pediatrics	Adults & Pediatrics	Adults & Pediatrics	Pediatrics
Fat Composition (Mean values or range % by weight)[2,3,20-23]				
Linoleic (omega-6)	44-62	48-58	**17.5**	**1.5**
Alpha-linolenic (omega-3)	4-11	4-11	**2.25**	**1.1**
Eicosapentaenoic (EPA omega-3)	0	0	**1-3.5**	**13-26**
Docosahexaenoic (DHA omega-3)	0	0	**1-3.5**	**14-27**
Oleic (omega-9)	19-30	17-30	**23-35**	**4-11**
Arachidonic (omega-6)	0	ND	**0.5**	**0.2-2**
Alpha-tocopherol (mg/L)	38	ND	**163-225**	**150-300**
Phytosterol Content[24] mcg/mL	381 ± 28.9†	ND	**165 ± 10.4†**	**3.66 ± 0.59**

*Distributed by; †Internal Data ND=No Data

Fatty acid pathways and impact on inflammation[22]



Adapted from Le HD, et al., with permission from Elsevier.[22]

> In pediatric patients, intravenous lipid emulsions (ILEs) should be an integral part of parenteral nutrition (PN) either exclusive or complementary to enteral feeding (LoE 1-, RG A, strong recommendation for).[11]

We are the **ONLY** provider of fish oil-containing ILEs for pediatric patients of all ages

Found in fish oil, DHA and EPA (omega-3 fatty acids) are considered to be important for healthy development of infants due to their special physiological roles[25,26]:

May be considered conditionally essential for growth and development.[27,28]

DHA is necessary for the normal development of the central nervous system and retina.[26,27]

Important structural elements of cell membranes.[26]

Primary precursors of the very long-chain fatty acids synthesized in the retina.[26]

Both SMOFlipid and Omegaven contain omega-3 fatty acids from fish oil.

Follow the recommended daily dose for SMOFlipid and Omegaven to meet your patient's energy requirements for growth.

Limitations of use: Omegaven is not indicated for the prevention of PNAC. It has not been demonstrated that Omegaven prevents PNAC in parenteral nutrition (PN)-dependent patients.

It has not been demonstrated that the clinical outcomes observed in patients treated with Omegaven are a result of the omega-6: omega-3 fatty acid ratio of the product.

 Please see Brief Summary of Prescribing Information for SMOFlipid on pages 11-12 and Omegaven on pages 13-14.

SMOFlipid®
Lipid Injectable Emulsion, USP 20%

SMOFLIPID (lipid injectable emulsion), for intravenous use

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR HEALTHCARE PROVIDERS

This brief summary does not include all the information needed to use SMOFlipid safely and effectively. Please see full prescribing information for intravenous use at https://qrco.de/bd4wCJ.

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 in adults is 1 to 2 grams/kg per day and should not exceed 2.5 grams/kg per day. Pediatric dosage is in Table 1, and do not exceed an infusion rate of 0.15 g/kg/hour.

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 Dosage

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Risk of Parenteral Nutrition-Associated Liver Disease (PNALD) and Other Hepatobiliary Disorders: 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.

- Death in Preterm Neonates: Deaths in preterm neonates after infusion of lipid injectable emulsions containing only soybean oil have been reported in the medical literature. Autopsy findings in these preterm neonates included intravascular lipid accumulation in the lungs. Preterm and small-for-gestational-age neonates have poor clearance of intravenous lipid emulsion and increased free fatty acid plasma levels following lipid emulsion infusion. This risk due to poor lipid clearance should be considered when administering intravenous lipid emulsions. Monitor patients receiving SMOFlipid for signs and symptoms of pleural or pericardial effusion.
- Hypersensitivity Reactions: SMOFlipid contains soybean oil, fish oil, and egg phospholipids, which may cause hypersensitivity reactions. Cross reactions have been observed between soybean and peanut. SMOFlipid is contraindicated in patients with known hypersensitivity to fish, egg, soybean, peanut protein, or to any of the active or inactive ingredients in SMOFlipid. If a hypersensitivity reaction occurs, stop infusion of SMOFlipid immediately and initiate appropriate treatment and supportive measures.
- 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 anemia, vomiting, gamma-glutamyltransferase increased, nosocomial infection, cholestasis, pyrexia, C-reactive protein increased, hyperbilirubinemia, abdominal pain, bilirubin conjugated increased, diarrhea, tachycardia, thrombocytopenia, hyperglycemia, 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 [*see Clinical Studies (14.2)*]. Use of SMOFlipid in older pediatric patients is supported by evidence from a short-term (i.e., <28 days) study in pediatric patients 28 days to 12 years of age and additional evidence from studies in adults [*see Clinical Studies (14)*]. The most common adverse reactions in SMOFlipid-treated pediatric patients were anemia, vomiting, gamma-glutamyltransferase increased, and nosocomial infection [*see Adverse Reactions (6.1)*]. PNALD, also referred to as IFALD, has been reported in pediatric patients who received SMOFlipid for more than 2 weeks. PNAC (a precursor to PNALD) was reported less frequently in SMOFlipid- treated patients compared to soybean oil lipid emulsion-treated patients in Pediatric Study 1 [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]. Although clinically significant cases of EFAD were not observed during short-term use in pediatric clinical studies, cases of EFAD have been reported with the use of SMOFlipid in the postmarketing setting [see Warnings and Precautions (5.9), Adverse Reactions (6.1)]. Monitor pediatric patients for laboratory evidence of EFAD because they may be particularly vulnerable to neurologic complications if adequate amounts of essential fatty acids are not provided [see Warnings and Precautions (5.9)]. Deaths in preterm infants after infusion of lipid injectable emulsions containing only soybean oil have been reported in medical literature [see Warnings and Precautions (5.2)]. Because of immature renal function, preterm infants receiving prolonged treatment with SMOFlipid may be at risk for aluminum toxicity [see Warnings and Precautions (5.8)].

OVERDOSAGE

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

Omegaven®

(fish oil triglycerides) injectable emulsion

OMEGAVEN (FISH OIL TRIGLYCERIDES) INJECTABLE EMULSION, FOR INTRAVENOUS USE

BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR HEALTHCARE PROVIDERS

This brief summary does not include all the information needed to use Omegaven safely and effectively. Please see full prescribing information for Omegaven (fish oil triglycerides) injectable emulsion for intravenous use at https://qrco.de/bd4nRi.

INDICATIONS AND USAGE

Omegaven is indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC).

Limitations of Use:

Omegaven is not indicated for the prevention of PNAC. It has not been demonstrated that Omegaven prevents PNAC in parenteral nutrition (PN)-dependent patients.

It has not been demonstrated that the clinical outcomes observed in patients treated with Omegaven are a result of the omega-6: omega-3 fatty acid ratio of the product.

DOSAGE AND ADMINISTRATION

Protect the admixed PN solution from light. Prior to administration, correct severe fluid and electrolyte disorders and measure serum triglycerides to establish a baseline level. Initiate dosing in PN-dependent pediatric patients as soon as direct or conjugated bilirubin levels are 2 mg/dL or greater. The recommended daily dose (and the maximum dose) in pediatric patients is 1 g/kg/day. Administer Omegaven until direct or conjugated bilirubin levels are less than 2 mg/dL or until the patient no longer requires PN.

CONTRAINDICATIONS

Omegaven is contraindicated in patients with known hypersensitivity to fish or egg protein or to any of the active ingredients or excipients, severe hemorrhagic disorders due to a potential effect on platelet aggregation, severe hyperlipidemia or severe disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglyceride concentrations greater than 1,000 mg/dL).

WARNINGS AND PRECAUTIONS

- Risk of Death in Preterm Infants due to Pulmonary Lipid Accumulation: Deaths in preterm infants after infusion of soybean oil-based intravenous lipid emulsions have been reported in medical literature. Autopsy findings in these preterm infants included intravascular lipid accumulation in the lungs. The risk of pulmonary lipid accumulation with Omegaven is unknown. 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. This risk due to poor lipid clearance should be considered when administering intravenous lipid emulsions. Monitor patients receiving Omegaven for signs and symptoms of pleural or pericardial effusion.
- Hypersensitivity Reactions: Omegaven contains fish oil and egg phospholipids, which may cause hypersensitivity reactions. 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, fever, or chills. If a hypersensitivity reaction occurs, stop infusion of Omegaven immediately and initiate appropriate treatment and supportive measures.
- Risk of 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 conditions or concomitant drugs. To decrease the risk of infectious complications, ensure aseptic technique in catheter placement and maintenance, as well as in the preparation and administration of Omegaven. Monitor for signs and symptoms of early infections including fever and chills, laboratory test results that might indicate infection (including leukocytosis and hyperglycemia), and frequently inspect the intravenous catheter insertion site for edema, redness, and discharge.
- Fat Overload Syndrome: A reduced or limited ability to metabolize lipids accompanied by prolonged plasma clearance may result in this syndrome, which is characterized by a sudden deterioration in the patient's condition including fever, anemia, leukopenia, thrombocytopenia, coagulation disorders, hyperlipidemia, hepatomegaly, deteriorating liver function, and central nervous system manifestations (e.g., coma).
- 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 the patient becomes 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: Impaired lipid metabolism with hypertriglyceridemia may occur in conditions such as inherited lipid disorders, obesity, diabetes mellitus, and metabolic syndrome. Serum triglyceride levels greater than 1,000 mg/dL have been associated with an increased risk of pancreatitis. To evaluate the patient's capacity to metabolize and eliminate the infused lipid emulsion, measure serum triglycerides before the start of infusion (baseline value), and regularly throughout treatment. If hypertriglyceridemia (triglycerides greater than 250 mg/dL in neonates and infants or greater than 400 mg/dL in older children) develops, consider stopping the administration of Omegaven for 4 hours and obtain a repeat serum triglyceride level. Resume Omegaven based on new result as indicated.
- Aluminum Toxicity: Aluminum may reach toxic levels with prolonged parenteral administration if kidney function is impaired. Preterm infants are particularly at 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 accumulate aluminum at levels associated with central nervous system and bone toxicity. Tissue loading may occur at even lower rates of administration.
- Monitoring and Laboratory Tests: Routine Monitoring: Monitor

serum triglycerides, fluid and electrolyte status, blood glucose, liver and kidney function, coagulation parameters, and complete blood count including platelets throughout treatment. Essential Fatty Acids: Monitoring patients for laboratory evidence 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.

- Interference with Laboratory Tests: The lipids contained in Omegaven may interfere with some laboratory blood tests (e.g., hemoglobin, lactate dehydrogenase, 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.

ADVERSE REACTIONS

The most common adverse drug reactions (>15%) are: vomiting, agitation, bradycardia, apnea and viral infection.

Clinical Trials Experience

The safety database for Omegaven reflects exposure in 189 pediatric patients (19 days to 15 years of age) treated for a median of 14 weeks (3 days to 8 years) in two clinical trials.

Adverse reactions that occurred in more than 5% of patients who received Omegaven and with a higher incidence than the comparator group are: vomiting, agitation, bradycardia, apnea, viral infection, erythema, rash, abscess, neutropenia, hypertonia and incision site erythema. Patients had a complicated medical and surgical history prior to receiving Omegaven treatment and the mortality was 13%. Underlying clinical conditions prior to the initiation of Omegaven therapy included prematurity, low birth weight, necrotizing enterocolitis, short bowel syndrome, ventilator dependence, coagulopathy, intraventricular hemorrhage, and sepsis.

Twelve (6%) Omegaven-treated patients were listed for liver transplantation (1 patient was listed 18 days before treatment, and 11 patients after a median of 42 days [range: 2 days to 8 months] of treatment); 9 (5%) received a transplant after a median of 121 days (range: 25 days to 6 months) of treatment, and 3 (2%) were taken off the waiting list because cholestasis resolved.

One hundred thirteen (60%) Omegaven-treated patients reached DBil levels less than 2 mg/dL and AST or ALT levels less than 3 times the upper limit of normal, with median AST and ALT levels for Omegaven-treated patients at 89 and 65 U/L, respectively, by the end of the study.

Median hemoglobin levels and platelet counts for Omegaven-treated patients at baseline were 10.2 g/dL and 173 x 10^9/L, and by the end of the study these levels were 10.5 g/dL and 217 x 10^9/L, respectively. Adverse reactions associated with bleeding were experienced by 74 (39%) of Omegaven-treated patients.

Median glucose levels at baseline and the end of the study were 86 and 87 mg/dL for Omegaven-treated patients, respectively. Hyperglycemia was experienced by 13 (7%) Omegaven-treated patients.

Median triglyceride levels at baseline and the end of the study were 121 mg/dL and 72 mg/dL for Omegaven-treated patients respectively. Hypertriglyceridemia was experienced by 5 (3%) Omegaven-treated patients.

The triene:tetraene (Mead acid:arachidonic acid) ratio was used to monitor essential fatty acid status in Omegaven-treated patients only in Study 1 (n = 123). The median triene:tetraene ratio was 0.02 (interquartile range: 0.01 to 0.03) at both baseline and the end of the study. Blood samples for analysis may have been drawn while the lipid emulsion was being infused and patients received enteral or oral nutrition.

Postmarketing Experience

The following adverse reaction has been identified with use of Omegaven in another country. Life-threatening hemorrhage following a central venous catheter change was reported in a 9 month-old infant with intestinal failure who received PN with Omegaven as the sole lipid source; he had no prior history of bleeding, coagulopathy, or portal hypertension.

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

Prolonged bleeding time has been reported in patients taking antiplatelet agents or anticoagulants and oral omega-3 fatty acids. Periodically monitor bleeding time in patients receiving Omegaven and concomitant antiplatelet agents or anticoagulants.

USE IN SPECIFIC POPULATIONS

- Pregnancy: There are no available data on Omegaven use in pregnant women to establish a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted with fish oil triglycerides. The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. 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.
- Lactation: No data available regarding the presence of fish oil triglycerides from Omegaven in human milk, the effects on the breastfed infant, or the effects on milk production. Lactating women receiving oral omega-3 fatty acids have been shown to have higher levels of omega-3 fatty acids in their milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Omegaven, and any potential adverse effects of Omegaven on the breastfed infant.
- Pediatric Use: The safety of Omegaven was established in 189 pediatric patients (19 days to 15 years of age). The most common adverse reactions in Omegaven-treated patients were vomiting, agitation, bradycardia, apnea and viral infection.
- Geriatric Use: Clinical trials of Omegaven did not include patients 65 years of age and older.

OVERDOSE

In the event of an overdose, fat overload syndrome may occur. Stop the infusion of Omegaven until triglyceride levels have normalized and any 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 serum.

References: 1. Data on File; 5/1/22; calculation includes all ILEs approved in the US. **2.** SMOFlipid Prescribing Information, Fresenius Kabi USA, LLC. 2022. **3.** Omegaven Prescribing Information, Fresenius Kabi USA, LLC. 2020. **4.** 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. **5.** Kalish BT, Fallon EM, Puder M. A tutorial on fatty acid biology. *JPEN J Parenter Enteral Nutr*. 2012;36(4):380-388. **6.** 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. **7.** Mertes N, Grimm H, Fürst P, Stehle P. 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