FRESENIUS KABI
caring for life

Omegaven®

(fish oil triglycerides) injectable emulsion

The first and only fish oil emulsion for pediatric patients with parenteral nutrition-associated cholestasis (PNAC) in the U.S.[1]

Omegaven is a source of calories and fatty acids in pediatric patients with PNAC[1]

Patients receiving Omegaven achieved age-appropriate growth[1]

Omegaven-treated patients experienced improvement in liver function parameters[1]

INDICATION

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.

Contraindications

Known hypersensitivity to fish or egg protein or to any of the active ingredients or excipients. Severe hemorrhagic disorders. Severe hyperlipidemia or severe disorders of lipid metabolism with serum triglycerides greater than 1,000 mg/dL.

Please see Important Safety Information on page 10 and click here for full Prescribing Information.

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

- Premature infants physically incapable of absorbing adequate nutrients from normal feeding require parenteral nutrition.[2]
- If the liver is not fully developed at birth, enterohepatic cycling is impaired, which results in cholestasis.[3-6]
- Infants with intestinal failure, including congenital malformations, short bowel syndrome (SBS), intestinal infections, such as necrotizing enterocolitis (NEC) or inflammatory bowel diseases often require long-term parenteral nutrition (PN).[4-8]
- **The average incidence rate of PNAC in neonates and infants is 29.9%.[8]**

What is PNAC?

Commonly known as intestinal failure-associated liver disease (IFALD) or parenteral nutrition-associated liver disease (PNALD).[9]

Most commonly defined as direct or conjugated bilirubin (DBIL) >2 mg/dL in patients who receive PN >2 weeks.[7,8,10,11]

Development of PNAC is associated with increased morbidity and mortality and can progress to liver fibrosis, hepatic failure, and death.[12]

Certain conditions may increase the risk of PNAC

- **Prematurity**[8,13]
- **Lack of enteral feeding**[12]
- **Low birth weight**[8]
- **Bacterial overgrowth**[8,13]
- **Genetic causes**[8]
- **Anatomic factors**[8]
- **Recurrent sepsis**[12]
- **Enzyme deficiencies**[8]
- **Factors relevant to PN**[8]
- **Susceptibility to cholestatic injury**[8]
- **Necrotizing enterocolitis (NEC)**[13]

An alteration in DBIL is the earliest laboratory test that can indicate liver injury that is associated with PN.[6]

Appropriate initiation of Omegaven is key.

- **Dosing: initiate in PN-dependent pediatric patients as soon as direct or conjugated bilirubin levels are 2 mg/dL or greater.**[1]
- **Duration:** administer Omegaven until direct or conjugated bilirubin levels are less than 2 mg/dL or until the patient no longer requires PN.[1]
  - Patients in our clinical trials conducted at Boston Children's Hospital and Texas Children's Hospital received Omegaven for a median of 2.7 months and up to 8 years.[1]

ESPEN Guidelines on Lipids in Pediatric PN[10]

- In pediatric patients, intravenous lipid emulsions (ILEs) should be an integral part of parenteral nutrition (PN) either exclusive or complementary to enteral feeding (LoE 1-, RG A, strong recommendation for).
- In preterm infants, lipid emulsions can be started immediately after birth and no later than on day two of life and for those in whom enteral feeding has been withdrawn, they can be started at time of PN initiation (LoE 1-, RG A, strong recommendation for).
- Markers of liver integrity and function, and triglyceride concentrations in serum or plasma should be monitored regularly in patients receiving ILEs, and more frequently in cases with a marked risk for hyperlipidemia (e.g., patients with high lipid or glucose dosage, sepsis, catabolism, extremely low birth weight infants) (LoE 2-, RG B, strong recommendation for).

ILE Composition Comparison

	Intralipid[14] 20% Emulsion	**Omegaven**[1] 10% Emulsion
Manufacturer	Fresenius Kabi/Baxter*	Fresenius Kabi
Oil Source	Soybean Oil	Fish Oil
Indication	Adults and Pediatrics	Pediatrics
	Fat Composition (mean value or range % by weight)[1,14]	
Linoleic	44-62	1.5
Alpha-Linolenic	4-11	1.1
Eicosapentaenoic (EPA)	0	13-26
Docosahexaenoic (DHA)	0	14-27
Oleic	19-30	4-11
Arachidonic	0	0.2-2
Alpha-Tocopherol (mg/L)	38	150-300
Phytosterol Content[20] mcg/mL	381 ± 28.9†	3.66 ± 0.59

*Distributed by. †Internal data.

DHA and EPA (ω-3 fatty acids) are considered to be important for healthy development of infants due to their special physiological roles.[15,16]

- **May be considered conditionally essential for growth and development**[17,18]
- **Important structural elements of cell membranes**[16]
- **DHA is necessary for the normal development of the central nervous system and retina**[16,17]
- **Primary precursors of the very long chain fatty acids synthesized in the retina**[16]

Omegaven[1,19]

Original study

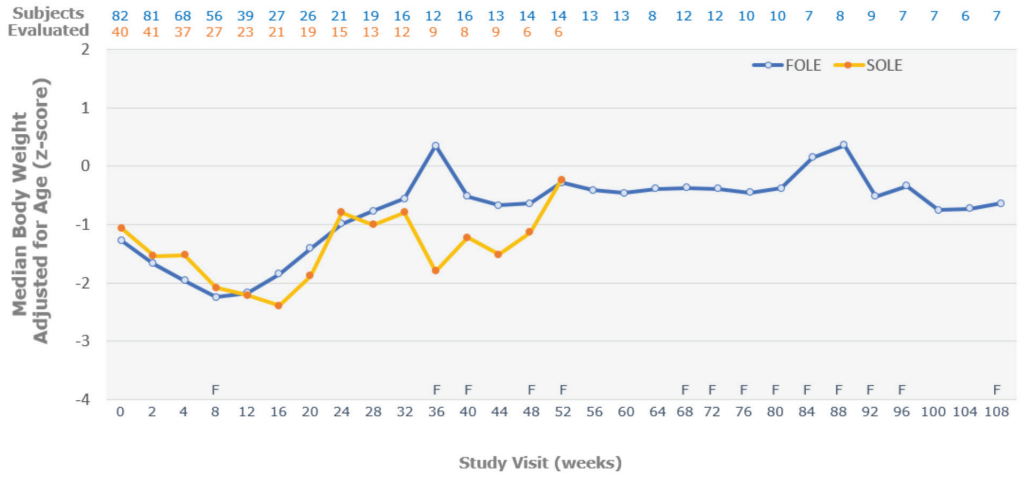
- 2 non-randomized, open-label, single-center clinical trials.
- Both studies were conducted at large intestinal rehabilitation centers – Boston Children's Hospital (BCH) and Texas Children's Hospital (TCH) – and included historical control patients who received soybean oil (SO) intravenous lipid emulsion (ILE) between 1999 and 2012 at BCH, TCH, or University of California Los Angeles.[1,19]
  - **BCH & UCLA:** patients <2 years of age; PN ≥30 days; DBIL ≥2 mg/dL
  - **TCH:** patients <5 years of age; PN ≥14 days; DBIL ≥2 mg/dL

Addition of historical control data

- Analysis of pair-matched recipients of a fish oil lipid emulsion (FOLE) (n = 82) to soybean oil lipid emulsion (SOLE) recipients (n = 41) using baseline serum direct bilirubin levels and postmenstrual age.[19]
  - Growth measures (changes in body weight, height/length, and head circumference), prealbumin, triglycerides, and glucose were compared between groups over time using the Wilcoxon rank-sum test.[19]

Pediatric patients treated with Omegaven attained and maintained age-appropriate growth[19]

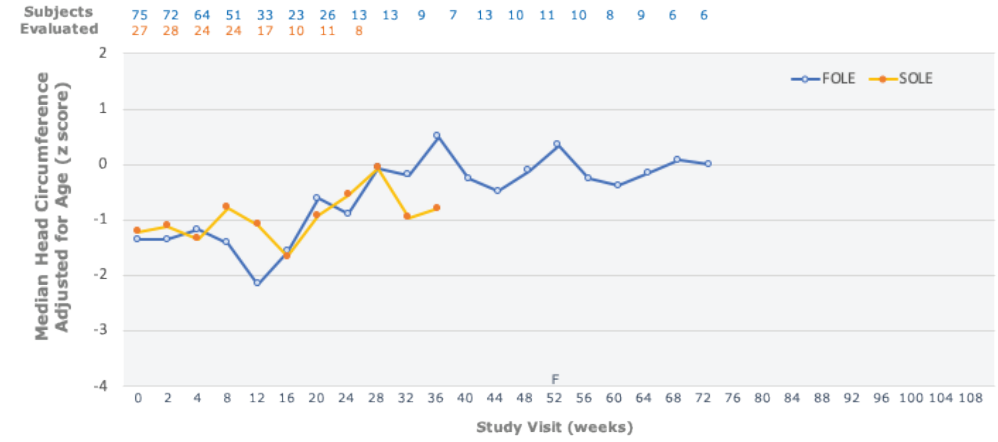
Body weight



84% of Omegaven-treated patients received concurrent lipids from enteral nutrition.

From week 28 onward, Omegaven recipients had a median body weight that was within a z-score range of -1.0 and 1.0. Body weight was not significantly different between the FOLE and SOLE groups at any time point.

Head circumference



From week 28 onward, Omegaven recipients had z-scores between -1.0 and 1.0 at all visits.

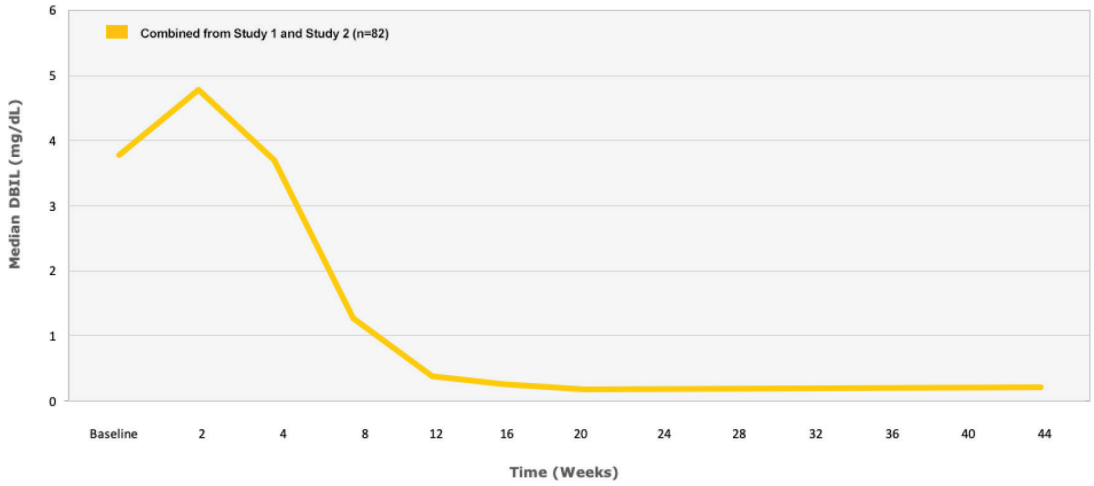
There was no significant difference between the FOLE and SOLE groups at any time point.

F represents a difference of *P* <.05 (Wilcoxon rank-sum test for difference from baseline for FOLE group).

Other outcomes:

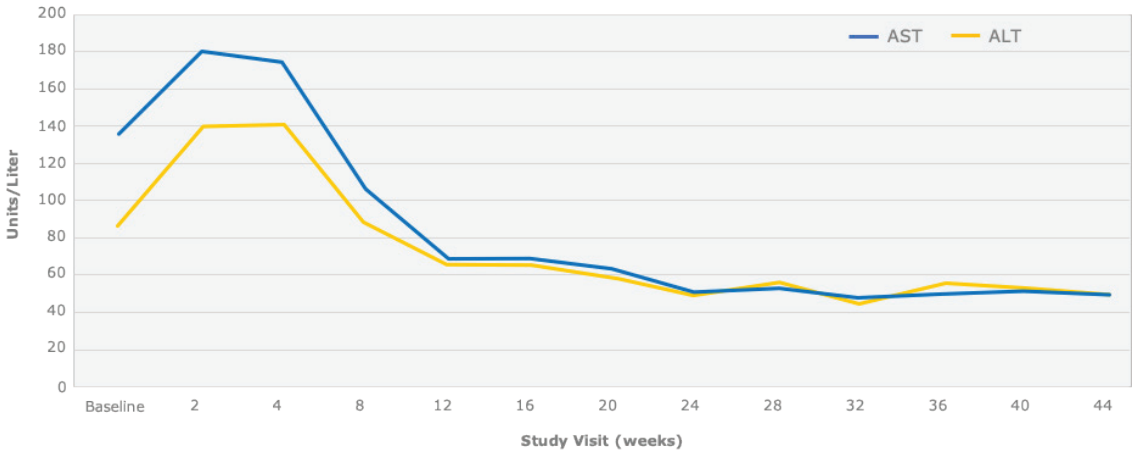
- In a study with 123 patients, 6 patients treated with Omegaven for up to 2 years, there were no biochemical signs of essential fatty acid deficiency reported.[1]

DBIL levels were effectively lowered in Omegaven-treated patients[1,20]



- Median DBIL first increased, then declined from week 4. Over time, median DBIL levels reached values close to the normal range of <0.3 mg/dL. At the end of the studies, the median DBIL level for Omegaven-treated patients was 0.60 mg/dL.
- The Kaplan Meier estimate of the median time for DBIL values to return to <2.0 mg/dL was approximately 5.7 weeks.

Omegaven-treated pediatric patients showed improvement in liver function parameters[1,20]



113/189 Omegaven-treated patients reached DBIL levels <2 mg/dL and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels <3 times the upper limit of normal at end of study.[1,20]

Of the 189 study participants, **12** (6%) Omegaven-treated patients were listed for liver transplantation[1]

3 (2%) were taken off of the waiting list because cholestasis resolved.

9 (5%) received a transplant after a median* of 121 days of treatment.

Of the 12 patients listed for transplantation, 1 patient was listed 18 days before treatment, and 11 patients after a median† of 42 days of treatment.

Liver transplants in the pair-matched population ($P<0.0001$)[20]:

FOLE[19]

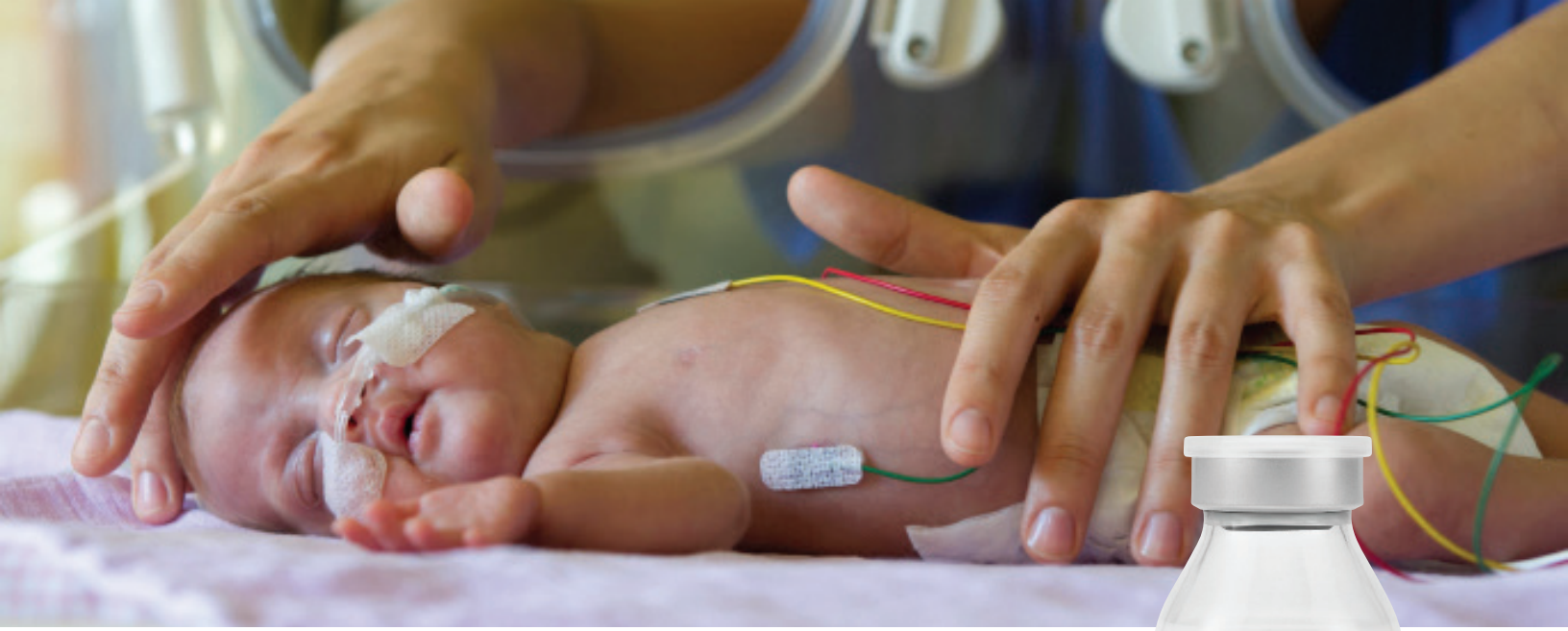
0 out of **82** (0%)

VS

SOLE

9 out of **41** (22%)

*Range: 25 days - 6 months. †Range: 2 days - 8 months.



We're pioneering the use of fish oil and omega-3s in PN

- Omegaven is the first and only fish oil ILE for pediatric patients with PNAC in the U.S.[1]
- Patients receiving Omegaven achieved age-appropriate growth and experienced improvement in liver function parameters in clinical trials.[1,19]

Omegaven®

(fish oil triglycerides) injectable emulsion

HCPCS Code: B4187

ORDERING INFORMATION		
Bottle Size	50 mL single-dose glass bottle	100 mL single-dose glass bottle
NDC Code	63323-205-50	63323-205-00
Bottles/Carton	10	10

To learn more about Fresenius Kabi's PN product portfolio, visit www.freseniuskabinutrition.com.

For information on coding and billing, visit www.kabicare.us or call 1-833-Kabicare (1-833-552-4227).

For more information about Omegaven®:

Website: www.freseniuskabinutrition.com/products/omegaven
To Order: 1-888-386-1300
Med Info phone: 1-800-551-7176 (option 4)
Med Info email: nutrition.medinfo.USA@fresenius-kabi.com

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.

IMPORTANT SAFETY INFORMATION

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.

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).

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: Monitor for signs or symptoms. Discontinue infusion if reaction occurs.

Risk of Infections, Fat Overload Syndrome, Refeeding Syndrome, and Hypertriglyceridemia: Monitor for signs and symptoms; monitor laboratory parameters.

Aluminum Toxicity: Increased risk in patients with renal impairment, including preterm infants.

Monitoring and Laboratory Tests: Routine laboratory monitoring is recommended, including monitoring for essential fatty acid deficiency.

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

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.

This Important Safety Information does not include all the information needed to use Omegaven safely and effectively. Please see full prescribing information for Omegaven (fish oil triglycerides) injectable emulsion for intravenous use at https://bit.ly/35TCgau.

References:

1. Omegaven Prescribing Information, Fresenius Kabi USA, LLC. 2018. **2.** Koletzko B, Goulet O, Hunt J, et al. 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(suppl 2):S1-87. **3.** 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 Pediatr Gastroenterol Nutr*. 2015;60(2):272-283. **4.** 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. **5.** Orso G, Mandato C, Veropalumbo C, Cecchi N, Garzi A, Vajro P. Pediatric parenteral nutrition-associated liver disease and cholestasis: Novel advances in pathomechanisms-based prevention and treatment. *Dig Liver Dis*. 2016;48(3):215-222. **6.** Satrom K, Gourley G. Cholestasis in preterm infants. *Clin Perinatol*. 2016;43(2):355-373. **7.** 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 Pediatr Gastroenterol Nutr*. 2016;62(5):776-792. **8.** 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. **9.** Cahova M, et al. Parenteral nutrition-associated liver disease: the role of the gut microbiota. *Nutrients*. 2017;9(9). **10.** Lapillonne A FMN, Goulet O, van den Akker C, Wu J, Koletzko B. ESPGHAN/ESPEN/ESPR Guidelines on pediatric parenteral nutrition: Lipids. *Clin Nutr*. 2018. **11.** Gupta K, Wang H, Amin SB. Parenteral nutrition-associated cholestasis in premature infants: role of macronutrients. *JPEN J Parenter Enteral Nutr*. 2016;40(3):335-341. **12.** Tillman E, et al. Omega-3 long chain polyunsaturated fatty acids for treatment of parenteral nutrition-associated liver disease: A Review of the Literature. *J Pediatr Pharmacol Ther* 2011;16(1):31-38. **13.** Rangel ST, et al. Parenteral nutrition–associated cholestasis: an American Pediatric Surgical Association Outcomes and Clinical Trials Committee systematic review. *J Pediatr Surg*. 2012;47:225-240. **14.** Intralipid Prescribing Information, Fresenius Kabi USA, LLC. 2015. **15.** Agostoni C. Role of long-chain polyunsaturated fatty acids in the first year of life. *J Pediatr Gastroenterol Nutr*. 2008;47(suppl 2):S41-S44. **16.** Cetin I, Koletzko B. Long-chain omega-3 fatty acid supply in pregnancy and lactation. *Curr Opin Clin Nutr Metab Care*. 2008;11(3):297-302. **17.** Lapillonne A, Groh-Wargo S, Gonzalez CH, Uauy R. Lipid needs of preterm infants: updated recommendations. *J Pediatr*. 2013;162(3 Suppl): S37-47. **18.** Bistrian B. Clinical aspects of essential fatty acid metabolism: Jonathan Rhoads Lecture. *JPEN J Parenter Enteral Nutr*. 2003;27(3):168-175. **19.** Gura KJ, Premkumar MH, Calkins KL, Puder M. Intravenous fish oil monotherapy as a source of calories and fatty acids promotes age-appropriate growth in pediatric patients with intestinal failure-associated liver disease. *J Pediatr*. 2020;219:98-105. **20.** Data on file.

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