FRESENIUS KABI

Fresenius Kabi USA Nutrition

Omegaven®

(fish oil triglycerides) injectable emulsion

Resource Guide

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Omegaven®

(fish oil triglycerides) injectable emulsion

Introduction

This resource guide is intended to help you expand your knowledge of **Omegaven® (fish oil triglycerides) injectable emulsion**

Omegaven is the first and only fish oil lipid emulsion for pediatric patients with parenteral nutrition-associated cholestasis (PNAC) in the U.S.[1] This parenteral nutrition product rich in omega-3s became commercially available for pediatric patients in November 2018. Prior to that, Omegaven was only available in the United States for compassionate care use. Fresenius Kabi was aware of the need for this product to be more broadly available to pediatric patients and worked hard to secure the necessary clinical evidence to support FDA approval.

Should you have additional questions about Omegaven, our Medical Affairs team welcomes your call. You can reach them via **phone** by calling (800) 551-7176 (option 4) or
email: nutrition.medinfo.USA@fresenius-kabi.com

Reference:

1. Omegaven Prescribing Information, Fresenius Kabi USA, LLC. 2020.

Parenteral Nutrition-Associated Cholestasis (PNAC)

Epidemiology and risk factors

Parenteral nutrition-associated cholestasis (PNAC), which falls under the umbrella of the commonly interchangeable terms of parenteral nutrition-associated liver disease (PNALD) and intestinal failure-associated liver disease (IFALD), is a significant complication that develops among pediatric patients who require long-term treatment with parenteral nutrition.[1] It is difficult to determine the true prevalence of PNAC due to a lack of standardization in its diagnosis; PNAC is diagnosed clinically based on a combination of clinical, biological, and histological criteria.[1-3] A meta-analysis of 23 studies evaluating infants and children receiving parenteral nutrition (PN) for >14 days found the incidence of PNAC in children <18 years of age to be 28.2%, with an incidence of 25.5% in premature infants.[1] In addition, the incidence of cholestasis among patients on PN was found to be directly proportional to the length of time they require PN, with a significant increase in incidence in patients requiring PN for >60 days (60.9%) as compared to patients requiring PN for 14 to 30 days (15.7%). Studies have estimated that 15%-25% of pediatric patients on long-term PN will develop end-stage liver disease, which frequently leads to the need for combined liver and intestinal transplant.[3,4] Liver failure is the most common cause of death among patients with PNALD.[3]

There are several patient- and treatment-related risk factors that are associated with the development of PNAC and associated liver disease.[2] Common patient-specific risk factors in infants include premature birth (gestational age less than 37 weeks) and birth weights <750 grams.[1-5] Patients with short bowel syndrome (SBS) due to congenital or acquired causes (such as infants with necrotizing enterocolitis [NEC]) are also at an increased risk for development of PN-related cholestasis and liver disease.[4-6] Risk factors related to treatment include lack of enteral feeding, prolonged need for PN, continuous administration of PN, individual PN components, infectious complications, and the use of medications such as antibiotics that can further exacerbate liver toxicity.[1-3,5,6]

Pathophysiology

The mechanism for development of cholestasis and eventual liver disease is multifaceted and varies based on individual patient characteristics and risk factors.[5] In premature infants, the liver is not fully developed at birth. The immature liver has impaired enterohepatic cycling, leading to reduced bile salt synthesis and diminished breakdown of toxic bile salts when compared to the liver of an infant born full-term; thus, the preterm liver is more susceptible to toxicity.[2-5] Similar effects on enterohepatic cycling can be seen in patients with a variety of conditions which may require long-term PN and potentially lead to intestinal failure, including congenital malformations, SBS (often due to significant intestinal resection), intestinal infections (such as NEC), or inflammatory bowel diseases.[1,2,4-6]

The mechanism for development of cholestasis and eventual liver disease is multifaceted and varies based on individual patient characteristics and risk factors.[5]

In all patients, enteral nutrition (EN) is the preferred method of feeding, as it stimulates the intestine to produce various hormones that cause gallbladder contraction (thus preventing stone and sludge formation due to stasis) and improves intestinal integrity, which prevents bacterial translocation.[2,4,5] In patients with the conditions previously mentioned, however, PN is often required as the intestine is physically incapable of absorbing nutrients enterally. Parenteral nutrition circumvents the gut entirely, which prevents the normal stimulation of intestinal motility that is brought on by the presence of food and can ultimately lead to cholestasis.

Although the mechanism for development of PNAC has yet to be fully elucidated, it is thought to be related to alteration of the activation of the farnesoid X receptor (FXR) by bile salts in the liver and intestines.[4,7] The FXR regulates the excretion of various metabolic byproducts including bilirubin, maintains bile acid homeostasis, regulates transporters that allow for bile salt uptake, and controls the synthesis of new bile acids.[7] The activity of the FXR is also regulated by bile acids, which have impaired recycling mechanisms in the setting of intestinal failure. The irregularity in bile acid cycling leads to a decrease in FXR activity. Multiple other factors have been implicated in the down-regulation of FXR activity, including infection and sepsis, PN (by allowing translocation of bacteria due to impaired intestinal barrier), and presence of plant-derived phytosterols in the lipid component of PN.[7]

Many of the components of PN have been considered as potential contributors to the development of cholestasis and liver disease in patients on long-term PN.[2] One of the components that is commonly implicated in the pathogenesis of PNALD is the lipid emulsion used in the preparation.[2-6] Lipids provide a non-protein energy source in PN. Although dextrose can be used as an energy source, lipid emulsions are necessary, in addition to dextrose, to provide essential fatty acids.[4,6] The first lipid injectable emulsion (ILE) product that became available in the United States, which is still commonly used today, is a 100% soybean oil-based emulsion. It contains essential fatty acids that consist of small amounts of ω-3 fatty acids and high amounts of ω-6 fatty acids.[2,5,6]

There are several potential mechanisms that have been suggested, which implicate ILEs (particularly those with high concentrations of ω-6 fatty acids), in the development of PNAC. One of the key ω-6 fatty acids that make up soybean oil products is linoleic acid, which is converted to arachidonic acid in the body.[6] Arachidonic acid acts as a precursor to multiple endogenous proinflammatory mediators, and it is thought that chronic inflammation may contribute to the development of cholestasis. In addition, long-chain polyunsaturated fatty acids (ω-6 fatty acids) within 100% soybean oil-based lipid emulsions undergo frequent oxidation and generate lipid peroxides. The process of peroxide formation and oxidization is highly cytotoxic, which can damage proteins, cell components, and can contribute to liver toxicity.[2,6] Another component of ILEs, phytosterols, are thought to antagonize the FXR, resulting in a reduction and inhibition of bile acid secretion.[2] Finally, it has been proposed that long-term lipid emulsion administration may overwhelm the reticuloendothelial cells of the liver, potentially leading to hematologic disorders, liver impairment, and cholestasis.[6]

Clinical presentation

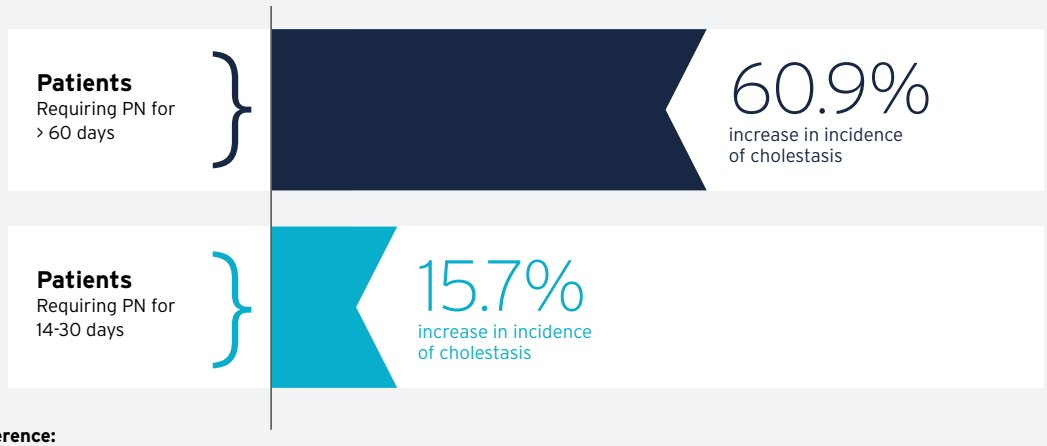
The characterization of PNAC varies among studies. One of the more common clinical definitions that is used for the development of PNAC is a direct or conjugated bilirubin (DBIL) that is >2 mg/dL (or 34 µmol/L) in conjunction with PN administration for at least 14 days.[1,5,6] The terms, "direct" and "conjugated" bilirubin are often used interchangeably in clinical practice; however, direct bilirubin may include both the conjugated fraction and bilirubin bound to albumin.[8] An alteration in bilirubin is the earliest laboratory test that can indicate liver injury that is specific to PN.[5] Other laboratory values that are reported in patients on PN that may indicate hepatobiliary disease include alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT).[3-6] An asymptomatic increase of the transaminases (AST, ALT) can be seen relatively early in the course of PN, and will be followed by increases in DBIL, ALP, and GGT.[4] Increased transaminases are sensitive tests to detect hepatocellular injury, but are not specific to PN-related injury.[5] Gamma-glutamyl transferase is a sensitive test that detects damage to the biliary tract when elevated.

As patients continue on PN therapy for longer periods of time, they may progress from cholestasis to other, more advanced signs of liver disease including liver fibrosis, cirrhosis, portal hypertension, and end-stage liver disease.[4] Laboratory values may not correlate well with the degree of injury to the liver; biopsy of the liver may be necessary to determine the degree of steatosis, cholestasis, fibrosis, and/or cirrhosis in a patient with evidence of liver injury. Increasing severity of hepatic damage over time can be evidenced by declining albumin levels, an abnormal coagulation profile, enlarged spleen, and development of varices, which indicate the presence of portal hypertension.[2,5] Once a patient has developed end-stage liver disease, the mortality rate is nearly 100% if they do not receive a hepatic and/or intestinal transplant within one year.[1]

Societal, humanistic, and/or economic burden

Cholestasis is one of the first stages of liver dysfunction that can be seen in patients who require PN due to intestinal failure. As noted previously, the incidence of cholestasis among patients on PN is directly proportional to the length of PN administration, with a significant increase in incidence in patients requiring PN for >60 days (60.9%) as compared to patients requiring PN for 14 to 30 days (15.7%).[1] Full recovery of enteral function may take several years in pediatric patients.[9]

Cholestasis is one of the first stages of liver dysfunction.[1]



Reference:

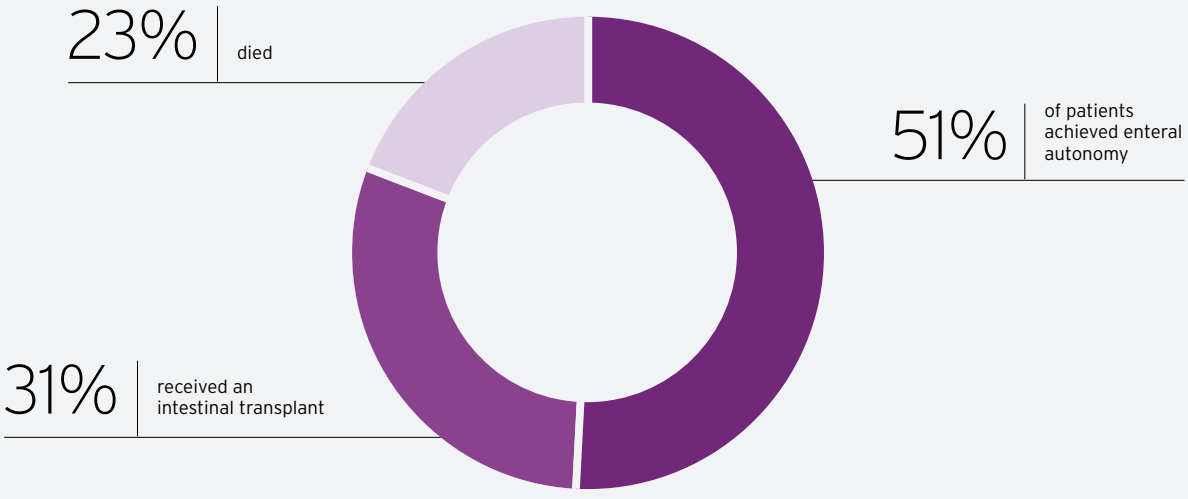
Lauriti G, Zani A, Aufieri R, et al. Incidence, prevention, and treatment of parenteral nutrition-associated cholestasis and intestinal failure-associated liver disease in infants and children: a systematic review. *JPEN J Parenter Enteral Nutr.* 2014;38(1):70-85.

Patients on long-term PN are subject to a variety of clinical, social, and economic issues that may reduce their overall quality of life. Some of the clinical issues that may arise in patients requiring long-term PN include development of catheter-related complications, liver disease, metabolic bone disease due to decreased vitamin and mineral intake, lack of sleep and associated fatigue, and depression.[10] Children with intestinal failure may also be at risk for impaired growth and cognitive delays compared to children who do not have intestinal failure.[11] In addition, the need for PN may affect relationships both inside and outside of the patient's family and lead to decreased participation in social activities.[10]

Finally, PN can be expensive. In 2002, the allowable charge from Medicare for home PN ranged between $75,000 and $122,000; this did not include costs related to physician visits, laboratory needs, home nursing, or inpatient admissions due to complications.[9]

As discussed previously, SBS is one of the most common causes of intestinal failure requiring PN in neonates. Although the incidence of SBS is rare (estimated to affect 3 to 5 per 100,000 live births), it is associated with significant morbidity and mortality.[12] A large database study of pediatric patients from 0 to 3 years of age found that patients with SBS (when compared with pediatric patients without SBS) had more severe illness, more chronic medical conditions and medical diagnoses, and a greater number of hospital admissions that required more procedures.[13] Additionally, when patients were admitted to the hospital, patients with SBS had a significantly longer length of stay and higher overall cost. They were also found to have a significantly higher mortality rate. Despite these findings, survival has increased over time in patients with intestinal failure; it has recently been estimated that more than 90% of pediatric patients with intestinal failure survive long-term.[11] In addition, 75% of patients with SBS on PN progress and are eventually able to consume a full enteral diet.[9] A retrospective review of infants with intestinal failure and PN administration greater than 60 days found that during a 2-year study period, 51% of patients achieved enteral autonomy, 31% received an intestinal transplant, and 23% died.[14]

Infants with intestinal failure and PN administration >60 days

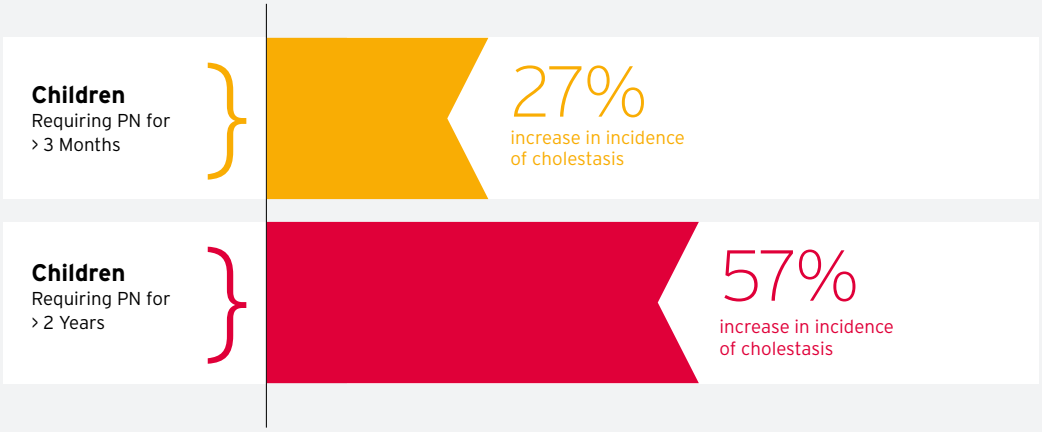


Reference:

Javid PJ, Oron AP, Duggan C, Squires RH, Horslen SP. The extent of intestinal failure-associated liver disease in patients referred for intestinal rehabilitation is associated with increased mortality: an analysis of the pediatric intestinal failure consortium database. *J Pediatr Surg*. 2018;53(7):1399-1402.

Post-transplant survival rates have increased over time.[11] One and 5-year survival rates among children who received transplants between 2007 and 2009 were estimated to be 90% and 75%, respectively, for intestinal transplant and 72% and 60%, respectively, for a combined intestinal and liver transplant. Overall, intestinal graft survival was found to be 65.1% at 1 year and 42.5% at the 5-year mark. Graft loss and death are most commonly attributed to sepsis in patients who have undergone intestinal and/or liver transplantation. Similarly, the most common causes of death among patients with intestinal failure include IFALD and sepsis, which typically manifests as the result of a central line associated bloodstream infection (CLABSI). Intestinal failure-associated liver disease has an estimated incidence between 27% and 57% in children requiring PN for >3 months and >2 years, respectively.[11]

Intestinal failure-associated liver disease



Reference:

Fullerton BS, Hong CR, Jaksic T. Long-term outcomes of pediatric intestinal failure. *Semin Pediatr Surg*. 2017;26(5):328-335.

References:

1. Lauriti G, Zani A, Aufieri R, et al. Incidence, prevention, and treatment of parenteral nutrition-associated cholestasis and intestinal failure-associated liver disease in infants and children: a systematic review. *JPEN J Parenter Enteral Nutr.* 2014;38(1):70-85.

2. Lacaille F, Gupte G, Colomb V, et al. Intestinal failure-associated liver disease: a position paper of the ESPGHAN Working Group of Intestinal Failure and Intestinal Transplantation. *J Pediat Gastroent Nutr.* 2015;60(2):272-283.

3. Wales PW, Allen N, Worthington P, George D, Compher C, Teitelbaum D. A.S.P.E.N. clinical guidelines: support of pediatric patients with intestinal failure at risk of parenteral nutrition-associated liver disease. *JPEN J Parenter Enteral Nutr.* 2014;38(5):538-557.

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5. Satrom K, Gourley G. Cholestasis in preterm infants. *Clin Perinatol*. 2016;43(2):355-373.

6. Hojsak I, Colomb V, Braegger C, et al. ESPGHAN Committee on Nutrition Position Paper. Intravenous lipid emulsions and risk of hepatotoxicity in infants and children: a systematic review and meta-analysis. *J Pediat Gastroent Nutr.* 2016;62(5):776-792.

7. Al-Shahwani NH, Sigalet DL. Pathophysiology, prevention, treatment, and outcomes of intestinal failure-associated liver disease. *Pediatr Surg Int.* 2017;33(4):405-411.

8. Harb R, Thomas DW. Conjugated hyperbilirubinemia: screening and treatment in older infants and children. *Pediatr Rev.* 2007;28(3):83-91.

9. Howard L. Home parenteral nutrition: survival, cost, and quality of life. *Gastroenterology.* 2006;130(2 Suppl 1):S52-59.

10. Winkler MF, Smith CE. Clinical, social, and economic impacts of home parenteral nutrition dependence in short bowel syndrome. *JPEN J Parenter Enteral Nutr.* 2014;38(1 Suppl):32s-37s.

11. Fullerton BS, Hong CR, Jaksic T. Long-term outcomes of pediatric intestinal failure. *Semin Pediatr Surg.* 2017;26(5):328-335.

12. Squires RH, Duggan C, Teitelbaum DH, et al. Natural history of pediatric intestinal failure: initial report from the Pediatric Intestinal Failure Consortium. *J Pediatr.* 2012;161(4):723-728.e722.

13. Pant C, Sferra TJ, Fischer RT, Olyaee M, Gilroy R. Epidemiology and healthcare resource utilization associated with children with short bowel syndrome in the United States. *JPEN J Parenter Enteral Nutr.* 2017;41(5):878-883.

14. Javid PJ, Oron AP, Duggan C, Squires RH, Horslen SP. The extent of intestinal failure-associated liver disease in patients referred for intestinal rehabilitation is associated with increased mortality: an analysis of the pediatric intestinal failure consortium database. *J Pediatr Surg.* 2018;53(7):1399-1402.

Dosing for Initiation and Advancement of PN Macronutrients

	Initiation		Advanced By		Goals	
Infants (<1 y)	**Preterm**	**Term**	**Preterm**	**Term**	**Preterm**	**Term**
Protein (g/kg/d)*	1-3 (3-4 max)	2.5-3	–	–	3-4	2.5-3
Dextrose (mg/kg/min)	6-8	6-8	1-2	1-2	10-14 (max 14-18)	10-14 (max 14-18)
SO ILE (g/kg/d)	0.5-1	0.5-1	0.5-1	0.5-1	3 (max 0.15 g/kg/h)	2.5-3 (max 0.15 g/kg/h)
FO ILE (g/kg/d)[1**†]	1	1	–	–	1 (max 0.15 g/kg/h)	1 (max 0.15 g/kg/h)
Children (1–10 y)						
Protein (g/kg/d)	1.5-2.5		–		1.5-2.5	
Dextrose (mg/kg/min)	3-6		1-2		8-10	
SO ILE (g/kg/d)[2]	1-2		0.5-1		2-2.5 (max 0.1 g/kg/h)	
FO ILE (g/kg/d)[1**†]	1		1		1 (max 0.15 g/kg/h)	
Adolescents (<17 y)						
Protein (g/kg/d)	0.8-2		–		0.8-2	
Dextrose (mg/kg/min)	2.5-3		1-2		5-6	
SO ILE (g/kg/d)[2]	1		1		1-2 (max 0.1 g/kg/h)	
FO ILE (g/kg/d)[1**†]	1		1		1 (max 0.15 g/kg/h)	

Adapted with permission from ASPEN. Appropriate Dosing for Parenteral Nutrition: ASPEN Recommendations. http://www.nutritioncare.org/uploadedFiles/Documents/Guidelines_and_Clinical_Resources/PN%20Dosing%201-Sheet-FINAL.pdf. Published 1.8.19, Accessed 04.22.

*Protein does not need to be titrated; protein needs are increased with critical illness.

**For pediatric patients with parenteral nutrition-associated cholestasis.

†The initial rate of infusion should not exceed 0.05 mL/min for the first 15-30 min of infusion. If tolerated, gradually increase until reaching the required rate after 30 minutes.

ILE = Lipid injectable emulsion; SO = Soybean Oil; FO = Fish Oil; GIR = glucose infusion rate; GIR calculation (mg/kg/m) = [dextrose (g/d) x 1000] / [24 (h/d) x 60 (m/hr) x weight (kg)]

References:

1. Omegaven Prescribing Information, Fresenius Kabi USA, LLC. 2020.

2. Intralipid 20% Prescribing Information, Fresenius Kabi USA, LLC. 2015.

Omegaven Lipid Injectable Emulsion Composition

	Soybean Oil		Omegaven
Indication	**Adults and Pediatrics**		**Pediatrics**
Concentration	20%	30%*	10%
Lipid (g/100 mL)	20	30	10
Calories (kcal/mL)	2	3	1.1
Calories (kcal/g)	20	30	11
	Fat Composition (Mean value or range % by weight)[1-5]		
Linoleic Acid	44–62	44–62	1.5
Alpha-Linolenic Acid	4–11	4–11	1.1
Eicosapentaenoic Acid	0	0	13–26
Docosahexaenoic Acid	0	0	14–27
Oleic Acid	19–30	19–30	4–11
Arachidonic Acid	0	0	0.2–2
Alpha-Tocopherol (mg/L)	38	ND	150–300
Phytosterol Content[6] (mcg/mL)	381 ± 28.9[7]	ND	3.66 ± 0.59

*Bulk packaging – not for direct infusion, for compounding only

ND = no data

References:

1. Intralipid 20% Prescribing Information. In: Fresenius Kabi; 2015.
2. Intralipid 30% Prescribing Information. In: Fresenius Kabi; 2015.
3. Omegaven Prescribing Information. In: Fresenius Kabi USA, LLC; 2020.
4. Le HD, Meisel JA, de Meijer VE, Gura KM, Puder M. The essentiality of arachidonic acid and docosahexaenoic acid. *Prostaglandins Leukot Essent Fatty Acids.* 2009;81(2-3):165-170.
5. Vanek VW, Seidner DL, Allen P, et al. A.S.P.E.N. position paper: Clinical role for alternative intravenous fat emulsions. *Nutr Clin Pract.* 2012;27(2):150- 192.
6. Vanek VW, Seidner DL, Allen P, et al. Update to A.S.P.E.N. position paper: clinical role for alternative intravenous fat emulsions. *Nutr Clin Pract.* 2014;29(6):841.
7. Internal Data. In: Fresenius Kabi USA, LLC.

Contraindications

Use of Omegaven is contraindicated in patients with[1]:

- Known hypersensitivity to fish or egg protein or to any of the active ingredients or excipients [see Warnings and Precautions (5.2)].
- 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) [see Warnings and Precautions (5.6)].

Reference:

1. Omegaven Prescribing Information. In: Fresenius Kabi USA, LLC; 2020.

Pediatric Essential Fatty Acid Minimum Requirements

	Recommendation from ESPGHAN[1]	Recommendation from ASPEN to avoid EFAD[2]	
Age Group	**LA g/kg/day**	**LA**	**ALA**
Preterm Infants	0.25	4.5% of total calories	0.5% of total calories
Term Infants and Children	0.1		

ALA = α-linolenic acid; ASPEN = American Society for Parenteral and Enteral Nutrition; ESPGHAN = European Society for Paediatric Gastroenterology, Hepatology and Nutrition; LA = linoleic acid

References:

1. Koletzko B, Goulet O, Hunt J, Krohn K, Shamir R. Guidelines on Paediatric Parenteral Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the European Society for Clinical Nutrition and Metabolism (ESPEN), Supported by the European Society of Paediatric Research (ESPR). *J Pediatr Gastroenterol Nutr*. 2005;41:S1-S4.

2. Mehta NM, Compher C, A.S.P.E.N. Board of Directors. A.S.P.E.N. clinical guidelines: nutrition support of the critically ill child. *JPEN J Parenter Enteral Nutr.* 2009;33(3):260-276

Estimated Essential Fatty Acid Needs of Preterm Neonates

Fatty Acid	Minimum recommendations for preterm infants	Estimated needs based on third trimester intrauterine accretion rates
Essential Fatty Acids		
LA	385–1540 mg/kg/day[1,2]	106 mg/kg/day[1]
ALA	≥55 mg/kg/day[1] or >50 mg/kg/day[2]	4 mg/kg/day[1]
Conditionally Essential Fatty Acids		
ARA	18–45 mg/kg/day[1,2] or 35-45 mg/kg/day[2]	212 mg/kg/day[1,2]
DHA*	12–60 mg/kg/day[1] or 55-60 mg/kg/day[2]	43–60 mg/kg/day[1,2]
EPA**	≤20 mg/kg/day[1]	Fetal accretion rate unknown

*No evidence for DHA provision without also giving ARA.[2]

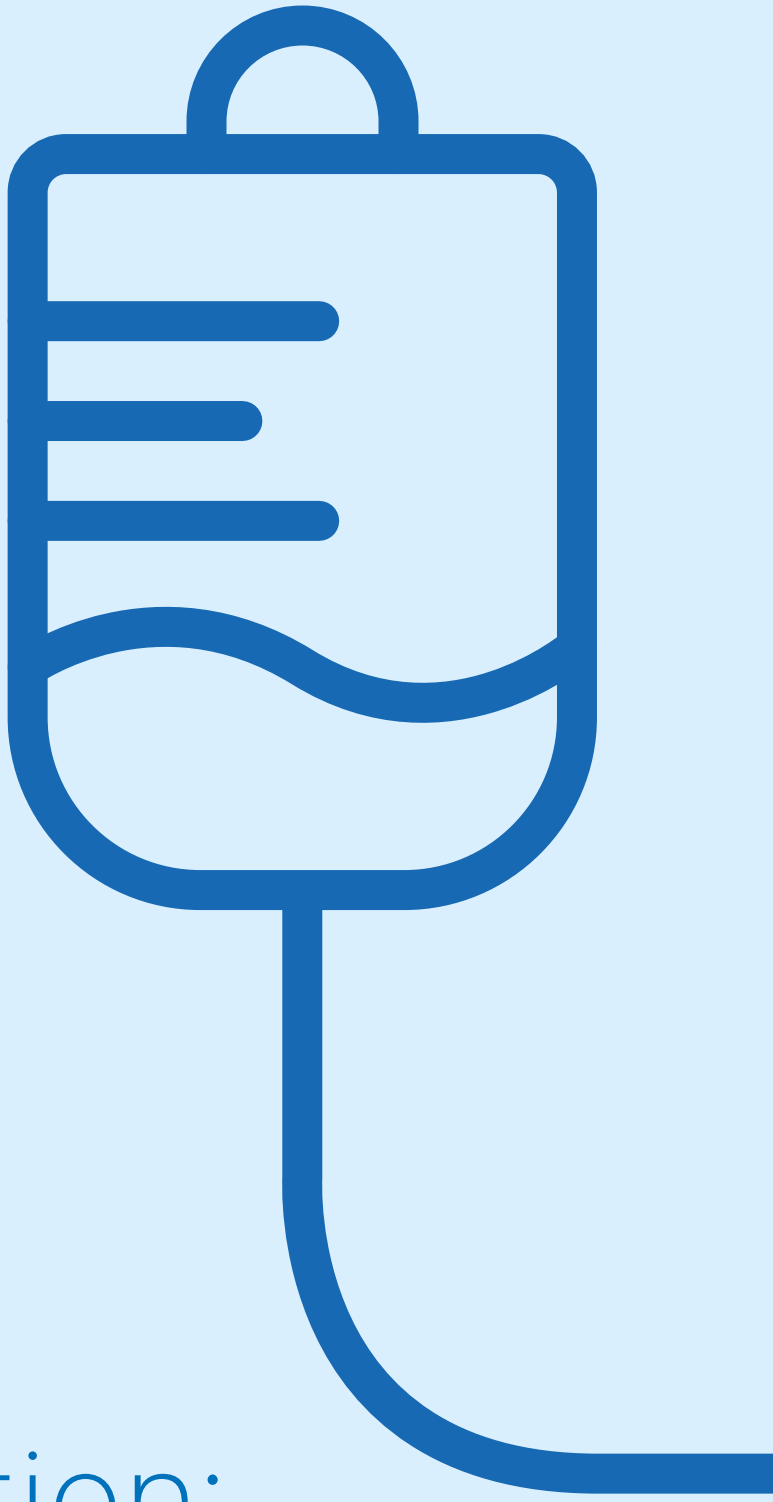
**Limited data available to determine if EPA is necessary in the infant diet and thus the limit is set at +1 standard deviation of the mean human milk content.[1]

LA = linoleic acid; ALA = α-linolenic acid ; ARA = arachidonic acid; DHA = docosahexanoic acid; EPA = eicosapentanoic acid

References:

1. Lapillonne A, Groh-Wargo S, Gonzalez CH, Uauy R. Lipid needs of preterm infants: updated recommendations. *J Pediatr.* 2013;162(3 Suppl):S37-47.

2. Robinson DT, Martin CR. Fatty acid requirements for the preterm infant. *Semin Fetal Neonatal Med.* 2017;22(1):8-14.



Administration:

Omegaven®(fish oil triglycerides) injectable emulsion

Administration: Omegaven® (fish oil triglycerides) injectable emulsion[1]

- Omegaven can be administered alone or as part of a PN admixture.
- Omegaven is for central or peripheral intravenous infusion. When administered with dextrose and amino acids, the choice of a central or peripheral venous route should depend on the osmolarity of the final infusate. Solutions with osmolarity of 900 mOsm/L or greater must be infused through a central vein.
- Use a 1.2 micron in-line filter during administration.
- Use a dedicated line for PN. Omegaven should be infused concurrently into the same vein as dextrose-amino acid solutions (as part of PN) by a Y-connector located closest to the infusion site; flow rates of each solution should be controlled separately by infusion pumps. Avoid multiple connections; do not connect multiple medications in series. Turn off the pump before the bottle runs dry.
- Use a vented infusion set when Omegaven is infused from the bottle.
- Do not use infusion sets and lines that contain di-2-ethylhexyl phthalate (DEHP).
- Prior to infusion, visually inspect Omegaven for particulate matter and discoloration. Discard the bottle if any particulates or discoloration are observed.
- Gently invert the bottle before use. Use Omegaven only if the emulsion is homogeneous and the container is undamaged.
- Strict aseptic techniques must be followed.
- Hang the bottle using the attached hanger and start infusion.
- After connecting the infusion set, start infusion of Omegaven immediately. Complete the infusion within 12 hours when using a Y-connector and within 24 hours when used as part of an admixture.
- For single use only. Discard unused portion.
- Protect the admixed PN solution from light.
- **When Omegaven is administered with other infusion solutions (e.g., amino acids, dextrose) the compatibility of the solutions used must be ensured. Questions related to compatibility may be directed to Fresenius Kabi USA, LLC, at 1-800-551-7176 (option 4) or nutrition.medinfo.USA@Fresenius-kabi.com**

Reference:

1. Omegaven Prescribing Information. In: Fresenius Kabi USA, LLC; 2020.

Lipid Injectable Emulsions

Publication	Practice Recommendation
ASPEN Parenteral Nutrition Safety Committee (2018)[1]	The ASPEN Parenteral Nutrition Safety Committee supports a 12-hour maximum infusion time when administered separately. If volume limitations require separate ILE administration for a period longer than 12 hours, strong consideration should be given to administering a new ILE container for the second 12-hour portion of the day.
ASPEN Clinical Guidelines: Parenteral Nutrition Ordering, Order Review, Compounding, Labeling and Dispensing (2014)[2]	The BUD for un-spiked [ILE] in the original container should be based on the manufacturer's provided information. The BUD for [ILE] in the original container spiked for infusion should be 12–24 hours. Repackaged [ILE] is not recommended, although when used, the BUD for [ILE] transferred from the original container to another container for infusion separately from a 2-in-1 PN solution should be 12 hours.
ASPEN Board of Directors and Task Force for the Revision of Safe Practices for Parenteral Nutrition (2004)[3]	Because of the concern for microbial contamination, the U.S. Pharmacopeia (USP) recommends that [ILE] products be used within 12 hours of opening the original container if they are to be infused as a separate infusion. If a slower infusion is desirable and the selected rate of administration exceeds 12 hours, then the lipids shall be given in two separate containers so as not to exceed a 12-hour hang time for any single container. If the [ILE] is admixed directly to the parenteral nutrition (PN) to form a total nutrient admixture (TNA), the final PN formulation can be infused over a 24-hour period since it provides a safe vehicle with respect to infectious risks.
CDC Guidelines for the Prevention of Intravascular Catheter-related Infections (2011)[4]	Replace tubing used to administer fat emulsions (those combined with amino acids and glucose in a 3-in-1 admixture or infused separately) within 24 hours of initiating the infusion. Replace tubing used to administer Propofol infusions every 6 or 12 hours, when the vial is changed, per the manufacturer's recommendation. (Propofol is provided in a 10% lipid emulsion.)
CDC Guidelines for the Prevention of Intravascular Catheter-Related Infections (2002)[5]	Complete the infusion of lipid emulsions alone within 12 hours of hanging the emulsion. If volume considerations require more time, the infusion should be completed within 24 hours.

References:

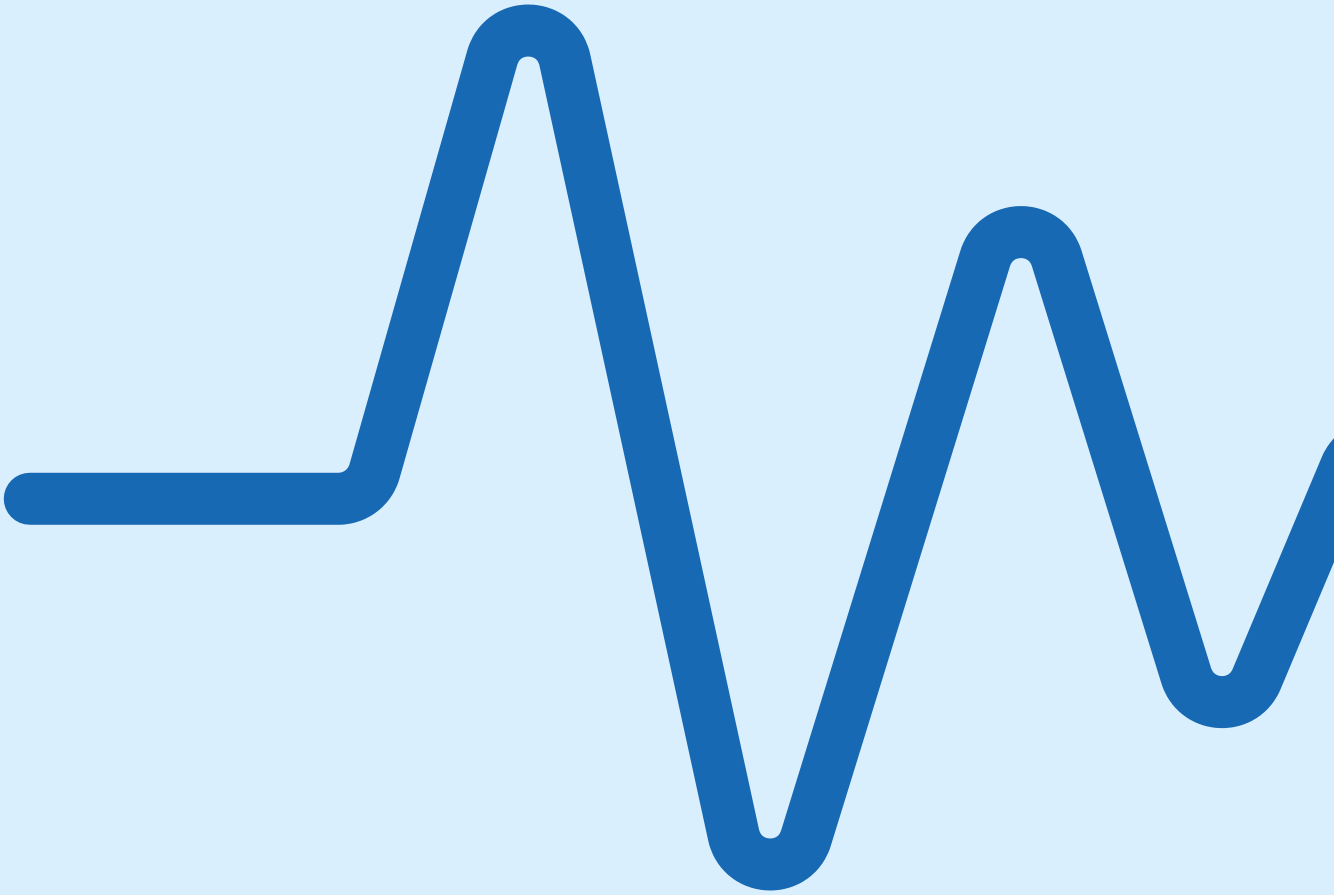
1. Ayers P BJ, Guenter P, Holcombe B. Lipid injectable emulsions: infusion confusion *JPEN Parenter Enteral Nutr.* 2018;42(4):675-676.

2. Boullata JI, Gilbert K, Sacks G, et al. A.S.P.E.N. Clinical Guidelines: parenteral nutrition ordering, order review, compounding, labeling, and dispensing. *JPEN J Parenter Enteral Nutr.* 2014;38(3):334-377.

3. Mirtallo J, Canada T, Johnson D, et al. Safe practices for parenteral nutrition. *JPEN J Parenter Enteral Nutr.* 2004;28(6):S39-70.

4. O'Grady NP, Alexander M, Burns LA, et al. Guidelines for the prevention of intravascular catheter-related infections. *Am J Infect Control.* 2011;39 (4 Suppl 1):S1-34.

5. Centers for Disease Control and Prevention. *MMWR.* 2002;51(RR):10.



Monitoring:

Omegaven®(fish oil triglycerides) injectable emulsion

Monitoring: Omegaven® (fish oil triglycerides) injectable emulsion

Highlights[1]

- Monitor for signs and symptoms of pleural or pericardial effusion
- Monitor for signs and symptoms of hypersensitivity reactions
- Monitor for signs and symptoms of infection, fat overload syndrome, refeeding syndrome and hypertriglyceridemia
- Routine laboratory monitoring is recommended, including monitoring for essential fatty acid deficiency

Recommended Pediatric Dosing section[1]

- Monitor triglyceride levels during treatment (See Warnings and Precautions)

Warnings and Precautions[1]

5.1: Risk of Death in Preterm Infants due to Pulmonary Lipid Accumulation
- Monitor patients receiving Omegaven for signs and symptoms of pleural or pericardial effusion.

5.2: Hypersensitivity Reactions
- If reaction occurs, stop infusion.

5.3 Risk of Infections:
- 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.

5.4 Fat Overload Syndrome:
- No monitoring recommended but describes s/s.

5.5 Refeeding Syndrome:
- To prevent these complications, closely monitor severely malnourished patients and slowly increase their nutrient intake.

5.6 Hypertriglyceridemia
- No monitoring recommended but warns about levels >1000 mg/dL (see section 5.8).

5.8 Monitoring and Laboratory Tests
- Routine Monitoring
  - Monitor serum triglycerides [see Warnings and Precautions (5.6)], 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. Increasing essential fatty acid intake (enterally or parenterally) is effective in treating and preventing EFAD.

Drug Interactions[1]

7.1: Antiplatelet agents and anticoagulants
- It is recommended to periodically monitor bleeding time in patients receiving Omegaven and concomitant antiplatelet agents or anticoagulants.

Recommended Laboratory Parameter Monitoring[1]

- Triglycerides
- Glucose
- WBC
- CBC including platelets
- Electrolytes, especially potassium, phosphorus, magnesium
- Liver function
- Kidney function
- Coagulation parameters
- Essential fatty acid status

Recommended Physical Signs/Symptoms Monitoring[1]

- **Fluid status**
- **Pleural effusion** (chest pain, dry cough, fever, difficulty breathing when lying down, difficulty taking deep breaths) or pericardial effusion (chest pain, SOB, heart palpitations, light-headedness, cool/clammy skin)
- **Hypersensitivity reactions:** tachypnea, dyspnea, bronchospasm, tachycardia, hypotension, cyanosis, vomiting, nausea, sweating, dizziness, altered mentation, flushing, rash, urticaria, erythema, fever, chills
- **Infections:** fever, chills, intravenous catheter site edema, redness, and discharge
- **Fat overload:** fever, central nervous system manifestations (e.g., coma)

Reference:

1. Omegaven Prescribing Information, Fresenius Kabi USA, LLC. 2020.

Academy of Nutrition and Dietetics Suggested Monitoring Schedule for Infants Receiving Parenteral Nutrition Support[1]

	Initial Phase	Stable Phase
Growth: • Weight • Length • Height Circumference	 • Daily • Baseline • Baseline	 • Daily • Weekly • Weekly
Intake and output	Daily	Daily
Glucose: • Serum • Urine	 • As indicated • As indicated	 • As indicated • As indicated
Electrolytes	2-3 times/wk	Every 1-2 wks
Calcium, magnesium, phosphorus	2-3 times/wk	Every 1-2 wks
Triglycerides	Daily during dose increase	Every 1-2 wks
BUN/creatinine	2-3 times/wk	Every 1-2 wks
Serum proteins	Baseline	Every 2-3 wks
Liver enzymes – including DBIL	Baseline	Every 2-3 wks
Alkaline phosphatase	Baseline	Every 2-3 wks
Blood cell count	Baseline	Every 2-3 wks
Vitamin and trace mineral status or other specific tests	As indicated	As indicated

Reference:

1. Academy of Nutrition and Dietetics Pocket Guide to Neonatal Nutrition. Second ed. Chicago, IL: Academy of Nutrition and Dietetics; 2016.

Photoprotection

ASPEN Summary and Recommendations[1]:

1. In vitro testing indicates PN and ILE integrity, including precompounding individual components as well as the final admixture, is optimized with light protection. Light exposure at any step in storage, compounding, delivery, and infusion can alter the admixture stability.

2. In vitro data indicate that partial photoprotection of PN products reduces markers of oxidative stress, although it is not as effective as complete photoprotection.

3. Data from clinical trials, evaluated individually and collectively in a meta-analysis, suggest complete photoprotection of PN admixtures and ILEs reduces indicators of oxidative stress in preterm infants and mitigates the risk of adverse clinical outcome measures. It remains noteworthy that statistically significant findings of benefit from light protection were sometimes found only with secondary analysis. No harm was identified as a result of photoprotection.

4. Materials required for complete photoprotection from the moment PN compounding is initiated in the pharmacy are not currently available in the US, yet materials are currently available for partial photoprotection.

5. ASPEN recommends photoprotection of PN admixtures and ILEs for infants. Insufficient literature exists to inform recommendations surrounding photoprotection of PN admixtures and ILEs administered to older children or adults. However, sufficient evidence suggests that PN components utilized in children and adults are susceptible to photo-oxidation.

6. Individual healthcare organizations should convene key stakeholders to define which steps in photoprotection can be achieved and implement such strategies.

7. Outsourcing sterile compounding facilities should review processes that may be amenable to reducing light exposure, both during the compounding process as well as during the transport process.

8. Research and development of cost-efficient materials are necessary for complete photoprotection of PN admixtures and ILEs.

9. ASPEN and the authors understand that the full implementation of complete photoprotection may not currently be feasible given current product availability; recommendations provided in this paper serve to represent the goal to which to strive as well as to highlight the importance of product availability to achieve these practices.

Reference: 1. Robinson DT, Ayers P, Fleming B, et al. Recommendations for photoprotection of parenteral nutrition for premature infants: An ASPEN position paper. *Nutr Clin Pract*. 2021;36(5):927-941.

Product Information

Omegaven®

(fish oil triglycerides) injectable emulsion

HCPCS Code: B4187

NDC Number	Product Number	Description	Concentration	Size	Bottles/ Carton	Minimum Order Qty
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

For more information or to order please contact your sales rep or visit www.FreseniusKabiNutrition.com/Omegaven.

Contact Information

For information on Fresenius Kabi, please visit www.fresenius-kabi.com/us.

For information on Omegaven (fish oil triglycerides) injectable emulsion, visit www.FreseniusKabiNutrition.com/Omegaven.

For Fresenius Kabi product availability and ordering call 1-888-386-1300.

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

Prescribing Information

FULL PRESCRIBING INFORMATION

1. 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 *[see Clinical Studies (14)]*.
- 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 *[see Clinical Studies (14)]*.

2. DOSAGE AND ADMINISTRATION

2.1. Administration Instructions

- Omegaven can be administered alone or as part of a PN admixture.
- Omegaven is for central or peripheral intravenous infusion. When administered with dextrose and amino acids, the choice of a central or peripheral venous route should depend on the osmolarity of the final infusate. Solutions with osmolarity of 900 mOsm/L or greater must be infused through a central vein.
- Use a 1.2 micron in-line filter during administration.
- Use a dedicated line for PN. Omegaven should be infused concurrently into the same vein as dextrose-amino acid solutions (as part of PN) by a Y-connector located closest to the infusion site; flow rates of each solution should be controlled separately by infusion pumps. Avoid multiple connections; do not connect multiple medications in series. Turn off the pump before the bottle runs dry.
- Use a vented infusion set when Omegaven is infused from the bottle.
- Do not use infusion sets and lines that contain di-2-ethylhexyl phthalate (DEHP). Infusion sets that contain polyvinyl chloride (PVC) components have DEHP as a plasticizer.
- Prior to infusion, visually inspect Omegaven for particulate matter and discoloration. Discard the bottle if any particulates or discoloration are observed.
- Gently invert the bottle before use. Use Omegaven only if the emulsion is homogeneous and the container is undamaged.
- Strict aseptic techniques must be followed.
- Hang the bottle using the attached hanger and start infusion.
- After connecting the infusion set, start infusion of Omegaven immediately. Complete the infusion within 12 hours when using a Y-connector and within 24 hours when used as part of an admixture.
- For single use only. Discard unused portion.

2.2. Admixing Instructions

If Omegaven is administered as part of a PN admixture, follow the instructions below.

- Prepare the admixture in PN containers using strict aseptic techniques to avoid microbial contamination.
- Do not add Omegaven directly to the empty PN container; destabilization of the lipid emulsion may occur.
- When Omegaven is administered with other infusion solutions (e.g., amino acids, dextrose), the compatibility of the solutions used must be ensured. Questions related to compatibility may be directed to Fresenius Kabi USA, LLC, at 1-800-551-7176.

- The following proper mixing sequence must be followed to minimize pH-related problems by ensuring that typically acidic dextrose solutions are not mixed with lipid emulsions alone:
    1. Transfer dextrose solution to the PN container.
    2. Transfer amino acid solution to the PN container.
    3. Transfer Omegaven to the PN container.

Simultaneous transfer of amino acid solution, dextrose solution, and Omegaven using an automated compounding device is also permitted; follow automated compounding device instructions as indicated.

Use gentle agitation during admixing to minimize localized concentration effects; shake container gently after each addition.

- The prime destabilizers of emulsions are excessive acidity (such as a pH less than 5) and inappropriate electrolyte content. Care should be taken if adding divalent cations (e.g., Ca++ and Mg++), which have been shown to cause emulsion instability. Amino acid solutions exert buffering effects that can protect the emulsion from destabilization.
- Inspect the admixture to ensure that precipitates have not formed during preparation of the admixture and the emulsion has not separated. Separation of the emulsion can be visibly identified by a yellowish streaking or the accumulation of yellowish droplets in the admixture. Discard the admixture if any of these are observed.

Stability and Storage

- Protect the admixed PN solution from light.
- Start infusion of admixtures containing Omegaven immediately. If not used immediately, admixtures may be stored for up to 6 hours at room temperature or up to 24 hours under refrigeration. Complete the infusion within 24 hours after removal from storage.
- Any remaining contents of a partly used PN container must be discarded.
- Follow the instructions of each product included in the admixture.

2.3. Dosing Information

Dosing Considerations

- Prior to administration of Omegaven, correct severe fluid and electrolyte disorders and measure serum triglycerides to establish a baseline level.
- 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.
- The dosing of Omegaven depends on each patient's energy requirements, which may be influenced by age, body weight, tolerance, clinical status, and ability to metabolize and eliminate lipids.
- When determining dose, take into account the energy supplied by dextrose and amino acids from PN, as well as energy from oral or enteral nutrition. Energy provided from lipid-based medications must also be taken into account (e.g., propofol).
- Omegaven contains 0.15 to 0.30 mg/mL of dl-alpha-tocopherol. Take into account the amount of alpha-tocopherol in Omegaven when determining the need for additional supplementation of vitamin E.

Recommended Pediatric Dosing

- The recommended Omegaven dosage for pediatric patients is 1 g/kg/day; this is also the maximum daily dose.
- The initial rate of infusion should not exceed 0.05 mL/minute for the first 15 to 30 minutes of infusion. If tolerated, gradually increase until reaching the required rate after 30 minutes. The maximum infusion rate should not exceed 1.5 mL/kg/hour, corresponding to 0.15 g/kg/hour.
- If hypertriglyceridemia (triglycerides greater than 250 mg/dL in neonates and infants or greater than 400 mg/dL in older children) develops once Omegaven has been initiated at the recommended dosage, consider stopping the administration of Omegaven for 4 hours and obtain a repeat serum triglyceride level. Resume Omegaven based on new result as indicated.

- In patients with elevated triglyceride levels, consider other reasons for hypertriglyceridemia (e.g., renal disease, other drugs). If triglycerides remain at elevated levels, consider a reduced dose of 0.5 g to 0.75 g/kg/day with an incremental increase to 1 g/kg/day.
- Monitor triglyceride levels during treatment *[see Warnings and Precautions (5.6, 5.8)]*.
- The recommended duration for infusion of Omegaven is between 8 and 24 hours, depending on the clinical situation.
- Administer Omegaven until DBil levels are less than 2 mg/dL or until the patient no longer requires PN.

3. DOSAGE FORMS AND STRENGTHS

Injectable Emulsion: 5 g/50 mL and 10 g/100 mL (0.1 g/mL) sterile, white, homogenous emulsion in a 50-mL and 100-mL single-dose bottle.

4. CONTRAINDICATIONS

Use of Omegaven is contraindicated in patients with:

- Known hypersensitivity to fish or egg protein or to any of the active ingredients or excipients *[see Warnings and Precautions (5.2)]*.
- 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) *[see Warnings and Precautions (5.6)]*.

5. WARNINGS AND PRECAUTIONS

5.1. 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.

5.2. 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 *[see Contraindications (4)]*.

5.3. Risk of Infections

Lipid emulsions, such as Omegaven, can support microbial growth and are an independent risk factor for the development of 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 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.

5.4. 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 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). The cause of fat overload syndrome is unclear. Although it has been most frequently observed when the recommended lipid dose was exceeded, cases have also been described where the lipid formulation was administered according to instructions. The syndrome is usually reversible when the infusion of the lipid emulsion is stopped.

5.5. 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.

5.6. 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 *[see Contraindications (4)]*.

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 *[see Dosage and Administration (2.3)]*.

5.7. Aluminum Toxicity

Omegaven contains no more than 25 mcg/L of aluminum. 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.

5.8. Monitoring and Laboratory Tests

Routine Monitoring

Monitor serum triglycerides *[see Warnings and Precautions (5.6)]*, 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. Increasing essential fatty acid intake (enterally or parenterally) is effective in treating and preventing EFAD.

5.9. 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.

6. ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Risk of death in preterm infants due to pulmonary lipid accumulation *[see Warnings and Precautions (5.1)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*
- Risk of infections *[see Warnings and Precautions (5.3)]*
- Fat overload syndrome *[see Warnings and Precautions (5.4)]*
- Refeeding syndrome *[see Warnings and Precautions (5.5)]*
- Hypertriglyceridemia *[see Warnings and Precautions (5.6)]*
- Aluminum toxicity *[see Warnings and Precautions (5.7)]*

6.1. Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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. Omegaven was administered at a maximum dose of 1 g/kg/day as the lipid component of a PN regimen which also included dextrose, amino acids, vitamins, and trace elements; 158 (84%) of these patients received concurrent lipids from enteral nutrition *[see Clinical Studies (14)]*.

Adverse reactions that occurred in more than 5% of patients who received Omegaven and with a higher incidence than the comparator group are shown in Table 1. 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.

Table 1 Adverse Reactions in Greater Than 5% of Omegaven-Treated Pediatric Patients with PNAC

Adverse Reaction	Omegaven (N=189) n (%)
Vomiting	87 (46)
Agitation	67 (35)
Bradycardia	66 (35)
Apnea	38 (20)
Viral Infection	30 (16)
Erythema	23 (12)
Rash	15 (8)
Abscess	14 (7)
Neutropenia	13 (7)
Hypertonia	11 (6)
Incision site erythema	11 (6)

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) *[see Warnings and Precautions (5.8)]*. 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.

6.2. Postmarketing Experience

The following adverse reaction has been identified with use of Omegaven in another country. Because this reaction was reported voluntarily from a population of uncertain size, it is not possible to reliably estimate its frequency or establish a causal relationship to drug exposure.

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.

7. DRUG INTERACTIONS

7.1. Antiplatelet Agents and Anticoagulants

Some published studies have demonstrated prolongation of bleeding time in patients taking antiplatelet agents or anticoagulants and oral omega-3 fatty acids. The prolongation of bleeding times reported in those studies did not exceed normal limits and there were no clinically significant bleeding episodes. Nonetheless, it is recommended to periodically monitor bleeding time in patients receiving Omegaven and concomitant antiplatelet agents or anticoagulants.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Risk Summary

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.

8.2. Lactation

Risk Summary

No data are 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.

8.4. Pediatric Use

The effectiveness of Omegaven was established in two open-label clinical trials of 82 pediatric patients, 3 to 42 weeks of age, including preterm neonates with estimated gestational age of greater than 24 weeks at birth. Patients administered Omegaven attained and maintained growth through at least 108 weeks of treatment *[see Clinical Studies (14)]*.

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, and bradycardia *[see Adverse Reactions (6.1)]*.

Deaths in preterm infants after infusion of intravenous soybean oil-based lipid emulsion have been reported in literature *[see Warnings and Precautions (5.1)]*.

Preterm neonates and infants who receive treatment with Omegaven may be at risk of aluminum toxicity and other metabolic abnormalities *[see Warnings and Precautions (5.7, 5.8)]*.

8.5. Geriatric Use

Clinical trials of Omegaven did not include patients 65 years of age and older.

10. OVERDOSAGE

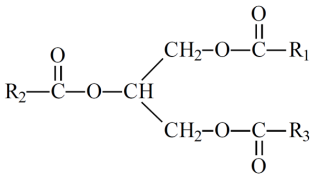
In the event of an overdose, fat overload syndrome may occur *[see Warnings and Precautions (5.4)]*. Stop the infusion of Omegaven until triglyceride levels have normalized and any symptoms have abated.

The effects are usually reversible by stopping the lipid infusion. If medically appropriate, further intervention may be indicated. Lipids are not dialyzable from serum.

11. DESCRIPTION

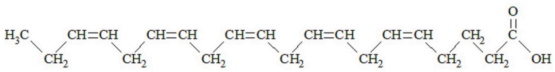
Omegaven (fish oil triglycerides) is a sterile, nonpyrogenic, white, homogenous emulsion for intravenous infusion as a supply of calories in patients with PNAC. Each mL of Omegaven contains 0.1 g of fish oil, 0.012 g egg phospholipids, 0.025 g glycerin, 0.15 to 0.3 mg dl-alpha-tocopherol, 0.3 mg sodium oleate, water for injection, and sodium hydroxide for pH adjustment (pH 6 to 9). The phosphate content is 0.015 mmol/mL.

The fish oil included in Omegaven is a triglyceride mixture consisting of esters of long-chain saturated fatty acids and unsaturated fatty acids with the following structure:

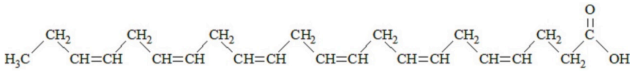


Where $R_1\overset{O}{\overset{\|}{C}}O-$, $R_2\overset{O}{\overset{\|}{C}}O-$, and $R_3\overset{O}{\overset{\|}{C}}O-$ are long chain acyl groups. Because triglycerides often contain different long chain fatty acids at each position, possible structures can have molecular weights ranging from 700 to 1000 g/mol. The main fatty acid components of the fish oil in Omegaven are EPA (13% to 26%) and DHA (14% to 27%). The fish oil also contains palmitic acid (4% to 12%), oleic acid (4% to 11%), palmitoleic acid (4% to 10%), myristic acid (2% to 7%), and arachidonic acid (0.2% to 2.0%). Additionally, the mean contents of linoleic acid and alpha-linolenic acid are 1.5% and 1.1%, respectively. The fish oil component has a total omega-3 fatty acid content of 40% to 54%. The empirical formula, molecular weight, and chemical structure of the main fatty acid components are:

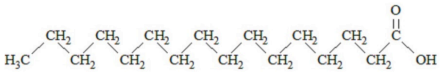
EPA
$C_{20}H_{30}O_2$
302.45



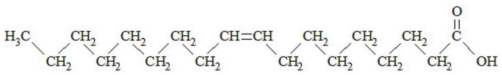
DHA
$C_{22}H_{32}O_2$
328.49



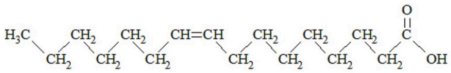
Palmitic acid
$C_{16}H_{32}O_2$
256.43



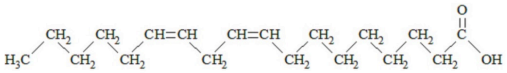
Oleic acid
$C_{18}H_{34}O_2$
282.47



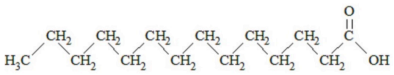
Palmitoleic acid
$C_{16}H_{30}O_2$
254.41



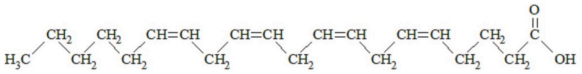
Linoleic acid
$C_{18}H_{32}O_2$
280.45



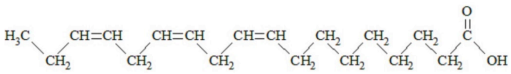
Myristic acid
$C_{14}H_{28}O_2$
228.38



Arachidonic acid
$C_{20}H_{32}O_2$
304.47



Alpha-linolenic acid
$C_{18}H_{30}O_2$
278.44



Omegaven 5 g/50 mL contains 5 grams of fish oil and 0.6 g egg phospholipids, 1.25 g glycerin, 7.5 to 15 mg dl-alpha-tocopherol, 0.015 g sodium oleate, water for injection, and sodium hydroxide for pH adjustment (pH 6 to 9) packaged in a single-dose 50-mL glass bottle enclosed with a rubber stopper. The phosphate content of the drug product is 0.75 mmol.

The mean content of the two major fatty acid components in 50 mL are 1.0 g EPA (range: 0.6 to 1.5 g) and 0.96 g DHA (range: 0.7 to 1.7 g). Additionally, the mean content of linoleic acid, alpha-linolenic acid, and arachidonic acid per 50 mL are 0.16 g, 0.07 g, and 0.13 g, respectively.

Omegaven 10 g/100 mL contains 10 grams of fish oil and 1.2 g egg phospholipids, 2.5 g glycerin, 15 to 30 mg dl-alpha-tocopherol, 0.03 g sodium oleate, water for injection, and sodium hydroxide for pH adjustment (pH 6 to 9) packaged in a single-dose 100-mL glass bottle enclosed with rubber stopper. The phosphate content of the drug product is 1.5 mmol. The mean content of the two major fatty acid components in 100 mL are 2.0 g EPA (range: 1.2 to 3.0 g) and 1.9 g DHA (range: 1.3 to 3.3 g). Additionally, the mean content of linoleic acid, alpha-linolenic acid, and arachidonic acid per 100 mL are 0.31g, 0.13 g, and 0.25 g; respectively.

The total energy content of Omegaven is 112 kcal/100 mL (1.12 kcal/mL), including lipids, phospholipids, and glycerol.

Omegaven has an osmolality of approximately 342 mOsm/kg water (which represents an osmolarity of 273 mOsm/L).

Omegaven contains no more than 25 mcg/L of aluminum.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

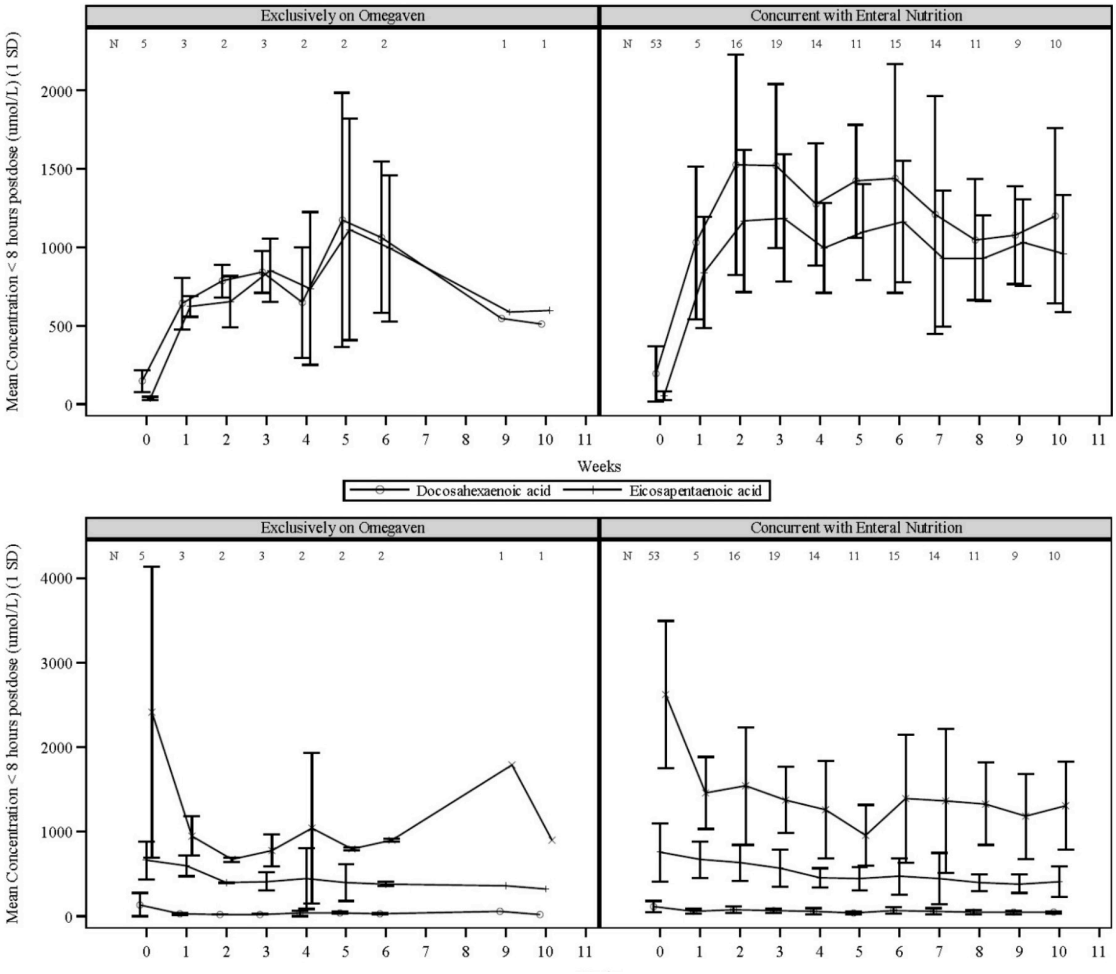
Omegaven provides a biologically utilizable source of calories and essential fatty acids.

Fatty acids serve as an important substrate for energy production. The most common mechanism of action for energy production derived from fatty acid metabolism is beta oxidation. Fatty acids are also important for membrane structure and function, as precursors for bioactive molecules (such as prostaglandins), and as regulators of gene expression.

12.3 Pharmacokinetics

The plasma concentrations of EPA and DHA, the major fatty acids in Omegaven, as well as linoleic acid and alpha-linolenic acid (essential fatty acids) were measured along with the markers of essential fatty acid status in 58 pediatric patients with PNAC after an intravenous infusion of 1 mg/kg/day of Omegaven over 10 weeks. Five patients received Omegaven as the exclusive lipid source, and all others received concurrent enteral or oral nutrition.

Figure 1 Mean Plasma Concentrations of Fatty Acids Over 10 Weeks of Omegaven Infusion in Pediatric Patients with PNAC



Error bars represent ± 1 standard deviation (SD).
Numbers at the top of plots represent the number of patients at each time point
If more than one value was available for a patient at any given time point, the average was used.

13.NONCLINICAL TOXICOLOGY

13.1.Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed with fish oil triglycerides to evaluate the carcinogenic potential or its effect on fertility.

Fish oil triglycerides was negative in the bacterial mutagenicity test with *Salmonella typhimurium* and the hypoxanthine phosphoribosyl transferase (HPRT) gene mutation assay in Chinese hamster V79 cells. Fish oil triglycerides was not clastogenic in cultured human peripheral lymphocytes or in a rat bone marrow cytogenetic study.

14. CLINICAL STUDIES

The efficacy of Omegaven was evaluated in two open-label single-center clinical trials (Study 1, NCT00910104, and Study 2, NCT00738101) in pediatric patients with PNAC (defined as direct or conjugated bilirubin [DBil] equal to or greater than 2 mg/dL) who required PN for at least 14 days. Although Study 1 and Study 2 were not adequately designed to demonstrate noninferiority or superiority of Omegaven to the soybean oil-based lipid emulsion comparator, the data from these studies support Omegaven as a source of calories in pediatric patients with PNAC. Nutritional efficacy was assessed by biomarkers of lipid metabolism, growth indices (body weight, length/height and head circumference), and/or mean changes in fatty acid parameters.

Both trials prospectively enrolled Omegaven-treated patients (maximum dose of 1 g/kg/day) and used historical control patients who received a soybean oil-based lipid emulsion (maximum dose of 3 g/kg/day) as a comparator. Patients were expected to require PN, which also included dextrose, amino acids, vitamins and trace elements, for at least 30 days (Study 1) or 14 days (Study 2), had PNAC, and had received standard therapies to prevent progression of liver disease. Study 1 enrolled patients less than 2 years of age and Study 2 enrolled patients less than 5 years of age. Patients with another cause of chronic liver disease (in the absence of intestinal failure) were excluded. Patients with an international normalized ratio (INR) greater than 2 and patients with portal vein thrombosis or reversal of portal flow by abdominal ultrasound were also excluded.

For the efficacy analyses of Studies 1 and 2, Omegaven-treated patients were pair-matched in a 2:1 manner to historical control patients primarily based on DBil levels and postmenstrual age at baseline. There were 123 patients (82 Omegaven; 41 historical control) in this population, 78 (52; 26) were from Study 1, and 45 (30; 15) were from Study 2. A summary of concurrent enteral/oral nutrition intake for each study is provided in Table 2.

Table 2 Summary of Median Enteral or Oral Intakes in Pediatric Patients with PNAC in Study 1 and Study 2

	Study 1		Study 2	
Parameter	**Omegaven (n=50)[a]**	**Historical Control (n=26)**	**Omegaven (n=30)**	**Historical Control (n=15)**
Number of patients who received concurrent enteral or oral nutrition	44 (88%)	26 (100%)	24 (80%)	14 (93%)
Percentage of total calories provided enterally or orally, median (Min - Max)	24% (1% – 53%)	25% (0.4% – 68%)	21% (1% – 75%)	12% (3% – 40%)

a. Two Omegaven-treated patients in Study 1 did not have data regarding enteral or oral intakes.

In the combined efficacy analysis population from Study 1 and Study 2, median chronological age was 9 weeks (range: 3 to 42 weeks) in the Omegaven group and 7 weeks (range: 0 to 41 weeks) in the historical control group. The majority of these patients were preterm infants at birth (90% Omegaven; 83% historical control), with gestational age categories as follows: extremely preterm (31%; 20%); very preterm (20%; 24%); moderate or late preterm (40%; 39%). A majority of patients were also considered to have low, very-low, or extremely-low birth weights (76%; 82%), with birth weight categories as follows: extremely-low birth weight (34%; 24%); very-low birth weight (17%; 21%); low birth weight (25%; 37%).

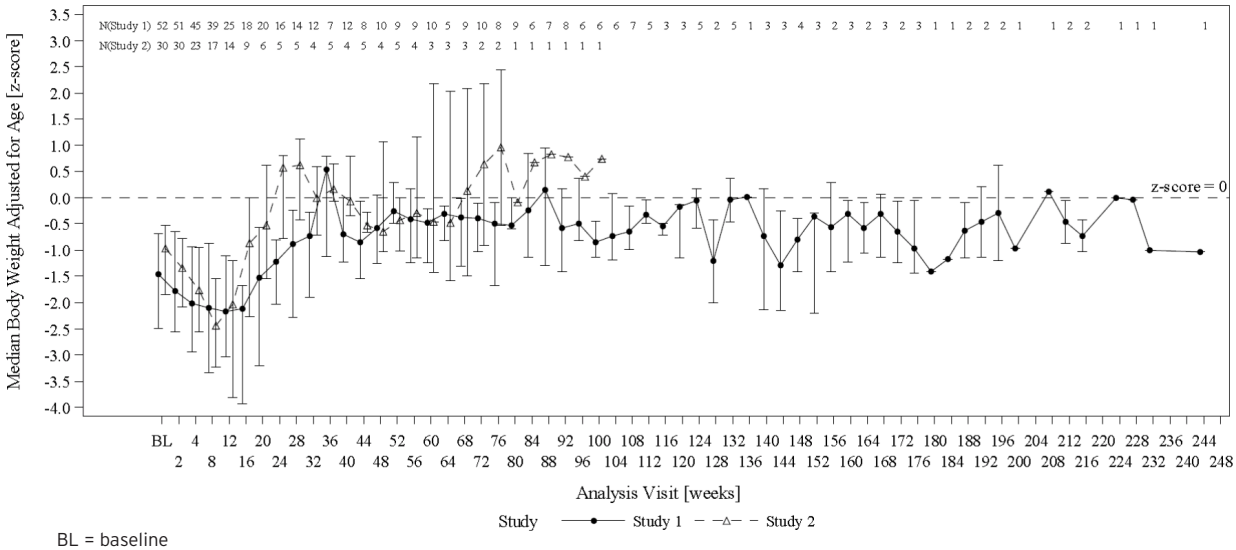
The efficacy analysis population had more males (51%; 59%) than females, and the majority of patients were White (60%; 66%).

At baseline, the median age-adjusted body weight (Z-score) was -1.3 for the Omegaven group and -1.1 for the historical control group; 27% and 28% were low-for-age in body weight, 43% and 40% were low-for-age in body height/length, and 25% and 15% were low-for-age in head circumference for the Omegaven and historical control groups, respectively (low-for-age corresponded to Z-scores less than or equal to -1.9 for each growth parameter). In the efficacy analysis population, baseline median DBil, AST, and ALT levels were 3.8 mg/dL, 101 U/L, and 67 U/L, respectively, for the Omegaven group; and 3.8 mg/dL, 115 U/L, and 52 U/L, respectively, for the historical control group.

The median (range) of the duration of treatment was 2.7 months (5 days to 8 years) for the Omegaven group and 3.6 months (16 days to 2 years) for the historical control group.

The changes in median age-adjusted body weight (Z-scores) over time for Omegaven-treated patients (Figure 2) appeared similar to those for historical control patients. In both the Omegaven and historical control groups, there was an initial decline in all growth parameters (weight, height/length, head circumference) over the initial weeks of treatment, followed by catch-up growth and more age-appropriate values through the remainder of the study. By comparing the Omegaven study data to age-standardized Fenton and World Health Organization (WHO) growth charts to assess age appropriate growth in patients with PNAC, patients treated with Omegaven as their exclusive lipid source also achieved age-appropriate growth.

Figure 2 Median Age-Adjusted Body Weight (Z-scores) Over Time in Omegaven-Treated Pediatric Patients with PNAC in Study 1 and Study 2*



BL = baseline

Error bars represent interquartile ranges.

*Data from pair-matched Omegaven patients were truncated at week 132. Median values are only shown for visits with data from at least 2 patients at a particular visit.

In the combined analysis from Study 1 and Study 2, the number of Omegaven and historical control patients who achieved full enteral feeding by the end of the study was 52 (63%) patients and 24 (59%) patients, respectively. The median time to full enteral feeding was approximately 15 weeks for both groups.

At the end of the studies, the median DBil level for Omegaven-treated patients was 0.60 mg/dL (interquartile range: 0.1 to 2.8 mg/dL). The Kaplan-Meier estimate of the median time for DBil values to return to less than 2.0 mg/dL was approximately 5.7 weeks *[see Dosage and Administration (2.3), Adverse Reactions (6.1)]*.

16. HOW SUPPLIED/STORAGE AND HANDLING

Omegaven (fish oil triglycerides) injectable emulsion, 5 g/50 mL and 10 g/100 mL (0.1 g/mL) is a white, homogenous, sterile emulsion supplied as follows:

50 mL single-dose glass bottle	NDC 63323-205-21
Carton of 10 x 50 mL	NDC 63323-205-50
100 mL single-dose glass bottle	NDC 63323-205-31
Carton of 10 x 100 mL	NDC 63323-205-00

The stopper used as the bottle closure is not made with natural rubber latex, PVC, or DEHP.

Storage and Handling

Store below 25°C (77°F). Avoid excessive heat. Do not freeze. If accidentally frozen, discard product.

Once the bottle is connected to the infusion set, use Omegaven immediately. Complete infusion within 12 hours when using a Y-connector *[see Dosage and Administration (2.1)]*.

Infuse admixtures containing Omegaven immediately. If not used immediately, admixtures can be stored for up to 6 hours at room temperature or up to 24 hours under refrigeration. Complete the infusion within 24 hours after removal from storage *[see Dosage and Administration (2.2)]*.

17. PATIENT COUNSELING INFORMATION

Inform patients, their families, or caregivers of the following risks of Omegaven:

- Risk of death in preterm infants due to pulmonary lipid accumulation *[see Warnings and Precautions (5.1)]*
- Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*
- Risk of infections *[see Warnings and Precautions (5.3)]*
- Fat overload syndrome *[see Warnings and Precautions (5.4)]*
- Refeeding syndrome *[see Warnings and Precautions (5.5)]*
- Hypertriglyceridemia *[see Warnings and Precautions (5.6)]*
- Aluminum toxicity *[see Warnings and Precautions (5.7)]*

Manufactured by:

FRESENIUS KABI

Graz, Austria
www.fresenius-kabi.com/us
451555A

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 ill and chronically ill patients in hospitals, long-term care facilities, and at home.

For more information about Fresenius Kabi, please visit **www.fresenius-kabi.com/us.**

For information on Omegaven (fish oil triglycerides) injectable emulsion, visit **www.freseniuskabinutrition.com/omegaven**.

For Fresenius Kabi product availability and ordering call 1-888-386-1300.

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

For Medical Information call 1-800-551-7176 (option 4) or email nutrition.medinfo.USA@fresenius-kabi.com.

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