FRESENIUS KABI

caring for life

Fresenius Kabi

The U.S. Lipid Injectable Emulsion (ILE) Market Leader in Parenteral Nutrition (PN)[1]

Fresenius Kabi's innovations in parenteral nutrition have advanced the level of care and quality of life for critically and chronically ill patients.

For Fresenius Kabi's full Acute Care Product Catalog, ask your sales rep or visit: www.fresenius-kabi.com/us/products

Please see Important Safety Information, including ***Boxed Warnings*** *for SMOFlipid and Kabiven, starting on pages 3 and 4.*

Omegaven®

(fish oil triglycerides) injectable emulsion

The first and only fish oil lipid emulsion for pediatric patients in the U.S.[2,3]

A source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC)

Patients receiving Omegaven achieved age-appropriate growth

Omegaven-treated patients experienced improvement in liver function parameters

- During clinical trials, 113/189 of Omegaven-treated patients reached dbil levels less than 2 mg/dL and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels less than 3 times the upper limit of normal at end of study

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.

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 1000 mg/dL).

Please see the Brief Summary of Prescribing Information on page 9.

SMOFlipid®

Lipid Injectable Emulsion, USP 20%

An advancement in lipid emulsion for adults

Balanced lipid profile containing: soybean oil, medium-chain triglycerides, olive oil, and fish oil

The only mixed oil lipid introduced to PN that contains fish oil, which is rich in omega-3s

SMOFlipid meets the essential fatty acid requirements of adults[4]

Increased AST, ALT, and triglyceride levels were lower in patients receiving SMOFlipid compared to intravenous lipid emulsions (ILEs) with a higher soybean oil content[5,6]

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

- 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.

Please see the continuation of the Brief Summary of Prescribing Information on page 10.

Kabiven®

(Amino Acids, Electrolytes, Dextrose, and Lipid Injectable Emulsion), for intravenous use

Perikabiven®

(Amino Acids, Electrolytes, Dextrose, and Lipid Injectable Emulsion), for intravenous use

The first and only three-chamber bag for PN in the U.S.

The unique design streamlines the delivery of parenteral nutrition therapy to simplify:

- Calculations for dietitians
- Compounding for pharmacists
- Prescription writing for physicians
- Administration for nurses

Two formulations for added flexibility:

- Kabiven for central PN[7]
- Perikabiven for peripheral or central PN[8]
- Facilitates standardization to minimize errors associated with ordering, transcription, and compounding[9]

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This brief summary does not include all the information needed to use KABIVEN and PERIKABIVEN safely and effectively. Please see full prescribing information, including Boxed Warning for KABIVEN® (Amino Acids, Electrolytes, Dextrose, and Lipid Injectable Emulsion), for intravenous use and PERIKABIVEN® (Amino Acids, Electrolytes, Dextrose, and Lipid Injectable Emulsion), for intravenous use at www.KabivenUSA.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

KABIVEN and PERIKABIVEN are each indicated as a source of calories, protein, electrolytes and essential fatty acids for adult patients requiring parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated. KABIVEN and PERIKABIVEN may be used to prevent essential fatty acid deficiency or treat negative nitrogen balance in adult patients.

Limitation of Use:
Neither KABIVEN nor PERIKABIVEN is recommended for use in pediatric patients < 2 years including preterm infants because the fixed content of the formulation does not meet nutritional requirements in this age group.

DOSAGE AND ADMINISTRATION

KABIVEN is indicated for intravenous infusion into a **central vein.** PERIKABIVEN is indicated for intravenous infusion into a **peripheral or central vein.** It is recommended to mix the contents thoroughly by inverting the bags upside down to ensure a homogenous admixture. Ensure the vertical seals between chambers are broken and the contents of all three chambers for KABIVEN and PERIKABIVEN are mixed together prior to infusion. The dosage of KABIVEN and PERIKABIVEN should be individualized based on the patient's clinical condition (ability to adequately metabolize amino acids, dextrose and lipids), body weight and nutritional/fluid requirements, as well as additional energy given orally/enterally to the patient. Prior to administration of KABIVEN and PERIKABIVEN, correct severe fluid, electrolyte and acid-base disorders. Before starting the infusion, obtain serum triglyceride levels to establish the baseline value. The recommended dosage of KABIVEN in adults is 19 to 38 mL/kg/day. The recommended dosage of PERIKABIVEN in adults is 27 to 40 mL/kg/day. The maximum daily dosage of KABIVEN and PERIKABIVEN in adults should not exceed 40 mL/kg/day.

CONTRAINDICATIONS

Kabiven and Perikabiven is contraindicated in patients with known hypersensitivity to egg, soybean proteins, peanut proteins, corn or corn products or to any of the active substances or excipients. Severe hyperlipidemia or severe disorders of lipid metabolism characterized by hypertriglyceridemia (serum triglyceride concentration >1,000 g/dL). Inborn error of amino acid metabolism. Cardiopulmonary instability (including pulmonary edema, cardiac insufficiency, myocardial infarction, acidosis and hemodynamic instability requiring significant vasopressor support). Hemophagocytic syndrome.

Please see the continuation of the Brief Summary of Prescribing Information on pages 10 and 11.

All you need in one bag

A leader in infusion and nutrition therapy, Fresenius Kabi is one of the largest manufacturers of IV bags in the world. By combining the latest concept in bag innovation and unique port design, **free***flex* promotes **safety** and **convenience.** Experience **free***flex* for yourself.

Integrated hanger

Non-PVC

Not made with natural rubber latex

Self-sealing additive port;
Semi-rigid port design

Unique ports with finger guard;
Wide spacing between ports

Non-DEHP;
Does not contain plasticizers

Self-sealing infusion port to prevent leakage;
Semi rigid port design

The following products are available in a free*flex* bag:

- -Kabiven/Perikabiven
- -Lactated Ringer's Solution
- -SMOFlipid
- -Sterile Water
- -5% Dextrose
- -10% Dextrose
- -0.9% Sodium Chloride
- -0.45% Sodium Chloride
- -3% Sodium Chloride

Electrolytes

	STRENGTH (Concentration)
Magnesium Sulfate Injection, USP 50% 2mL, 10mL, 20mL, 50mL	50% (1 gram per 2 mL) (500 mg per mL)
	50% (5 grams per 10 mL)+ (500 mg per mL)
√ Preservative Free ✚ AP Rated ✱ The container closure is not made with natural rubber latex. **Therapeutic Class:** Electrolytes	50% (10 grams per 20 mL)* (500 mg per mL)
	50% (25 grams per 50 mL)* (500 mg per mL)

	STRENGTH (Concentration)
Calcium Gluconate Injection, USP 10% 10mL, 50mL, 100mL (plastic vial)	1,000 mg per 10 mL (100 mg per mL)
√ The container closure is not made with natural rubber latex. √ Preservative Free **Therapeutic Class:** Electrolytes	5,000 mg per 50 mL (100 mg per mL)
	10,000 mg per 100 mL (100 mg per mL)

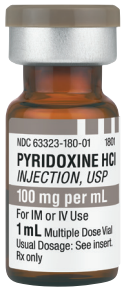
	STRENGTH (Concentration)
Potassium Chloride for Injection Concentrate, USP 5mL, 10mL, 20mL, 30mL (plastic vial)	10 mEq per 5 mL~ (2 mEq per mL)
	20 mEq per 10 mL~ (2 mEq per mL)
√ The container closure is not made with natural rubber latex. ~ Preservative Free √ AP Rated **Therapeutic Class:** Electrolytes	40 mEq per 20 mL~ (2 mEq per mL)
	60 mEq per 30 mL (2 mEq per mL)

For Fresenius Kabi's full Acute Care Product Catalog, ask your sales rep or visit:

Vitamins

	STRENGTH (Concentration)
Cyanocobalamin Injection, USP 1mL Vitamin B_{12} ✓ AP Rated **Therapeutic Class: Vitamins**	1,000 mcg per mL (1,000 mcg per mL)

	STRENGTH (Concentration)
Folic Acid Injection, USP 10mL ✓ The container closure is not made with natural rubber latex. **Therapeutic Class: Vitamins**	50 mg per 10mL (5 mg per mL)



	STRENGTH (Concentration)
Pyridoxine Hydrochloride Injection, USP 1mL Vitamin B_6 **Therapeutic Class: Vitamins**	100 mg per mL (100 mg per mL)

	STRENGTH (Concentration)
Thiamine Hydrochloride Injection, USP 2mL ✓ AP Rated Vitamin B_1 **Therapeutic Class: Vitamins**	200 mg per 2 mL (100 mg per mL)

SMOFlipid®
Lipid Injectable Emulsion, USP 20%

NDC Number	Product Number	Description/Strength	Container Size	Container Type	Unit of Sale
63323-820-00	830307310	SMOFlipid 20%	100 mL	Bag	1 x 10
63323-820-74	830570310	SMOFlipid 20%	250 mL	Bag	1 x 10
63323-820-50	830820310	SMOFlipid 20%	500 mL	Bag	1 x 12
63323-820-10	830920310	SMOFlipid 20%	1000 mL	Bag	1 x 6

Kabiven®
(Amino Acids, Electrolytes, Dextrose, and Lipid Injectable Emulsion), for intravenous use

Perikabiven®
(Amino Acids, Electrolytes, Dextrose, and Lipid Injectable Emulsion), for intravenous use

NDC Number	Product Number	Description	Volume/Calories	Units/Case
63323-712-10	831220310	**Kabiven** (central PN)	1026 mL/870 kcal	4
63323-712-15	831221310		1540 mL/870 kcal	4
63323-712-20	831222310		2053 mL/1745 kcal	4
63323-712-25	831223310		2566 mL/2180 kcal	3
63323-714-14	831231310	**Perikabiven** (peripheral or central PN)	1440 mL/970 kcal	4
63323-714-19	831232310		1920 mL/1300 kcal	4
63323-714-24	831233310		2400 mL/1620 kcal	3

Omegaven®
(fish oil triglycerides) injectable emulsion

NDC Number	Product Number	Description	Concentration	Size	Bottles/ Carton	Minimum Order Quantity
63323-205-50	255050	Single Dose Glass Bottle	5 g/50 mL (0.1 g/mL)	50 mL	10	1 x 10
63323-205-00	255100	Single Dose Glass Bottle	10 g/100 mL (0.1 g/mL)	100 mL	10	1 x 10

Omegaven®

(fish oil triglycerides) injectable emulsion

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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 www.fresenius-kabi.com/us.

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

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 foanalysis 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.

SMOFlipid®
Lipid Injectable Emulsion, USP 20%

Kabiven®
(Amino Acids, Electrolytes, Dextrose, and Lipid Injectable Emulsion), for intravenous use

Perikabiven®
(Amino Acids, Electrolytes, Dextrose, and Lipid Injectable Emulsion), for intravenous use

(Brief Summary of Prescribing Information continued from page 3)

- Risk of Catheter-Related Infections: Lipid emulsions, such as Smoflipid, can support microbial growth and is an independent risk factor for the development of catheter-related bloodstream infections. The risk of infection is increased in patients with malnutrition-associated immunosuppression, long-term use and poor maintenance of intravenous catheters, or immunosuppressive effects of other concomitant conditions or drugs.
- 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.

(Brief Summary of Prescribing Information continued from page 4)

WARNINGS AND PRECAUTIONS (also see BOXED WARNING)

- Death in Preterm Infants: Deaths in preterm infants after infusion of intravenous lipid emulsions have been reported. Autopsy findings included intravascular lipid accumulation in the lungs. Preterm and small for gestational age infants have poor clearance of intravenous lipid emulsion and increased free fatty acid plasma levels following lipid emulsion infusion. The safe and effective use of KABIVEN and PERIKABIVEN injection in pediatric patients, including preterm infants, has not been established. KABIVEN and PERIKABIVEN is not recommended for use in pediatric patients under the age of 2 years including preterm infants.
- Hypersensitivity Reactions: Stop infusion immediately and treat patient accordingly if signs or symptoms of a hypersensitivity or allergic reaction develop. Signs or symptoms may include: tachypnea, dyspnea, hypoxia, bronchospasm, tachycardia, hypotension, cyanosis, vomiting, nausea, headache, sweating, dizziness, altered mentation, flushing, rash, urticaria, erythema, pyrexia and chills.
- Infections: Patients who require parenteral nutrition are at high risk of infections due to malnutrition and their underlying disease state. Infection and sepsis may occur as a result of the use of intravenous catheters to administer parenteral nutrition, poor maintenance of catheters, or immunosuppressive effects of illness, drugs, and parenteral formulations. Decrease the risk of septic complications. Monitor for signs and symptoms (including fever and chills) of early infections, including laboratory test results (including leukocytosis and hyperglycemia) and frequent checks of the parenteral access device.
- Fat Overload Syndrome: Fat overload syndrome is a rare condition that has been reported with intravenous lipid emulsions. A reduced or limited ability to metabolize lipids accompanied by prolonged plasma clearance may result in a syndrome characterized by a sudden deterioration in the patient's condition accompanied by fever, anemia, leukopenia, thrombocytopenia, coagulation disorders, hyperlipidemia, liver fatty infiltration (hepatomegaly), deteriorating liver function, and central nervous system manifestations (e.g., coma).
- Refeeding Syndrome: Refeeding severely undernourished patients with parenteral nutrition 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.
- Diabetes/Hyperglycemia: KABIVEN and PERIKABIVEN should be used with caution in patients with diabetes mellitus or hyperglycemia. With the administration of KABIVEN and PERIKABIVEN, hyperglycemia and hyperosmolar syndrome may result. Administration of dextrose at a rate exceeding the patient's utilization rate may lead to hyperglycemia, coma and death. Monitor blood glucose levels and treat hyperglycemia to maintain optimum levels while infusing KABIVEN or PERIKABIVEN.
- Monitoring/Laboratory Tests: Routine Monitoring: Monitor fluid status closely in patients with heart failure or pulmonary edema. Monitor serum triglycerides, fluid and electrolyte status, serum osmolarity, blood glucose, liver and kidney function, and blood count, including platelet and coagulation parameters, throughout treatment. In situations of severely elevated electrolyte levels stop KABIVEN or PERIKABIVEN until levels have been corrected. Essential Fatty Acids: Monitoring patients for signs and symptoms of essential fatty acid deficiency (EFAD) is recommended. Laboratory tests are available to determine serum fatty acids levels. Reference values should be consulted to help determine adequacy of essential fatty acid status. Increasing essential fatty acid intake (enterally or parenterally) is effective in treating and preventing EFAD.
- Vein Damage and Thrombosis: **KABIVEN** is indicated for administration into a **central vein only,** such as the superior vena cava. The infusion of hypertonic nutrient injections into a peripheral vein may result in vein irritation, vein damage, and/or thrombosis.
- Thrombophlebitis: **PERIKABIVEN** is indicated for **peripheral administration or may be infused into a central vein.** Peripheral catheters should not be used for solutions with osmolarity of ≥ 900 mOsm/L. The primary complication of peripheral access is venous thrombophlebitis, which manifests as pain, erythema, tenderness or a palpable cord. The catheter should be removed as soon as thrombophlebitis develops.
- Precipitation with Ceftriaxone: Precipitation of ceftriaxone-calcium can occur when ceftriaxone is mixed with calcium-containing parenteral nutrition solutions, such as KABIVEN or PERIKABIVEN in the same intravenous administration line. Ceftriaxone must not be administered simultaneously with KABIVEN or PERIKABIVEN via a Y-site. However, ceftriaxone and KABIVEN or ceftriaxone and PERIKABIVEN may be administered sequentially if the infusion lines are thoroughly flushed between infusions with a compatible fluid.
- Hepatobiliary Disorders: Hepatobiliary disorders are known to develop in some patients without preexisting liver disease who receive parenteral nutrition, including cholecystitis, cholelithiasis, cholestasis, hepatic steatosis, fibrosis and cirrhosis, possibly leading to hepatic failure. The etiology of these disorders is thought to be multifactorial and may differ between patients. Increase of blood ammonia levels and hyperammonemia may occur in patients receiving amino acid solutions. In some patients this may indicate hepatic insufficiency or the presence of an inborn error of amino acid metabolism or hepatic insufficiency. Monitor liver function parameters and ammonia.
- Electrolyte Imbalance and Fluid Overload in Renal Impairment: Patients with renal impairment, such as pre-renal azotemia, renal obstruction and protein-losing nephropathy may be at increased risk of electrolyte and fluid volume imbalance. KABIVEN and PERIKABIVEN should be used with caution in patients with renal impairment. KABIVEN and PERIKABIVEN dosage may require adjustment with specific attention to fluid, protein and electrolyte content in these patients. Monitor renal function parameters.

- Hypertriglyceridemia: To evaluate the patient's capacity to eliminate and metabolize the infused lipid emulsion, measure serum triglycerides before the start of infusion (baseline value), with each increase in dosage, and regularly throughout treatment. Reduce dose of KABIVEN or PERIKABIVEN and monitor serum triglyceride levels in patients with serum triglyceride concentrations above 400 mg/dL to avoid the clinical consequences associated with hypertriglyceridemia. Serum triglyceride levels above 1,000 mg/dL have been associated with an increased risk of pancreatitis. Impaired lipid metabolism with hypertriglyceridemia may occur in conditions such as inherited lipid disorders, obesity, diabetes mellitus, and metabolic syndrome.
- Aluminum Toxicity: KABIVEN and PERIKABIVEN contains no more than 25 mcg/L of aluminum. The aluminum contained in KABIVEN and PERIKABIVEN may reach toxic levels with prolonged parenteral administration in patients with impaired kidney function. Preterm infants are at greater risk because their kidneys are immature, and they require large amounts of calcium and phosphate solutions that 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 of total parenteral nutrition products.
- Interference with Laboratory Tests: High levels of lipids in plasma may interfere with some laboratory blood tests such as hemoglobin, triglycerides, bilirubin, LDH, and oxygen saturation, if blood is sampled before lipid has been cleared from the bloodstream. Lipids are normally cleared after a lipid-free interval of 5 to 6 hours in most patients. KABIVEN and PERIKABIVEN contains Vitamin K1 which may interfere with anticoagulant activity.
- Risk of Parenteral Nutrition Associated Liver Disease: Parenteral Nutrition Associated Liver Disease (PNALD) has been reported in patients who receive parenteral nutrition 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 KABIVEN and PERIKABIVEN treated patients develop liver test abnormalities, consider discontinuation or dose reduction.

ADVERSE REACTIONS

Clinical Trials Experience

Adverse reactions occurring in >1% of patients who received **KABIVEN** were nausea, pyrexia, hypertension, vomiting, decreased hemoglobin, decreased total protein, hypokalemia, decreased blood potassium, increased gamma-glutamyltransferase, hyperglycemia, increased blood alkaline phosphatase, decreased blood calcium, prolonged prothrombin time, pruritus and tachycardia.

Less common adverse reactions in ≤1% of patients who received **KABIVEN** were hyperkalemia, hypertriglyceridemia, headache, dizziness, dysgeusia, rash, eczema, blood glucose increased, and increase in blood triglycerides.

Adverse reactions occurring in >2% of patients who received **PERIKABIVEN** were hyperglycemia, hypokalemia, pyrexia, increased blood triglycerides, phlebitis, nausea, pruritus, increased gamma-glutamyltransferase, increased blood alkaline phosphatase, increased alanine aminotransferase, increased blood glucose, increased C-reactive protein, increased blood urea and hypoalbuminemia.

Less common adverse reactions in ≤1% of patients who received **PERIKABIVEN** were hyperkalemia, hypomagnesaemia, hypernatremia, tachycardia, hypertension, thrombophlebitis, vomiting, jaundice, rash and increased blood bilirubin.

Post-Marketing Experience

The following additional adverse reactions have been identified during post-approval use of **KABIVEN** in countries where it is registered. Hepatobiliary disorders: cholestasis. Infections and infestations: infection. Nervous system disorders: subependymal hemorrhage.

The following additional adverse reactions have been identified during post-approval use of **PERIKABIVEN** in countries where it is registered. Gastrointestinal disorders: abdominal distension, abdominal pain. General disorders and administration site conditions: chest tightness. Hepatobiliary disorders: cholestasis. Immune system disorders: allergic reaction, anaphylaxis. Infections and infestations: infection. Vascular disorders: flushed face.

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: The limited available data on the use of KABIVEN and PERIKABIVEN in pregnant women are not sufficient to inform a drug-associated risk. There are clinical considerations if KABIVEN or PERIKABIVEN is used in pregnant women. Animal reproduction studies have not been conducted with KABIVEN and PERIKABIVEN.
- Lactation: There are no data available to assess the presence of KABIVEN and PERIKABIVEN and/or its active metabolite(s) in human milk, the effects on the breastfed child or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for KABIVEN or PERIKABIVEN, and any potential adverse effects of KABIVEN and PERIKABIVEN on the breastfed child or from the underlying maternal condition.
- Pediatric Use: The safety and effectiveness of KABIVEN and PERIKABIVEN in pediatric patients has not been established. Deaths in preterm infants after infusion of intravenous lipid emulsion have been reported. Patients, particularly preterm infants, are at risk for aluminum toxicity.
- Geriatric Use: Clinical studies of KABIVEN and PERIKABIVEN did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from other younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or drug therapy.
- Hepatic Impairment: In patients with impaired liver function KABIVEN and PERIKABIVEN should be administered with caution. Frequent clinical evaluation and laboratory tests to monitor liver function such as bilirubin and liver function parameters should be conducted.
- Renal Impairment: In patients with impaired renal function, KABIVEN and PERIKABIVEN should be administered with caution. Frequent clinical evaluation and laboratory tests to monitor renal function such as serum electrolytes (especially phosphate and potassium) and fluid balance should be conducted.

OVERDOSAGE

In the event of an overdose, fat overload syndrome may result. Stop the infusion KABIVEN or PERIKABIVEN to allow lipids to clear from serum. The effects are usually reversible after the lipid infusion is stopped. If medically appropriate, further intervention may be indicated. The lipid administered and fatty acids produced are not dialyzable.

REFERENCES: 1. Data on File; 1/1/20; calculation includes: all ILEs approved in the US. **2.** Omegaven Prescribing Information, Fresenius Kabi USA, LLC. 2019. **3.** Data on File **4.** Smoflipid Prescribing Information, Fresenius Kabi USA, LLC. 2019. **5.** 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. **6.** 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.**7.** KABIVEN Prescribing Information, Fresenius Kabi LLC, USA, 2014. **8.** PERIKABIVEN Prescribing Information, Fresenius Kabi LLC, USA, 2014. **9.** Institute for Safe Medication Practices (ISMP). *ISMP Guidelines for Safe Preparation of Compounded Sterile Preparations*; 2016. https://www.ismp.org/guidelines/sterile-compounding. Accessed February 24, 2020.

About Fresenius Kabi

Fresenius Kabi is a global healthcare company that specializes in lifesaving medicines and technologies for infusion, transfusion, and clinical nutrition. Our products are used to help care for critically and chronically ill patients. The people of Fresenius Kabi are driven by a common purpose: to put lifesaving medicines and technologies in the hands of people who care for patients, and to find answers to the challenges they face.

For more information about Fresenius Kabi, please visit:

www.fresenius-kabi.com/us

Please see Important Safety Information, including **Boxed Warnings** for SMOFlipid and Kabiven, starting on pages 3 and 4.

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