

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210589Orig1s000**

**OTHER REVIEW(S)**

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)**

**Epidemiology: ARIA Sufficiency Memo  
Version: 2018-01-24**

Date: July 26, 2018

Reviewer/  
Team Leader: Patricia Bright, PhD, MSPH  
Division of Epidemiology I

Associate Director: Wei Hua, PhD  
Division of Epidemiology I

Subject: Active Risk Identification and Assessment (ARIA) Sufficiency Memo

Drug Name: Omegaven (fish oil) 10% inj. emulsion

Application Type/#: NDA 210589

Applicant/Sponsor: Fresenius Kabi, USA, LLC

OSE RCM #: 2018-1533



## EXECUTIVE SUMMARY

<b>Memo type</b>	
-Initial	
-Interim	
-Final	X
<b>Source of safety concern</b>	
-Peri-approval	X
-Post-approval	
<b>Is ARIA sufficient to help characterize the safety concern?</b>	
-Yes	
-No	X
<b>If "No", please identify the area(s) of concern.</b>	
-Surveillance or Study Population	X
-Exposure	X
-Outcome(s) of Interest	X
-Covariate(s) of Interest	X
-Surveillance Design/Analytic Tools	

## **1. BACKGROUND INFORMATION**

### **1.1. Medical Product**

Omegaven is a fish oil triglyceride that predominantly contains the omega 3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The oil-in-water emulsion is administered as an intravenous (IV) infusion into a peripheral or central vein. It comes in 50 ml and 100 ml glass bottles.

IV lipid emulsions (ILEs), such as Omegaven, are intended for patients with gastrointestinal dysfunction, who lack the capacity to absorb adequate nutrients to maintain or recover body mass and function and who cannot tolerate oral or enteral feeding [1]. Administration of IV lipid emulsions to such patients reduces the amount of glucose needed to achieve the necessary calories per 24-hour period, and which may cause hyperglycemia [1].

Soybean oil-based ILEs contain high levels of pro-inflammatory omega-6 fatty acids and phytosterols; both have been implicated in the multifactorial pathogenesis of parenteral nutrition-associated cholestasis (PNAC) and parenteral nutrition-associated liver disease (PNALD), including impairment of bile flow, the development of hepatic steatosis, and pro-inflammatory effects [1]. There is an unmet need for an alternative source of nutrition for parenteral nutrition (PN) dependent patients with PNAC. In particular, there is a need to reduce administration of soy based lipid emulsions in these patients, which may contribute to progression of the manifestations of PNAC [1].

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

### **1.2. Describe the Safety Concern**

The safety of Omegaven appears to be acceptable and was generally comparable to the known safety profile described in the product labels for other intravenous fat emulsions. However, the Division of Gastroenterology and Inborn Errors (DGIEP) remains concerned about the theoretical risk of the following safety issues:

#### Serious Bleeding Events

Some published studies have demonstrated prolongation of bleeding time in patients taking antiplatelet agents or anticoagulants and oral omega 3 fatty acids. It is recommended that patients receiving Omegaven and concomitant antiplatelet agents or anticoagulants are periodically monitored for bleeding time.

#### Essential Fatty Acid Deficiency (EFAD)

Preterm infants, particularly infants with short bowel syndrome (SBS) with decreased fat stores, and with insignificant oral/enteral nutrient absorption and low parenteral lipid intake are at high risk for EFAD. Extremely low birth weight infants are particularly vulnerable to insufficient lipid supply because significant in utero fat accumulation does not occur until the third trimester. Specific essential fatty acid requirements are currently unknown for preterm infants with PNAC/PNALD who remain dependent on parenteral nutrition [1].

Although the safety data did not demonstrate an increased frequency of EFAD with Omegaven compared to the historical control, the safety database from the two trials of Omegaven was too small to rule out an increased risk of EFAD with Omegaven use.

### Longer-term neurocognitive effects

The longer-term neurocognitive effects of EFAD would not be apparent during the time course of the Omegaven trials. Furthermore, neurodevelopmental assessment was not part of the development program for Omegaven. DGIEP remains concerned about the theoretic risk of neurodevelopmental delays assessed later in life (e.g., ages 2, 5, and 10 years).

### Pleural/Pericardial Effusion

Deaths of preterm infants reported in the literature with a finding of intravascular fat accumulation in the lungs subsequently resulted in the black boxed warning of soybean oil-based lipids, and is now applied across the soybean oil-based lipid emulsion class labeling [1]. Almost all the reported deaths were in infants who received 100% soybean oil-based lipid emulsion at an infusion rate well above the recommended maximum rate of 0.15 g/kg/hr in preterm and low birthweight infants who have poor clearance of intravenous lipid emulsions. There are no published reports of pleural effusion specifically associated with Omegaven use and the black box warning is not in the Omegaven labeling. However, DGIEP remains concerned about the theoretic risk of life-threatening pleural or pericardial effusions and will monitor the reporting of such events along with the clinical narratives to determine whether pulmonary effusions might be clinically related to the infusions.

## 1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

## 1.4. Statement of Purpose

The question is whether ARIA could provide adequate data on:

- outcomes of EFAD and provide long-chain polyunsaturated fatty acid (LCPUFA) serum profiles with prespecified thresholds
- neurodevelopmental delays assessed later in childhood (e.g., ages 2, 5, and 10 years)
- serious bleeding events
- life-threatening pleural or pericardial effusions with clinical narratives to support labeling decisions.

## 1.5. Effect Size of Interest or Estimated Sample Size Desired

No sample size is projected for the evaluation of the outcomes of interest stated in Section 1.4 given that ARIA is ultimately deemed insufficient in this memo.

## 2. SURVEILLANCE OR DESIRED STUDY POPULATION

### 2.1 Population

The patient population of interest is pediatric patients with PNAC who are administered Omegaven. In the combined efficacy analysis population of Omegaven users, median chronological age of patients was 9 weeks. Most patients were preterm infants at birth (90%), with gestational age categories as follows: extremely preterm (31%), very preterm (20%); moderate or late preterm (40%). Therefore, it is expected that the majority of patients receiving Omegaven will be neonates in the hospital setting.



The patient population may be identified through ICD-10 codes indicating a hospital diagnosis of PNAC. However, validation studies are not available that assess the sensitivity and specificity of the ICD-10 codes.

## **2.2 Is ARIA sufficient to assess the intended population?**

Although ICD-10 codes may identify the intended population, the sensitivity and specificity of the ICD-10 codes for PNAC are unknown. Furthermore, the extent of capture of the pediatric population with PNAC who might be eligible for Omegaven administration is unknown. It is uncertain whether ARIA in Sentinel is sufficient to adequately assess the intended population. (ARIA is ultimately deemed insufficient in this memo due to the inability to address the question in Section 1.4.)

## **3 EXPOSURES**

### **3.1 Treatment Exposure**

Most neonates will receive Omegaven in a hospital setting. However, medications administered in a hospital may not be readily distinguishable in claims data, but may be bundled for reimbursement by episode of care.

Some pediatric patients, especially patients chronically dependent on total parenteral nutrition (TPN) with pre-transplant intestinal failure, may start Omegaven in a hospital then continue outpatient treatment at home. Those outpatients would have regular clinic visits where the TPN prescriptions are managed by their physicians. Sentinel would likely capture such outpatient Omegaven dispensings.

### **3.2 Is ARIA sufficient to identify the exposure of interest?**

ARIA will likely capture Omegaven dispensings in the outpatient setting; ARIA is not likely to fully capture dispensings in the hospital setting. Most patients receiving Omegaven will be neonates in a hospital setting. Therefore, ARIA is deemed insufficient to identify the exposure of interest.

## **4 OUTCOMES**

### **4.1 Outcomes of Interest**

The outcomes of interest include:

- EFAD measured by long-chain polyunsaturated fatty acid (LCPUFA) serum profiles with prespecified thresholds
- neurodevelopmental delays assessed later in (b) (4)
- serious bleeding events
- life-threatening pleural or pericardial effusions with clinical narratives

### **4.2 Is ARIA sufficient to assess the outcomes of interest?**

EFAD: ARIA is insufficient to provide the needed lab data and does not allow for prospective sample collection needed to capture LCPUFA serum profiles.

Neurodevelopmental delays assessed later in (b) (4): Sentinel is unlikely to provide long term follow-up (b) (4) for most neonates that receive Omegaven. Therefore, ARIA is insufficient to provide the needed long-term assessment of neurocognitive delays during childhood.



### Life-threatening pleural or pericardial effusions with clinical narratives:

Although in-hospital deaths would likely be captured, given the rarity of the event and the comorbidities in the population, autopsy findings would likely be needed to definitively confirm that pleural or pericardial effusions were the cause or contributing factor in the deaths. ARIA would not provide the clinical narratives required to help determine whether the pulmonary effusions were clinically related to the infusions. Therefore, ARIA is insufficient to fully monitor for these outcomes.

Serious bleeding events: Outcomes of gastrointestinal bleeding and intracranial hemorrhage have been assessed in Sentinel through inferential analysis; however, these outcomes are unlikely to capture the full range of serious bleeding events in this patient population. Furthermore, temporality could not be established for those administered Omegaven in the hospital setting limiting a determination of whether the bleeding event occurred before or after Omegaven administration (versus the underlying comorbidities in this patient population). For these reasons, ARIA is deemed insufficient to fully capture serious bleeding events in the context of this patient population and in the hospital setting.

## **5 COVARIATES**

### **5.1 Covariates of Interest**

Pediatric patients receiving Omegaven are likely to have multiple serious comorbid conditions that required the administration of PN and that predispose patients to adverse events.

Pediatric patients receiving Omegaven are also likely to be exposed to multiple therapies.

These comorbid conditions and concomitant therapies might lead to unmeasured confounding.

### **5.2 Is ARIA sufficient to assess the covariates of interest?**

Patients using Omegaven may experience a wide variety of comorbidities including, but not limited to: intrauterine growth retardation, immaturity of the biliary excretory system, absence of enteral feeding, bacterial overgrowth, sepsis, hypotension or hypoxia, gastrointestinal surgeries, short bowel syndrome, steatosis, steatohepatitis, fibrosis, cirrhosis, etc. The range in underlying conditions and concomitant medications present a challenge, especially when the covariates arise in a hospital setting (where temporality of events and capture of exposure data may be suboptimal). ARIA is deemed not sufficient to capture the comorbid conditions and therapies that might increase the risk of some outcomes of interest.

## **6 SURVEILLANCE DESIGN / ANALYTIC TOOLS**

### **6.1 Surveillance or Study Design**

Lab results from the prospective collection of serum are likely unavailable in Sentinel. The analytical tools are not designed to address prospective measurement of long-chain polyunsaturated fatty acid (LCPUFA) serum profiles and clinical narratives of life-threatening pleural or pericardial effusions.

### **6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?**

The analytic tools in ARIA are a major limiting factor to feasibility in addressing the totality of the question posed in Section 1.4.

## **7 SUMMARY**

The Division of Epidemiology-I (DEPI-I) discussed ARIA sufficiency through email and in-person conversations with staff from DGIEP and with the Office of Surveillance and Epidemiology (OSE). **This Memo documents the conclusion that ARIA is not sufficient for**



**assessing the outcomes of interest (identified in Section 4.1) among Omegaven exposed pediatric patients.**

## **8 NEXT STEPS**

Because ARIA was deemed insufficient, DGIEP may choose to issue a postmarketing requirement to the Sponsor for an observational study to evaluate the outcomes identified in Section 4.1.

FDA preliminary PMR language includes the following:

“Conduct a prospective, longitudinal cohort study with an external control of the long-term safety (defined as patient monitoring for  $\geq 1$  year continuous treatment (b) (4) ) of Omegaven in pediatric patients with PNAC evaluating the potential for EFAD by measuring:

- 1.) long-chain polyunsaturated fatty acid (LCPUFA) serum profiles with prespecified thresholds to assess essential fatty acid deficiency (EFAD), and
- 2.) neurodevelopmental delays assessed later in life (b) (4) and further
- 3.) assess the occurrence of serious bleeding events.

In addition, life-threatening pleural or pericardial effusions will also be reported. These evaluations will be performed in patients during infusion and 4 weeks after discontinuation of lipid emulsion treatment and clinical narratives will be assessed to determine whether the pulmonary effusions were clinically related to the infusions.”

The finalized PMR language will be issued upon approval.

## **REFERENCE:**

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<sup>1</sup> BLA Multi-Disciplinary Review and Evaluation – NDA 210589, Omegaven (fish oil), Accessed July 20, 2018, DARRTS Reference ID: Pending.



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/s/  
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MICHELLE R IANNAcone on behalf of PATRICIA L BRIGHT  
07/26/2018

WEI HUA  
07/26/2018

JUDITH W ZANDER  
07/27/2018

MICHAEL D NGUYEN  
07/29/2018

ROBERT BALL  
07/30/2018

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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<b>Date of This Memorandum:</b>	July 5, 2018
<b>Requesting Office or Division:</b>	Division of Gastroenterology and Inborn Error Products (DGIEP)
<b>Application Type and Number:</b>	NDA 210589
<b>Product Name and Strength:</b>	Omegaven (fish oil triglycerides) injectable emulsion 5 g per 50 mL and 10 g per 100 mL (0.1 g per mL)
<b>Total Product Strength:</b>	5 g per 50 mL and 10 g per 100 mL
<b>Submission date:</b>	July 2, 2018
<b>Applicant/Sponsor Name:</b>	Fresenius Kabi USA, LLC
<b>OSE RCM #:</b>	2018-49-1
<b>DMEPA Primary Reviewer:</b>	Sherly Abraham, RPh
<b>DMEPA Team Leader:</b>	Sarah K. Vee, Pharm.D.

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#### 1 PURPOSE OF MEMO

Division of Gastroenterology and Inborn Error Products (DGIEP) requested that we review the revised carton labeling and container labels (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review, OSE RCM #: 2018-49<sup>a</sup>.

#### 2 CONCLUSION

We find the revised container labels and carton labeling acceptable and have no further recommendations at this time.

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<sup>a</sup>Abraham.S. Label and Labeling Review for Omegaven (NDA 210589). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2018 May 04. 32 p. OSE RCM No.:2018-49

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/s/  
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SHERLY ABRAHAM  
07/05/2018

SARAH K VEE  
07/05/2018

## Clinical Inspection Summary

<b>Date</b>	May 7, 2018
<b>From</b>	Susan Leibenhaut, M.D., OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
<b>To</b>	Suna Seo, M.D., Medical Officer, DGIEP
<b>NDA #</b>	210589
<b>Applicant</b>	Fresenius Kabi, USA LLC
<b>Drug</b>	Omegaven
<b>NME</b>	Yes
<b>Division Classification</b>	LVP Lipid (lipid + products)
<b>Proposed Indication</b>	Source of calories and fatty acids in pediatric patients with parenteral nutrition associated cholestasis
<b>Consultation Request Date</b>	January 19, 2018
<b>Summary Goal Date</b>	April 1, 2018
<b>Action Goal Date</b>	August 1, 2018
<b>PDUFA Date</b>	August 1, 2018

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

This addendum updates the original clinical inspection summary (CIS) entered into DARRTS on March 36, 2018. This addendum includes the preliminary results of the inspection of the applicant of the NDA, Fresenius Kabi (FK), the final results of the three inspections contained in the original clinical inspection summary, and the final results of the inspection of (b) (4) the contract research organization (CRO) responsible for data extraction from the source documents, that was conducted concurrently with the clinical investigator inspection at Boston Children's Hospital. (b) (4) was responsible for data extraction from the source documents at the two clinical sites and at UCLA. The inspections of the clinical sites, the UCLA site and the CRO have the final classifications of no action indicated (NAI). The inspection of inspection of FK has the preliminary classification of NAI.

The data generated by the two clinical sites and at UCLA, a site of the extraction of historical control data only, are reliable. This data may be used in support of the application.

**II. BACKGROUND**

See original CIS for complete background.

**III. RESULTS (by site):**

Name and Type of Inspected Entity/Address	Protocol # / # of Subjects (safety population/matched)	Inspection Dates	Classification
CI: Dr. Mark Puder, M.D. Boston Children's Hospital 300 Longwood Ave. Boston, MA 02115	OMEG-034-IP3 Active: 128/52 Historical: 47/14 <sup>+</sup>  OMEG-035-IP3 Historical: 6/6	February 14 to 22, 2018	NAI
CI: Dr. Muralidhar H. Premkumar Texas Children's Hospital 6621 Fannin St., W6104 Houston, TX 77030	OMEG-034-IP3 Historical: 6/6  OMEG-035-IP3 Active: 61/30 Historical: 15/4 <sup>^</sup>	February 6 to 9, 2018	NAI
CI: Dr. Kara L. Calkins UCLA Mattel Children's Hospital 10833 Le Conte, Room B2375 Los Angeles, CA 90095	OMEG-034-IP3 Historical: 6/6  OMEG-035-IP3 Historical: 5/5  Met eligibility but not matched: 7	March 1 to 8, 2018	NAI
Applicant: Fresenius Kabi Archive, Borkenberg 14, 61440 Oberursel (Taunus), Germany	OMEG-034-IP3  OMEG-035-IP3	April 23 to 27, 2018	*NAI
CRO: (b) (4)  <u>Inspection Location:</u> Boston Children's Hospital 300 Longwood Ave. Boston, MA 02115	OMEG-034-IP3 Active: 128/52 Historical: 47/14 <sup>+</sup>  OMEG-035-IP3 Historical: 6/6	(b) (4)	NAI

Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

\*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

+Additional historical controls are from TCH and UCLA

^ Additional historical controls are from BCH and UCLA

1. Fresenius Kabi  
Borkenberg 14, Germany

Note: Observations below for this applicant inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report.

This inspection evaluated compliance with applicant responsibilities concerning the conduct of collection of data generated from studies conducted at Boston Children's Hospital (BCH) under sponsor investigator IND 73488 and Texas Children's Hospital (TCH) under sponsor investigator IND 102843 as well as historical control data that were extracted at three sites, BCH, TCH, and UCLA Mattel Children's Hospital. Clinical investigators (CI) at BCH and TCH opened sponsor-investigator INDs with the FDA to administer this product to their patients. Inspection included review of contracts concerning the above activities as well as the contracts covering data analysis, financial disclosure, and other applicant responsibilities.

The applicant contracted with (b) (4) to conduct and supervise the extraction of the data from source documents and to develop the Data Management Plan. This included developing paper CFRs for the collection of critical data based upon the BCH and TCH Sponsor-Investigators' protocols. The CFRs and data collected was reviewed and approved by the Sponsor-Investigator.

The applicant did not oversee the administration of test article, so no monitoring activities were required. The sponsor did oversee the extraction of the data by conducting site visits at the respective clinical sites. The applicant made contracts with the institutions and not with the Principle Investigators for access to the data. The applicant established through the respective institution's IRBs that there were no conflicts of interest with the Principle Investigators at two of the three institutions and reported the conflicts of interest for the investigators at BCH. No violations were noted and no Form FDA 483 was issued.

The data appear to have been collected reliably. The data generated by this sponsor may be used in support of the respective indication.

2.

(b) (4)

Inspection of this CRO was conducted at Boston Children's Hospital, 300 Longwood Ave., Boston, MA 02115 during the inspection of Dr. Mark Puder at this site

At this site, the activities of the CRO were inspected concerning the collection and transmission of data to the sponsor. Although no assignment had originally been issued for a CRO inspection, it was decided to issue a Form FDA 482 to the CRO at this site because the CRO, not the CI, had the primary responsibility of data collection and transmission to the sponsor. The FDA investigator performed a detailed review of the data collection documents including the data management plan and the CRF completion documents and verification of the 30 records chosen by the review division. These records were a sample of active treatment and historical controls that were in each of the analysis groups for the FDA investigator to review. There was review of inclusion/exclusion criteria, demographics, medical history, laboratory test results, liver function tests, evolution of direct bilirubin, administration of comparator product (Intralipid), development and growth of subjects, outcome of assessments and tests, information on liver transplants and deaths, concomitant medications, primary and secondary efficacy endpoints, and adverse events.

The data verification at all the sites was conducted under the inspection of the clinical investigators, and, as noted in the original CIS, the data were able to be verified.

{See appended electronic signature page}

Susan Leibenhaut, M.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

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OSI/Database PM/Dana Walters



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/s/  
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SUSAN LEIBENHAUT  
05/07/2018

SUSAN D THOMPSON  
05/07/2018

KASSA AYALEW  
05/08/2018



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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Food and Drug Administration  
Office of New Drugs, ODE-IV  
Division of Pediatric and Maternal Health  
Silver Spring, MD 20993  
Telephone 301-796-2200  
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**MEMORANDUM TO FILE**

**From:** Ethan D. Hausman, MD, Medical Officer  
Division of Pediatric and Maternal Health (DPMH)

**Through:** Hari Cheryl Sachs, MD, Medical Team Leader  
John J. Alexander, MD/MPH, Deputy Director  
DPMH

**NDA Number:** 210,589

**Sponsor:** Fresenius Kabi USA, LLC

**Drug:** Omegaven (fish oil injectable emulsion), 10%, for  
intravenous (IV) infusion

**Proposed Indication:** Indicated as a source of calories and fatty acids in  
pediatric patients with parenteral nutrition  
associated cholestasis (PNAC)

**Proposed Pediatric Regimen:** Not to exceed 10 mL/kg/day of Omegaven  
(1g/kg/day)

**Division Consult Request:** The Division of Gastroenterology and Inborn Error  
Products (DGIEP) requested DPMH assistance in  
labeling this product.

## Background

Omegaven (an omega-3 type lipid product) is a not-previously-marketed, fish-oil based, lipid emulsion submitted under NDA 210,589 for use as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis [PNAC; also referred to as parenteral nutrition-associated liver disease (PNALD)]. The sponsor's development program for this indication was studied under IND 114,141, and the NDA was received on December 1, 2017.

On February 27, 2008, the sponsor received orphan drug designation for omegaven for treatment of PNALD. DGIEP also (b) (4)

granted fast-track designation for Omegaven 10% emulsion for injection as a "source of calories and fatty acids in pediatric patients with PNAC", (IND 114,141; Fast Track Designation Letter, Mulberg A; January 2, 2016).

The sponsor observes, and FDA acknowledges, that long-term administration of soybean-oil-based lipid emulsion has been identified as a contributing factor for PNAC. While the mechanism of action of omega-3 lipids in reducing the occurrence of PNAC is unclear, animal studies report a decrease in occurrence and severity of parenteral nutrition (PN) associated steatosis compared to traditional soy-based (omega-6) PN lipid product.<sup>1,2</sup> DGIEP and DPMH agree that an effective treatment of PNAC in children including neonates and young infants could reduce incidence and severity of PNAC and associated complications (e.g. liver transplant or death).<sup>3</sup>

The sponsor contends two open-label studies with historical controls to support approval for treatment of PNAC. Upon review, DGIEP determined that data are adequate to support a claim of improved growth (specifically, increased weight gain) for patients with PNAC treated with omegaven. The weight gain in omegaven treated patients approximated improved growth trajectory compared to standardized trajectories, from baseline in Omegaven treated patients.

SMOFLipid (NDA 207,648) is the only currently marketed product, and is indicated *in adults* "as a source of calories and essential fatty acids for parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated."

## DPMH Labeling Recommendations

Because Omegaven will be approved for pediatric use, pediatric information will be distributed throughout labeling. This labeling review will address the proposed boxed warning, indication (Section 1), dosage and administration (Section 2), warnings and precautions (Section 5), and pediatric use (Section 8.4). Review of safety (Section 6) and clinical trials (Section 14) sections of labeling is deferred to DGIEP. DPMH participated

<sup>1</sup> Chen W. Effects of fat emulsions with different fatty acid composition on plasma and hepatic lipids in rats receiving total parenteral nutrition. *Clinical Nutrition* 1996;15:24.

<sup>2</sup> Yeh S. Effects of fish oil and safflower oil emulsions on diet-induced hepatic steatosis in rats receiving total parenteral nutrition. *Clinical Nutrition* 1996;15:80.

<sup>3</sup> IND 114,141; Hausman E. Consult Review, Pediatric and Maternal Health Staff (PMHS), December 12, 2013.

in discussion of the Highlights section of labeling and there are no suggested changes to Highlights not otherwise discussed in this review; therefore, the Highlights will not be separately reviewed in this document. Maternal Health recommendations will be addressed in a separate consultative review.

In this review, newly proposed language by the sponsor or DGIEP are noted in **bold font**, additions by DPMH are noted in **red font**, and recommended deletions are noted by ~~strike-through font~~. The rationale for DPMH recommendations are noted in *italics*. DPMH suggestions for minor word changes are not included in this review.

Comments regarding the highlights sections are addressed in the individual sections of labeling and have been discussed at internal labeling meetings and placed in the working version of labeling.

### Boxed Warning

DGIEP is considering a boxed warning for IV lipid formulations related to rare deaths in preterm and low birth-weight infants where autopsy showed intravascular lipid deposits in pulmonary vasculature.<sup>4,5</sup> The proposed boxed warning is shown below:

#### WARNING: DEATH IN PRETERM INFANTS

See full prescribing information for complete boxed warning.

- Deaths in preterm infants have been reported in literature. (5.1, 8.4)
- Autopsy findings included intravascular fat accumulation in the lungs. (5.1, 8.4)
- Preterm and low-birth-weight infants have poor clearance of intravenous lipid emulsion and increased free fatty acid plasma levels follows lipid emulsion infusion. (5.1, 8.4)

*Reviewer comment: The proposed boxed warning is identical to the current boxed warning for SMOFLipid.*

*Case reports describe similar autopsy findings in central nervous system (CNS) vasculature<sup>6</sup> as well as widespread end-organ failure,<sup>7</sup> and should be classified within the overall framework of Fat Overload Syndrome (section 5.4 of labeling). Given the rarity of such reports in the literature and the lower number of reports of CNS and end organ dysfunction compared to reports of pulmonary findings (also rare), the proposed boxed warning is generally acceptable. However, DGIEP should consider whether to stress the pulmonary findings, which are more commonly reported in the literature, or to stress the potential for widespread endotheliopathy (note: deaths in preterm infants and fat-overload syndrome are described separately in sections 5.1 and 5.4, respectively).*

<sup>4</sup> Puntis JW, Wilkins KM, Ball PA, et al. Hazards of parenteral treatment: do particles count? Arch Dis Child. 1992 Dec;67(12):1475-1477.

<sup>5</sup> Levene MI, Batisti O, Wigglesworth JS, et al. A prospective study of intrapulmonary fat accumulation in the newborn lung following intralipid infusion. Acta Paediatr Scand. 1984 Jul;73(4):454-460.

<sup>6</sup> Schulz PE, Weiner SP, Haber LM, et al. Neurologic complications from fat emulsion. Ann Neurol. 1994 May;35(5):628-630.

<sup>7</sup> Haber LM, Hawkins EP, Seilheimer DK, Saleem A. Fat overload syndrome. An autopsy study with evaluation of the coagulopathy. Am J Clin Pathol. 1988 Aug;90(2):223-227.

## 1 Indications and Usage

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

*Reviewer comment: DGIEP's analysis supports sustained weight gain with a sustained trajectory along predicted curves supporting a conclusion that the weight gain is related to growth rather than short-term fluid overload. Since the conditions of study required patients to have a diagnosis of PNAC for entry, DGIEP concludes that the proposed indication is acceptable (also see discussion under Dosage and Administration).*

*DGIEP is also considering adding the following limitation of use, which is found in SMOFLipid labeling (NDA 207,648; Labeling version July 13, 2016), a similar fish-oil based IV lipid emulsion. DPMH agrees with adding this limitation of use.*

### Limitations of Use

***The omega-6: omega-3 fatty acid ratio and Medium Chain Triglycerides in Omegaven have not been shown to improve clinical outcomes compared to other intravenous lipid emulsions.***

## 5 Dosage and Administration

*Reviewer comment: Dosing and administration have been reviewed with DGIEP and Clinical Pharmacology and are acceptable with the modifications shown below. The reader is directed to final labeling for the text of the entire passage.*

### 2.3 Dosing Information

Initiate Omegaven dosing in **pediatric patients who are PN-dependent for at least two weeks** (b) (4)

#### Recommended Pediatric Dosing

- The recommended dosage of Omegaven for pediatric patients [**NOTE to DGIEP: please state the age range for whom the drug will indicated**] is (b) (4) 1 g (b) (4)/kg/day); this is the maximum daily dose.
- **If hypertriglyceridemia [greater than 250 mg/dL in neonates and infants; 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 (b) (4), consider other reasons for hypertriglyceridemia (e.g. renal disease, other drugs). If triglycerides remain at elevated levels, consider a reduced dose of (b) (4) 0.5 g to 0.75 g/kg/day (b) (4) with an incremental increase to (b) (4) 1 g/kg/day (b) (4).
- 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 (b) (4) DBil<sup>(b) (4)</sup> levels are less than 2 mg/dL or until the patient no longer requires PN.

## Warnings and Precautions

(b) (4)

### 5.1 Death in Preterm infants

(b) (4)

### 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.

*Reviewer comment: The text of these sections is acceptable. As noted in the discussion of the potential box warning above, DGIEP should consider if death in preterm infants associated with pulmonary findings, central nervous system findings, and multiple end-organ failure are all related to a common pathophysiologic insult. If such a conclusion is reached, DGIEP could consider if death associated with CNS and widespread end organ endotheliopathy should also be noted in the box warning.*

### 5.8 Monitoring for Laboratory Tests

#### Routine Monitoring

Monitor serum triglycerides [see Warnings and Precautions (5.5)], 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.

(b) (4)

*Reviewer comment: The first two paragraphs reflect class labeling and are unchanged. DGIEP and Clinical Pharmacology are considering modification to or deletion of the third paragraph. Irrespective of whether the first two sentences of the third paragraph may be factually accurate, the sentences relate to*

(b) (4)

### **8.4 Pediatric Use**

(b) (4)

**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 gestation age of  $\geq 24$  weeks at birth. Patients administered Omegaven attained and maintained age-appropriate, growth (in terms of age-adjusted body weight) through at least 108 weeks of treatment [see Clinical Studies (14)].**

**The safety of omegaven as established in 189 pediatric patients (ages 19 days to 15 years). Patients administered Omegaven attained and maintained age-appropriate growth (in terms of age-adjusted body weight) through at least 108 weeks of treatment. The most common adverse reactions events in Omegaven treated patients were vomiting, respiratory failure and bradycardia [(see Adverse Reactions (6))].**

(b) (4)

**Preterm neonates and infants who receive (b) (4) treatment with Omegaven may be at greater risk of aluminum toxicity and other metabolic abnormalities,**

(b) (4)

(b) (4)

*Reviewer comment:*

(b) (4)

*DPMH agrees with this deletion.*

### **Conclusion and Recommendations**

The above findings and recommendations were presented to DGIEP at the internal labeling meetings of April 2 and April 19, 2018. The reader is directed to final labeling which may reflect changes not discussed in this review.

The reader is reminded that DPMH and the Pediatric Review Committee (PeRC) are distinct operational units, and recommendations from DPMH and PeRC may differ.



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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ETHAN D HAUSMAN  
05/07/2018

HARI C SACHS  
05/07/2018  
I agree with these recommendations.

JOHN J ALEXANDER  
05/07/2018

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## **LABEL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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<b>Date of This Review:</b>	May 4, 2018
<b>Requesting Office or Division:</b>	Division of Gastrointestinal and Inborn Errors Products (DGIEP)
<b>Application Type and Number:</b>	NDA 210589
<b>Product Name and Strength:</b>	Omegaven (fish oil) <sup>a</sup> injectable emulsion 5g/50mL and 10g/100mL (0.1g/mL)
<b>Total Product Strength:</b>	5 g/50 mL and 10 g/100 mL
<b>Product Type:</b>	Single ingredient
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Fresenius Kabi USA, LLC
<b>Submission Dates:</b>	December 1, 2017 April 18, 2018
<b>OSE RCM #:</b>	2018-49
<b>DMEPA Primary Reviewer:</b>	Sherly Abraham, R.Ph.
<b>DMEPA Team Leader:</b>	Sarah K. Vee, Pharm.D.

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<sup>a</sup>Established name is currently under review.

## 1 REASON FOR REVIEW

This review evaluates the labels and labeling for Omegaven (NDA 210589), New Molecular Entity (NME) NDA, submitted on December 1, 2017. On April 18, 2018, revised prescribing information (PI) was submitted. The Division of Gastroenterology and Inborn Error Products (DGIEP) requested that DMEPA review the proposed PI, container labels, and carton labeling for any areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Fresenius Kabi USA, LLC submitted a NME NDA for Omegaven which is indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC).

We identified areas in the PI, container labels, and carton labeling that can be improved to increase the clarity of information to promote the safe use of the product. DMEPA communicated our recommendations for the proposed PI to the DGIEP team in the labeling meeting setting. We provide letter-ready recommendations for the Applicant in Section 4.1 to address these concerns.

## 4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed PI, container labels, and carton labeling can be improved to increase the clarity of information to promote the safe use of the product. We provide our recommendations in Section 4.1 below.

### 4.1 RECOMMENDATIONS FOR FRESENIUS KABI USA, LLC

We recommend the following be implemented prior to approval of this NDA:

#### A. Container Labels and Carton Labeling:

1. Delete all (b) (4) error-prone because not all health care professionals are familiar or adept at calculating doses in mg for drugs (b) (4).<sup>b</sup>
2. Established name for your product has not been finalized. Revise the established name to be consistent with the prescribing information once the established name is determined for your product.
3. Revise the statement (b) (4) to read “Single-Dose bottle– Discard Unused Portion” to be consistent with the prescribing information and minimize risk of the entire contents of the bottle being given as a single dose.

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<sup>b</sup> Institute for Safe Medication Practices. It doesn’t pay to play the percentages. ISMP Med Saf Alert Acute Care. 2002;7(21):1-2.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Omegaven that Fresenius Kabi USA, LLC submitted on December 1, 2017.

Table 2. Relevant Product Information for Omegaven	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	fish oil <sup>a</sup>
<b>Indication</b>	Omegaven is indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC)
<b>Route of Administration</b>	intravenous
<b>Dosage Form</b>	injectable emulsion
<b>Strength</b>	5 g/50mL (0.1 g/mL) and 10 g/100mL (0.1 g/mL)
<b>Dose and Frequency</b>	The recommended daily dose in pediatric patients is 1 g/kg/day
<b>How Supplied</b>	50 mL bottle, carton of 10 x 50 mL, 100 mL bottle and carton of 10 x 100 mL
<b>Storage</b>	Store below 25°C (77°F). Avoid excessive heat. Do not freeze. If accidentally frozen, discard product.

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>c</sup> along with postmarket medication error data, we reviewed the Omegaven labels and labeling submitted by Fresenius Kabi USA, LLC on December 1, 2017.

- Container labels
- Carton labeling
- Prescribing Information (Image not shown)

### **G.2 Label and Labeling Images**

#### **Container label**



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<sup>c</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SHERLY ABRAHAM  
05/04/2018

SARAH K VEE  
05/07/2018



**DEPARTMENT OF HEALTH & HUMAN SERVICES**      Public Health Service

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Division of Pediatric and Maternal Health  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
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**Division of Pediatric and Maternal Health Review**

**Date:** 5/3/2018      **Date consulted:** 4/2/2018

**From:** Miriam Dinatale, D.O., Team Leader Maternal Health  
Division of Pediatric and Maternal Health (DPMH)

**Through:** Lynne P. Yao, M.D., OND, Division Director  
Division of Pediatric and Maternal Health

**To:** Division of Gastroenterology and Inborn Errors Products (DGIEP)

**Drug:** Omegaven 10% (fish oil injectable emulsion)

**NDA:** 210589

**Applicant:** Fresenius Kabi USA, LLC

**Subject:** Pregnancy and Lactation Labeling

**Indication:** source calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC)

**Consult Question:** DGIEP requests MHT assistance with review of labeling to meet the requirements of PLLR.

**Materials Reviewed:**

- 4/2/2018, DPMH consult form, NDA 210589, DARRTS Reference ID 4243076
- 7/14/2017, New Drug Application submission, NDA 210589, Omegaven 10% (fish oil injectable emulsion)



## INTRODUCTION AND BACKGROUND

On July 14, 2017, the applicant (Fresenius Kabi USA, LLC) submitted a 505(b)(1) new drug application for Omegaven 10% (fish oil injectable emulsion) to be used as a source of calories and fatty acids for pediatric patients with parenteral nutrition associated cholestasis (PNAC). DGIEP consulted DPMH on April 2, 2018 to assist with the Pregnancy and Lactation subsections of labeling.

### Omegaven and Drug Characteristics

Omegaven is a fish oil whose major active components are omega-3 fatty acids, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The recommended dosage for Omegaven is 10mL/kg/day (1g/kg/day). Each 100 mL of Omegaven contains 10 grams of fish oil and the mean content of the two major fatty acid components in 100mL are (b) (4) of EPA and (b) (4) of DHA. Omegaven contains smaller amounts of alpha-linolenic acid (omega-3 fatty acid), linoleic acid and arachidonic acid (omega-6 fatty acids), oleic acid (omega-9 fatty acids), palmitic acid (saturated fatty acid found in animals, plants and microorganisms) palmitoleic acid (omega-7 monounsaturated fatty acid found in plants), and myristic acid (saturated fatty acid). Omegaven also contains 0.025mg of aluminum.

### *Reviewer comment:*

*Over a 24 hour period, a 50kg person treated with intravenous Omegaven would be expected to receive 500ml of Omegaven per day (10ml x50kg) with a total of (b) (4) of EPA (b) (4) of DHA.*

### Omega-3 Fatty Acids and Recommended Daily Intake<sup>1</sup>

The table from the National Institutes of Health (NIH) included below includes the adequate daily intake of Omega-3 Fatty Acids

Table 1: Adequate Intakes (AIs) for Omega-3s [5]

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months*	0.5 g	0.5 g		
7–12 months*	0.5 g	0.5 g		
1–3 years**	0.7 g	0.7 g		
4–8 years**	0.9 g	0.9 g		
9–13 years**	1.2 g	1.0 g		
14–18 years**	1.6 g	1.1 g	1.4 g	1.3 g
19–50 years**	1.6 g	1.1 g	1.4 g	1.3 g
51+ years**	1.6 g	1.1 g		

\*As total omega-3s

\*\*As ALA

The NIH notes the following:

“The Food and Nutrition Board of the Institute of Medicine (IOM) did not establish an upper limit for any omega-3s, although it noted that high doses of DHA and/or EPA (900 mg/day of EPA plus 600 mg/day DHA or more for several weeks) might reduce immune function due to suppression of inflammatory responses. Doses of 2–15 g/day EPA and/or DHA might also increase bleeding time by reducing platelet aggregation. However,

<sup>1</sup> <https://ods.od.nih.gov/factsheets/Omega3FattyAcids-HealthProfessional/>. Accessed 4/17/2018.

according to the European Food Safety Authority, long-term consumption of EPA and DHA supplements at combined doses of up to about 5 g/day appears to be safe. It noted that these doses have not been shown to cause bleeding problems or affect immune function, glucose homeostasis, or lipid peroxidation. The FDA recommends not exceeding 3 g/day EPA and DHA combined, with up to 2 g/day from dietary supplements. Some doses used in clinical trials exceed these levels.”

*Reviewer comment:*

*Pregnant women should take 1.4 grams of omega-3 fatty acids daily during pregnancy and 1.3 grams of omega-3 fatty acids daily during lactation. The amount of omega-3 fatty acids present in Omegaven is higher than would be expected from oral exposure through diet.*

## **REVIEW**

### ***PREGNANCY***

#### Parenteral Nutrition Associated Cholestasis and Pregnancy<sup>2</sup>

Liver disease occurs in 15-40% of adults on long-term parenteral nutrition (PN), with steatosis being more common than cholestasis in the adult population. Twenty-two percent of deaths in patients on long-term PN are related to PN-related liver failure, which is well reported in the pediatric population and seen less often in adults. Prolonged use of PN (usually  $\geq 3$  weeks) can lead to intrahepatic cholestasis, also known as Parenteral Nutrition Associated Cholestasis (PNAC). PNAC increases the risk of sepsis, cirrhosis and mortality.<sup>3</sup>

There are pregnant women with severe hyperemesis gravidarum or other serious medical or surgical conditions where oral or enteral nutrition are not possible who may have a need for prolonged PN.<sup>4</sup> Although there are no reports of PNAC in pregnant women, it is possible that PNAC may be seen if a pregnant woman requires prolonged PN.

#### Nonclinical Experience

Animal reproduction studies were not performed.

#### Review of Pharmacovigilance Database

Omegaven has been approved in Europe since March 30, 1998. From 1998 through April 2017, there are been two pregnancies that have occurred with off-label use of Omegaven. The two cases are described below:

- A female patient (unknown age), pregnant in the 4th week was prescribed Omegaven for immune therapy to prevent miscarriage. No adverse reaction was reported.
- A female patient (unknown age) in the first trimester of pregnancy received Omegaven as part of off-label use, but reported no adverse reaction during administration.

#### Applicant's Review of Literature<sup>5</sup>

<sup>2</sup>

(b) (4)

<sup>3</sup> Teitelbaum, D. and Tracy, T. Parenteral Nutrition-Associated Cholestasis. Seminars in Pediatric Surgery. 2001; 10(2): 72-80.

<sup>4</sup> ACOG Practice Bulletin number 153 Nausea and Vomiting of Pregnancy. September 2015.

<sup>5</sup> NDA 210589 Omegaven 10%, Fish Oil Injectable Emulsion Amendment-Prescribing Information updated per PLLR requirements. Submitted 4/18/2018.

The applicant performed a literature search in Medline and Embase to identify published literature with the use of Omegaven, DHA and EPA administered IV or as part of parenteral nutrition in pregnant women. See the applicant's submission for search parameters. The applicant identified 94 publications that discussed dietary DHA or EPA in pregnant or lactating women or their effect on fertility, but there was no published literature regarding the use of IV or parenteral administration of Omegaven, DHA or EPA in pregnant women. There were several studies that reported a reduction of preterm deliveries in pregnant women treated with oral DHA or EPA.<sup>6,7,8,9,10</sup> Other studies showed that DHA plays a role in the synthesis and absorption of neurotransmitters and that low levels of DHA in pregnancy may lead to major depressive disorders.<sup>11,12,13</sup>

The applicant concluded the following:

“Overall, published literature on DHA or EPA supplementation during pregnancy... did not identify any adverse effects in pregnant women or their offspring; on the contrary, DHA and EPA supplementation had beneficial effects on pregnancy outcomes such as a reduction of preterm deliveries and depressive disorders during and after pregnancy.”

#### DPMH Review of Literature:

DPMH conducted a review of the literature using PubMed, Micromedex<sup>14</sup>, and *Drugs in Pregnancy and Lactation*<sup>15</sup> using the search terms, “Omegaven/ omega-3 fatty acids/omega-6 fatty acids/omega-9 fatty acids/docosahexaenoic acid/ eicosapentaenoic acid/ intravenous fish oils/intravenous docosahexaenoic acid/intravenous eicosapentaenoic acid and pregnancy and fetal malformations/birth defects/miscarriage/spontaneous abortion/stillbirth.” There is no information regarding Omegaven or intravenous fish oils, intravenous docosahexaenoic acid or intravenous eicosapentaenoic acid and use during pregnancy. In addition to the articles reviewed by the applicant, DPMH reviewed the following additional relevant published articles regarding oral fish oils, oral docosahexaenoic acid, and oral eicosapentaenoic acid and use during pregnancy.

In a double-blind randomized study of 590 healthy, pregnant women (19-35 years old) in weeks 17-19 of pregnancy were given 10mL of either cod liver oil or corn oil daily until three months after delivery. The authors found that there were neither harmful nor beneficial effects of

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<sup>6</sup> Facchinetti F, Fazzio M, Venturini P. Polyunsaturated fatty acids and risk of preterm delivery. *Eur Rev Med Pharmacol Sci.* 2005;9(1):41-8.

<sup>7</sup> Borod E, Atkinson R, Barclay WR, Carlson SE. Effects of third trimester consumption of eggs high in docosahexaenoic acid on docosahexaenoic acid status and pregnancy. *Lipids.* 1999;34 Suppl:S231.

<sup>8</sup> Olsen SF, Sorensen JD, Secher NJ, Hedegaard M, Henriksen TB, Hansen HS, Grant A. Randomised controlled trial of effect of fish-oil supplementation on pregnancy duration. *Lancet.* 1992;339(8800):1003-7.

<sup>9</sup> Olsen SF, Secher NJ, Tabor A, Weber T, Walker JJ, Glud C. Randomised clinical trials of fish oil supplementation in high risk pregnancies. *Fish Oil Trials In Pregnancy (FOTIP) Team. BJOG.* 2000;107(3):382-95.

<sup>10</sup> Smuts CM, Huang M, Mundy D, Plasse T, Major S, Carlson SE. A randomized trial of docosahexaenoic acid supplementation during the third trimester of pregnancy. *Obstet Gynecol.* 2003;101(3):469-79.

<sup>11</sup> Ramakrishnan U, Imhoff-Kunsch B, DiGirolamo AM. Role of docosahexaenoic acid in maternal and child mental health. *Am J Clin Nutr.* 2009;89(3):958S-62S.

<sup>12</sup> Rechenberg K, Humphries D. Nutritional interventions in depression and perinatal depression. *Yale J Biol Med.* 2013;86(2):127-37.

<sup>13</sup> Al MD, van Houwelingen AC, Hornstra G. Long-chain polyunsaturated fatty acids, pregnancy, and pregnancy outcome. *Am J Clin Nutr.* 2000;71(1 Suppl):285S-91S.

<sup>14</sup> Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 4/4/2018.

<sup>15</sup> Briggs, G and Freeman, R. *Drugs in Pregnancy and Lactation*, 10<sup>th</sup> Edition. 2015. Wolters Kluwer.

maternal supplements of long-chain n-3 polyunsaturated fatty acids regarding pregnancy outcome, cognitive development or growth. Neonates with high concentrations of DHA in umbilical plasma phospholipids (cod liver oil group) had longer gestational length than infants with low concentrations of DHA (corn liver oil group).<sup>16</sup> In another study, patients with persistent antiphospholipid syndrome (PAPS) and recurrent miscarriage were treated with fish oil, containing EPA and DHA. Out of 23 pregnancies, 21 pregnancies resulted in a live birth; the authors noted that the results are encouraging for a therapeutic role of fish oil to prevent recurrent miscarriage in PAPS.<sup>17</sup>

In a prospective study (Carta, et al.), 30 pregnant patients with a history of recurrent miscarriage were alternatively assigned to either low-dose aspirin or fish oil. Among patients treated with low-dose aspirin, 12 out of the 15 (80%) pregnancies ended in live births. In the fish oil group, 11 out of the 15 (73.3%) ended in live births ( $p > 0.05$ ). There were no significant differences between the low-dose aspirin and the fish oil with respect to gestational age at delivery (39.9 +/- 0.4 vs 39 +/- 1.5 weeks), fetal birth weight (3290 +/- 200g vs 3560 +/- 100 g), number of cesarean sections (25% vs 18%), or complications.<sup>18</sup>

In a systemic review of literature, Chen, et al., found no benefit from fish oil supplementation regarding the risk of intrauterine growth restriction or stillbirth; however, fish oil use during pregnancy is associated with reduced risk of preterm delivery and improved size of the newborn.<sup>19</sup>

Oral EPA and DHA are referenced in Micromedex,<sup>4</sup> which notes that oral EPA and DHA are “considered safe in therapeutic doses. Large doses combined with fat-soluble vitamins may increase risk due to vitamin A and D toxicity. No specific cases were identified.” Micromedex also states:

“Administration of fish oil to mothers in the third trimester of pregnancy increased duration of pregnancy without negatively altering growth weight or course of labor....

Three grams of eicosapentaenoic acid daily did not produce significant effects in pregnant women with histories of pregnancies with intrauterine growth retardation and pregnancy- induced hypertension...

Dietary intake of omega-3 fatty acids during pregnancy affects maternal and infant polyunsaturated fatty acid (PUFA) status and may play a role in infant neurodevelopment. The National Institute of Health (NIH) proposed that Omega-3 fats are only 20 to 60 percent of recommended adequate intakes. NIH recommends 0.22 gram EPA daily. Currently the mean daily intake of EPA is only 0.022 gram.”

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<sup>16</sup> Helland, et al. Similar effects on infants of n-3 and n-6 fatty acid supplementation to pregnant and lactating women.

<sup>17</sup> Rossi, E and Costa, M. Fish oil derivatives as a prophylaxis of recurrent miscarriage associated with antiphospholipid antibodies (APL): a pilot study. *Lupus*. 1993; 2(5): 319-323.

<sup>18</sup> Carta, et al. Recurrent miscarriage associated with antiphospholipid antibodies: prophylactic treatment with low-dose aspirin and fish oil derivatives. *Clin Exp Obstet Gynecol*. 2005;32(1):49-51.

<sup>19</sup> Chen, et al. Fish oil supplementation improves pregnancy outcomes and size of the newborn: a meta-analysis of 21 randomized controlled trials. *J Matern Fetal Neonatal Med*. 2016;29(12):2017-27.

Oral supplementation with omega-3 fatty acid, including oral DHA and EPA, are referenced in *Drugs in Pregnancy and Lactation*,<sup>5</sup> and include a pregnancy recommendation of “compatible.” Briggs and Freeman note that although no official recommended daily allowance for omega-3 fatty acids has been established, the U.S. Institute of Medicine and the Food and Nutrition Board recommend 1.4 grams/day of fatty acids during pregnancy. Briggs and Freeman also note that the majority of studies in humans show that increased intake of EPA and DHA during pregnancy have potential benefits on maternal and fetal outcomes, including reduced incidence of preterm birth, increased birth length, weight and head circumference, improved infant and child cognitive development and improved visual development and reduced risk of allergies; however, the authors note that more studies are needed.

*Reviewer’s comment:*

*The applicant conducted a thorough review of literature, and DPMH agrees with the applicant’s conclusion that oral DHA and EPA are not associated with adverse pregnancy outcomes.*

Pregnancy and Aluminum Toxicity

Although proposed Omegaven labeling<sup>20</sup> notes the potential for aluminum toxicity in preterm infants who are directly administered Omegaven, published literature notes that there is no clear evidence of reproductive toxicity with intravenous exposure to aluminum-containing products.<sup>21</sup> Since aluminum is processed renally, women with normal renal function should be able to metabolize aluminum.

***LACTATION***

Nonclinical Experience

Animal lactation studies were not performed.

Review of Pharmacovigilance Database

There are no reports of Omegaven use during lactation.

Applicant’s Review of Literature

The applicant performed a literature search in Medline and Embase to identify published literature with the use of Omegaven, DHA and EPA administered IV or as part of parenteral nutrition in lactating women. See the applicant’s submission for search parameters. The applicant identified 94 publications that discussed dietary DHA or EPA in pregnant or lactating women or their effect on fertility, but there was no published literature regarding the use of IV or parenteral administration of Omegaven, DHA or EPA in lactating women. The applicant reviewed several articles that described the use of oral DHA and EPA during lactation or in preterm infants and the critical role of DHA in brain development.<sup>22,23,24,25,26,27</sup>

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<sup>20</sup> Proposed Omegaven labeling. Warnings and Precautions, Aluminum Toxicity, 5.7, and Use in Specific Populations, Pediatric Use, 8.4.

<sup>21</sup> Krewski, et al. Human Health Risk Assessment for Aluminum, Aluminum Oxide, and Aluminum Hydroxide. J Toxicol Environ Health B Crit Review. 2007; 10 (Suppl 1): 1-269.

<sup>22</sup> Innis SM. Dietary omega 3 fatty acids and the developing brain. Brain Res. 2008;1237:35-43.

<sup>23</sup> Lapillonne A, Groh-Wargo S, Gonzalez CH, Uauy R. Lipid needs of preterm infants: updated recommendations. J Pediatr. 2013;162(3 Suppl):S37-47

The applicant concluded that there did not appear to be any adverse effects of DHA or EPA on the lactating infant.

#### DPMH Review of Literature:

DPMH conducted a search of *Medications in Mother's Milk*<sup>28</sup>, *Drugs in Pregnancy and Lactation*,<sup>5</sup> the Drugs and Lactation Database (LactMed),<sup>29</sup> Micromedex,<sup>4</sup> and of the published literature in PubMed using the search terms "Omegaven/omega-3 fatty acids/omega-6 fatty acids/omega-9 fatty acids/docosahexaenoic acid/ eicosapentaenoic acid/ intravenous fish oils/ intravenous docosahexaenoic acid/intravenous eicosapentaenoic acid" and "lactation," or "breast-feeding." There is no information regarding Omegaven or intravenous fish oils, intravenous docosahexaenoic acid or intravenous eicosapentaenoic acid and use during lactation. The following relevant published articles regarding oral fish oils, oral docosahexaenoic acid, and oral eicosapentaenoic acid and use during lactation were reviewed.

Micromedex<sup>4</sup> notes the following about oral omega-3 fatty acids and lactation:

"Human milk normally supplies the infant with adequate amounts of omega-3 fatty acids. Elevating the maternal intake of DHA can increase the amount of this compound in milk and in the infant...Cod liver oil supplementation (2.5-10 mL/day) in lactating women increased DHA concentration; EPA increased in groups that took 5 or 10 mL/day.... A study of Danish mothers supplemented with oral fish oil or olive oil during the first 4 months of lactation found a negative effect on offspring cognitive ability at 7 years of age as measured by processing speed, Stroop task, and a strength and difficulties questionnaire.

In the past, the omission of essential fatty acids in parenteral food supplements and infant formulas produced iatrogenic deficiencies. Standards have been adopted for the inclusion of minimum amounts of these agents in infant formulas, but an optimum ratio of omega-6 to omega-3 fatty acids has not been defined. Some data suggest that the ratios do not have significant effects on visual function and that elevating linolenic acid may slightly reduce infant growth. Concerns were expressed in 1993 about the adequacy of human infant formulas for supplying linolenic acid or DHA, particularly in preterm infants... A study

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<sup>24</sup> Baack ML, Puumala SE, Messier SE, Pritchett DK, Harris WS. What is the relationship between gestational age and docosahexaenoic acid (DHA) and arachidonic acid (ARA) levels? *Prostaglandins Leukot Essent Fatty Acids*. 2015;100:5-11.

<sup>25</sup> Bernhard W, Raith M, Koch V, Kunze R, Maas C, Abele H, Poets CF, Franz AR. Plasma phospholipids indicate impaired fatty acid homeostasis in preterm infants. *Eur J Nutr*. 2014;53(7):1533-47.

<sup>26</sup> Martinez M. Tissue levels of polyunsaturated fatty acids during early human development. *J Pediatr*. 1992;120(4 Pt 2):S129-38.

<sup>27</sup> Pawlik D, Lauterbach R, Walczak M, Hurkala J. Docosahexaenoic acid (DHA) concentration in very low birth weight newborns receiving a fish-oil based fat emulsion from the first day of life. Preliminary clinical observation. *Med Wieku Rozwoj*. 2011;15(3):312-7.

<sup>28</sup> Hale, Thomas (2016). *Medications and Mother's Milk*. Amarillo, Texas. Hale Publishing.

<sup>29</sup> <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

in full-term infants showed higher neurodevelopmental scores in 4-month-old infants after feeding a polyunsaturated fatty acid-supplemented formula compared to an unsupplemented formula; however, differences between the groups were no longer seen at 2 years of age. In a 2000 study, supplemental DHA was associated with elevation of scores in the Bayley Psychomotor Development Index but not the Mental Development Index at 30 months of age. A study in 17 women found that infants of mothers with high DHA plasma phospholipid concentrations, compared to infants of mothers with low DHA concentrations, had sleep patterns indicative of greater CNS maturity. Although DHA was associated with increased growth in premature infants, most studies failed to show an advantage for DHA supplementation of term infants. Milk effects are possible. Evidence suggests this drug may alter milk production or composition. If an alternative to this drug is not prescribed, monitor the infant for adverse effects and/or adequate milk intake.”

Omegaven is not referenced in *Medications in Mother’s Milk*; however, Dr. Hale<sup>30</sup>, a lactation expert, does reference oral EPA and DHA. Dr. Hale rates EPA and DHA as, “L-3- limited data-probably compatible.” Dr. Hale notes the following:

“Eicosapentaenoic acid is a polyunsaturated lipid commonly found in human milk. In one study, cod liver oil supplementation increased breastmilk composition of EPA by 0.15% and DHA by 0.36%. Another study suggested that infant serum EPA increased from 0.11% to 0.7% after breastfeeding women were given fish oil supplementation consisting of 3,092 mg/day of total omega-3 fatty acid...Research in humans has so far failed to provide strong evidence for or against the efficacy of DHA supplementation in pregnancy and lactation. It is not known whether omega-3-acid ethyl esters are excreted in human milk.... DHA is a common lipid in human milk... in varying levels depending on maternal diet; thus high dose supplementation could be hazardous.. The American Academy of Pediatrics recommends that breastfeeding women have an average of 200-300mg per day of omega-3 long chain polyunsaturated fatty acids (DHA).”

Oral supplementation with omega-3 fatty acids, including oral DHA and oral EPA, are referenced in *Drugs in Pregnancy and Lactation*,<sup>5</sup> and include a lactation recommendation of “compatible.” Briggs and Freeman note the following:

“DHA and EPA are present in breast milk. The infant need for DHA during breastfeeding is about 70-80 mg daily... Supplementation with omega-3 fatty acids results in increased levels in breastmilk... The U.S. Institute of Medicine and the Food and Nutrition Board have suggested an adequate intake of 1.3 grams/day [of omega-3 fatty acids] during lactation.”

LactMed<sup>8</sup> does not reference Omegaven but does provide information on oral marine oils and includes the following summary:

“DHA and EPA are normal components of breastmilk in which concentrations reflect maternal intake. The DHA level in breastmilk is typically between 0.2% and 0.3% in Western countries.<sup>31</sup> This is usually sufficient to meet the DHA requirements of term

<sup>30</sup> Hale, Thomas and Rowe, Hilary E. (2017). *Medications and Mother’s Milk*. NY, New York. Springer Publishing. pg. 493.

<sup>31</sup> Jackson KH, Harris WS. Should there be a target level of docosahexaenoic acid in breast milk? *Curr Opin Clin Nutr Metab Care*. 2016;19:92-6.

breastfed infants, but not the higher requirements of pre-term infants, where additional maternal supplementation is needed.<sup>32</sup> Maternal supplementation increases breastmilk levels of DHA and EPA.<sup>33</sup> Higher milk levels result in higher infant plasma and erythrocyte levels of omega-3 fatty acid-derived phospholipid....<sup>34</sup> Current dietary recommendations for nursing mothers is 250 to 375 mg daily of DHA plus EPA.<sup>35</sup> Lactating women require a daily dosage of about 1000 mg DHA plus EPA to reach a milk DHA plus EPA of 1 g/dL at 4 weeks postpartum....<sup>36</sup>

A meta-analysis of randomized, controlled trials on infant neurodevelopmental outcomes found that maternal supplementation with essential fatty acids during pregnancy and breastfeeding for the first 4 months postpartum did not improve the child's problem solving ability, intelligence, or psychomotor or motor development. Weak evidence for improved vision and attention was found in one study.<sup>37</sup> Two meta-analyses found that maternal supplementation with omega-3-polyunsaturated fatty acids during lactation had little or no beneficial effect on childhood allergic diseases.<sup>38,39</sup> Another meta-analysis using different selection criteria found that supplementation of the mother with omega-3-fatty acids during pregnancy and/or breastfeeding had no beneficial effect on visual acuity, growth or language development. Some aspects of motor, cardiovascular health, behavior and immunity were found to be differentially affected by supplementation, with the more desired effect occurring more often in breastfed infants than in formula-fed infants.<sup>40</sup> One subsequent study found fewer allergies in the breastfed infants of supplemented mothers, but could not distinguish between supplementation during pregnancy and during breastfeeding.<sup>41</sup> Long-term follow-up of a small group of children whose mothers received fish oil supplements during lactation found that boys had a delayed puberty, shorter average height, and higher systolic blood pressure at age 13

<sup>32</sup> Koletzko B. Should women providing milk to their preterm infants take docosahexaenoic acid supplements? *Clin Perinatol*. 2017;44:85-93

<sup>33</sup> Amaral YN, Marano D, Silva LM et al. Are there changes in the fatty acid profile of breast milk with supplementation of omega-3 sources? A systematic review. *Rev Bras Ginecol Obstet*. 2017;39:128-41.

<sup>34</sup> Meldrum SJ, D'Vaz N, Casadio Y et al. Determinants of DHA levels in early infancy: Differential effects of breast milk and direct fish oil supplementation. *Prostaglandins Leukot Essent Fatty Acids*. 2012;86:233-9.

<sup>35</sup> U.S. Department of Health and Human Services and U.S. Department of Agriculture. Dietary Guidelines for Americans 2015-2020. Eighth Edition. 2015. <https://health.gov/dietaryguidelines/2015/guidelines/>

<sup>36</sup> Stoutjesdijk E, Schaafsma A, Dijck-Brouwer DAJ et al. Fish oil supplemental dose needed to reach 1 g% DHA+EPA in mature milk. *Prostaglandins Leukot Essent Fatty Acids*. 2018;128:53-61.

<sup>37</sup> Delgado-Noguera MF, Calvache JA, Bonfill Cosp X et al. Supplementation with long chain polyunsaturated fatty acids (LCPUFA) to breastfeeding mothers for improving child growth and development. *Cochrane Database Syst Rev*. 2015;7:CD007901.

<sup>38</sup> Klemens C, Berman D, Mozurkewich E. The effect of perinatal omega-3 fatty acid supplementation on inflammatory markers and allergic diseases: A systematic review. *BJOG*. 2011;118:916-25.

<sup>39</sup> Gunaratne AW, Makrides M, Collins CT. Maternal prenatal and/or postnatal n-3 long chain polyunsaturated fatty acids (LCPUFA) supplementation for preventing allergies in early childhood. *Cochrane Database Syst Rev*. 2015;7:CD010085.

<sup>40</sup> Quin C, Erland BM, Loeppky JL et al. Omega-3 polyunsaturated fatty acid supplementation during the pre and post-natal period: A meta-analysis and systematic review of randomized and semi-randomized controlled trials. *J Nutr Intermediary Metab*. 2016;5:34-54.

<sup>41</sup> Warstedt K, Furuholm C, Falth-Magnusson K et al. High levels of omega-3 fatty acids in milk from omega-3 fatty acid supplemented mothers are related to less immunoglobulin E-associated disease in infancy. *Acta Paediatr*. 2016;105:1337-47.



years.<sup>42</sup> Another study found that maternal fish oil supplementation during pregnancy and lactation reduced oxidative stress in their breastfed infants.<sup>43</sup>

Fish oil up to 3 grams daily is ‘generally recognized as safe’ (GRAS) as a food by the U.S. Food and Drug Administration. The most common complaint is burping a fishy taste after ingestion. However, breast milk odor is not changed by maternal fish oil consumption.<sup>44,,</sup>

*Reviewer’s comment:*

*Based on the applicant and DPMH’s review of literature there is no information regarding exposure to Omegaven or to IV omega 3-fatty acids and effects on the breastfed infant. It does not appear that oral DHA and EPA are associated with adverse outcomes in the lactating infant. As noted above under Omegaven and Drug Characteristics, over a 24 hour period, a 50kg person treated with intravenous Omegaven would be expected to receive (b) (4) of EPA and (b) (4) grams of DHA. The amount of EPA and DHA present in a 24 hour dose would be higher than the amount present in oral omega-3 fatty acid supplementation and higher than the 1.3 grams of omega-3 fatty acids recommended by lactating women. It is unknown how much IV Omegaven, EPA and DHA would ultimately be taken in orally by the breastfed infant.*

Lactation and Aluminum

As noted above, Omegaven may contain up to 25 mcg/L of aluminum. According to LactMed<sup>8</sup>, “Additional intake of [aluminum] by a nursing mother is unlikely to surpass that found in other infant foods. In addition, oral absorption of aluminum... is poor.”

The Agency for Toxic Substance & Disease Registry (ATSDR) notes, “Aluminum is found in breast milk, but only a small amount of this aluminum will enter the infant’s body through breastfeeding.

*Reviewer comment:*

*There is no information regarding IV aluminum use during lactation. Since aluminum is poorly absorbed orally, even if a significant amount of aluminum was present in the breast milk, it would be unlikely that the breastfed infant would absorb significant amounts of aluminum.*

***FEMALES AND MALES OF REPRODUCTIVE POTENTIAL***

Nonclinical Experience

Animal fertility studies were not performed.

Applicant’s Review of Literature

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<sup>42</sup> Lauritzen L, Eriksen SE, Hjorth MF et al. Maternal fish oil supplementation during lactation is associated with reduced height at 13 years of age and higher blood pressure in boys only. Br J Nutr. 2016;116:2082-90.

<sup>43</sup> Kajarabille N, Hurtado JA, Pena-Quintana L et al. Omega-3 LCPUFA supplement: A nutritional strategy to prevent maternal and neonatal oxidative stress. Matern Child Nutr. 2017;13:e12300.

<sup>44</sup> Sandgruber S, Much D, Amann-Gassner U et al. Sensory and molecular characterisation of human milk odour profiles after maternal fish oil supplementation during pregnancy and breastfeeding. Food Chem. 2011;128:485-94.

The applicant performed a literature search in Medline and Embase to identify published literature with the use of Omegaven, DHA and EPA administered IV or as part of parenteral nutrition and fertility. See the applicant's submission for search parameters. The applicant identified 94 publications that discussed dietary DHA or EPA in pregnant or lactating women or their effect on fertility, but there was no published literature regarding the use of IV, parenteral or oral administration of Omegaven, DHA or EPA and effects on fertility.

#### DPMH Review of Literature:

DPMH conducted a review of Micromedex<sup>4</sup> and PubMed using the terms, "omega-3 fatty acids/omega-6 fatty acids/omega-9 fatty acids and fertility/contraception/oral contraceptives/infertility."

Studies have shown that increased levels of polyunsaturated fatty acids in women undergoing *in vitro* fertilization are associated with increased implantation and pregnancy rates.<sup>45,46</sup> Other studies have shown that infertile men had lower concentrations of omega-3 fatty acids in spermatozoa compared to fertile men<sup>47</sup> and that omega-3 fatty acids may be positively associated with testicular function.<sup>48</sup>

Micromedex notes the following about omega-3 fatty acids and fertility:

"Fertile men had higher sperm concentrations of omega-3 fatty acids than infertile men. Supplementation of these men with EPA and DHA at 1.84 g/day for 32 weeks increased sperm counts and nearly doubled sperm concentrations. It was suggested that a low DHA concentration in human sperm was a cause of poor sperm quality.

Higher serum concentrations of long-chain omega-3 polyunsaturated fatty acids were associated with higher probability of clinical pregnancy and live birth after assisted reproductive treatments. A prospective study at a different fertility center found no association between serum omega-3 fatty acids and *in vitro* fertilization outcomes."

## **DISCUSSION AND CONCLUSIONS**

### Pregnancy

There are no randomized, well-controlled trials on the use of omega-3 fatty acids, in particular EPA or DHA given IV as part of TPN therapy, in pregnant women. There are two reports of IV Omegaven used off-label in the first trimester but no reports of adverse pregnancy outcomes. There are no additional reports of IV Omegaven or IV omega-3 fatty acid use during pregnancy in published literature. The available data from published literature suggest that there are no identifiable adverse maternal or fetal outcomes with use of oral omega-3 fatty acids during pregnancy.

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<sup>45</sup> Jungheim, ES. Relationship between serum polyunsaturated fatty acids and pregnancy in women undergoing *in vitro* fertilization. J Clin Endocrinol Metab. 2013 Aug;98(8):E1364-8.

<sup>46</sup> Hammiche, et al. Increased preconception omega-3 polyunsaturated fatty acid intake improves embryo morphology. Fertil Steril. 2011 Apr;95(5):1820-3

<sup>47</sup> Safarinejad, M. Relationship of omega-3 and omega-6 fatty acids with semen characteristics, and anti-oxidant status of seminal plasma: a comparison between fertile and infertile men. Clin Nutr. 2010 Feb;29(1):100-5

<sup>48</sup> Minguez-Alarcon, et al. Fatty acid intake in relation to reproductive hormones and testicular volume among young healthy men. Asian J Androl. 2017 Mar-Apr; 19(2): 184–190.

### Lactation

Oral omega-3 fatty acids are present in human milk and are required by breast fed infants for normal growth and development. There have been no harmful effects seen in breastfed infants whose mothers are taking oral fish oil supplementation. Fish oils, including Omegaven, should be compatible with breastfeeding.

### Females and Males of Reproductive Potential

Omega-3 fatty acids appear to improve fertility. Therefore, DPMH recommends that subsection 8.3 not be included in labeling.

## **LABELING RECOMMENDATIONS**

DPMH revised sections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

### **DPMH Proposed Pregnancy and Lactation Labeling for Omegaven**

## **USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

#### Risk Summary

There are no available data on Omegaven use during 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 Omegaven.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

### **8.2 Lactation**

#### Risk Summary

No data are available regarding the presence of Omegaven in human milk, the effects on the breastfed infant, or the effects on milk production. Oral omega-3 fatty acids are present in human 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 or from the underlying maternal condition.

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/s/  
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MIRIAM C DINATALE  
05/03/2018

LYNNE P YAO  
05/03/2018

## Clinical Inspection Summary

<b>Date</b>	March 26, 2018
<b>From</b>	Susan Leibenhaut, M.D., OSI/DCCE/GCPAB Susan Thompson, M.D., Team Leader, OSI/DCCE/GCPAB Kassa Ayalew, M.D., M.P.H., Branch Chief, OSI/DCCE/GCPAB
<b>To</b>	Suna Seo, M.D., Medical Officer, DGIEP
<b>NDA #</b>	210589
<b>Applicant</b>	Fresenius Kabi, USA LLC
<b>Drug</b>	Omegaven
<b>NME</b>	Yes
<b>Division Classification</b>	LVP Lipid (lipid + products)
<b>Proposed Indication</b>	Source of calories and fatty acids in pediatric patients with parenteral nutrition associated cholestasis
<b>Consultation Request Date</b>	January 19, 2018
<b>Summary Goal Date</b>	April 1, 2018
<b>Action Goal Date</b>	August 1, 2018
<b>PDUFA Date</b>	August 1, 2018

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Inspections for this NDA were requested by the review division for two clinical investigator (CI) sites, Boston Children's Hospital (BCH) and Texas Children's Hospital (TCH), in addition to UCLA Mattel Children's Hospital, the site where only historical data were extracted. Because this is a new molecular entity (NME), OSI plans to inspect the applicant Fresenius Kabi (FK). Inspection of FK has not yet been conducted and an addendum to this Clinical Inspection Summary (CIS) will be entered DARRTS when the inspection report is available.

The data generated by the two clinical sites and at UCLA, a site of the extraction of the historical control data, are reliable. This data may be used in support of the application.

## II. BACKGROUND

The applicant Fresenius Kabi submitted this NDA for Omegaven® (Omega Fatty Acids) for the indication of a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis (PNAC) defined in this population as (direct bilirubin) DBil value  $\geq 2$  mg/dL. Omegaven® is currently approved in countries in Europe, Asia, and South America for parenteral nutrition supplementation with long-chain  $\omega 3$  fatty acids, especially DHA and EPA, when oral or enteral nutrition is impossible, insufficient, or contraindicated.

Drug: Omegaven® (Omega Fatty Acids)

Overview of the Studies (refer to “Explanation of the use of study data collected at the three sites” on the following page concerning active participants and extraction of historical data for use in each of the studies):

Study– Protocol number and title for all studies that were inspected

1. Protocol OMEG-034-IP3 entitled “Cholestasis Reversal: Efficacy of Intravenous Fish Oil”

Number of subjects:

- Analyzed for efficacy (Pair-Matched [PM] Population): 52 Omegaven-treated patients; 26 HC patients (14 from BCH; 6 from TCH; 6 from UCLA)
- Analyzed for safety (Safety Population): 128 Omegaven-treated patients; 59 HC patients (47 from BCH; 6 from TCH; 6 from UCLA)

Number of sites: one for active treatment (BCH), three provided historical controls

Number of countries where subjects were enrolled: U.S. only

Dates that study was conducted: September 2004 with data cutoff of June 2012

Efficacy endpoint: Changes over time in body weight adjusted for age.

2. Protocol OMEG-035-IP3 entitled, “Compassionate Use of an Intravenous Fat Emulsion Comprised of Fish Oil in the Treatment of Parenteral Nutrition Induced Liver Injury in Children”

Number of subjects:

- Analyzed for efficacy (Pair-Matched [PM] Population): 30 Omegaven-treated patients; 15 HC patients (4 from TCH, 6 from BCH, 5 from UCLA)
- Analyzed for safety (Safety Population): 61 Omegaven-treated patients; 26 HC patients (15 from TCH; 6 from BCH; 5 from UCLA)

Number of sites: one for active treatment (TCH), three provided historical controls

Number of countries where subjects were enrolled: U.S. only

Dates that study was conducted: September 2007 with data cutoff of June 2012

Efficacy endpoint: Changes over time in body weight adjusted for age.

**Explanation of the use of study data collected at the three sites:**

For this application, test article was administered at two sites, Boston Children's Hospital (BCH) under IND 73488 and Texas Children's Hospital (TCH) under IND 102843. Historical control data was extracted at three sites, BCH, TCH, and UCLA Mattel Children's Hospital. Clinical investigators (CI) at BCH and TCH opened sponsor-investigator INDs with the FDA in order to administer this product to their patients. At that time, the product was approved in Europe for use in adults. The protocols submitted by the sponsor investigators to their respective INDs are similar. Any differences in the protocols are a result of the individual institutions' templates for IRB submission, the institutional requirements for subject protection, outpatient supervision and other administrative issues as well as the state of the collaboration at the two institutions at which test product was administered.

When Fresenius Kabi, the license holder of the marketing application for this product in Europe, decided to use data from these studies in support of a marketing application to the FDA, it was agreed that historical controls would be drawn from patients at these sites and also from UCLA Mattel Children's Hospital. No test article was administered at UCLA. Protocol OMEG-034-IP3 analyzed data from subjects that were administered test article at BCH and their respective matched historical controls from all three institutions. Protocol OMEG-035-IP3 analyzed data from subjects that were administered test article at TCH and their respective matched historical controls from all three institutions. Representatives of the applicant retrospectively extracted data from the records and entered the data into case report forms that were transmitted to the sponsor for analysis. The following are the definitions of the three analysis populations:

- The analysis population for efficacy:

Patients treated with Omegaven at the clinical site and the pair matches with historical controls (HC) from BCH, TCH, or UCLA. Pair matches were matched 2:1, active: control based on a computer algorithm.

- The analysis population for safety population:

All patients who received Omegaven and all Historical Control patients from Boston Children's Hospital, as well as all HC patients from Texas Children's Hospital and the University of California Los Angeles (Mattel Children's Hospital) who could be matched to Omegaven-treated patients at Boston Children's Hospital.

**III. RESULTS (by site):**

Name and Type of Inspected Entity/Address	Protocol # / # of Subjects (safety population/matched)	Inspection Dates	Classification
CI: Dr. Mark Puder, M.D. Boston Children's Hospital 300 Longwood Ave. Boston, MA 02115	OMEG-034-IP3 Active: 128/52 Historical: 47/14 <sup>+</sup>  OMEG-035-IP3 Historical: 6/6	February 14 to 22, 2018	*NAI
CI: Dr. Muralidhar H. Premkumar Texas Children's Hospital 6621 Fannin St., W6104 Houston, TX 77030	OMEG-034-IP3 Historical: 6/6  OMEG-035-IP3 Active: 61/30 Historical: 15/4 <sup>^</sup>	February 6 to 9, 2018	*NAI
CI: Dr. Kara L. Calkins UCLA Mattel Children's Hospital 10833 Le Conte, Room B2375 Los Angeles, CA 90095	OMEG-034-IP3 Historical: 6/6  OMEG-035-IP3 Historical: 5/5  Met eligibility but not matched: 7	March 1 to 8, 2018	*NAI
Sponsor: Fresenius Kabi Archive, Borkenberg 14, 61440 Oberursel (Taunus), Germany	OMEG-034-IP3  OMEG-035-IP3	Pending April 23 to 27, 2018	Pending

Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

\*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

<sup>+</sup>Additional historical controls are from TCH and UCLA<sup>^</sup> Additional historical controls are from BCH and UCLA



## 1. Dr. Mark Puder

Boston Children's Hospital, 300 Longwood Ave., Boston, MA 02115

Note: Observations below for this clinical investigator (CI) inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

At this site, 198 records were screened for both active and controls. Of the patients that received Omegaven, 52 subjects were matched 2:1 to historical controls. Of the 26 historical controls that were matched in this study, 14 were from BCH, 6 were from TCH, and 6 were from UCLA. This site also contributed 6 of the 15 matched historical controls for Study OMEG-035-IP3. The review division chose a list of 30 records that were a sample of active treatment and historical controls that were in each of the analysis groups for the FDA investigator to review. The FDA investigator performed a detailed review of the thirty charts. This included review of inclusion/exclusion criteria, demographics, medical history, laboratory test results, liver function tests, evolution of direct bilirubin, administration of comparator product (Intralipid), development and growth of subjects, outcome of assessments and tests, information on liver transplants and deaths, concomitant medications, primary and secondary efficacy endpoints and adverse events.

The data from the active patients and the historical controls appear to have been collected adequately at this site and the data generated by this site may be used in support of the respective indication.

## 2. Dr. Muralidhar H. Premkumar

Texas Children's Hospital, 6621 Fannin St., Houston, TX 77030

Note: Observations below for this CI inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final Establishment Inspection Report (EIR).

At this site, a total of 89 subject records were evaluated for the analyses, 61 active and 28 historical controls. Of the patients that received Omegaven, 30 subjects were matched 2:1 to historical controls. Of the 15 historical controls that were matched in Study OMEG-035-IP3, 4 were from TCH; 6 were from BCH and 5 were from UCLA. This site also contributed 6 of the 26 matched historical controls for Study OMEG-034-IP3. The review division chose a list of 21 records that were a sample of active treatment and historical controls that were in each of the analysis groups for the FDA investigator to review. The FDA investigator performed a detailed review of the 21 charts and an additional review of 15 additional charts. This included review of inclusion/exclusion criteria, demographics, medical history, laboratory test results, liver function tests, evolution of direct bilirubin, administration of historical control

product, development and growth of subjects, outcome of assessments and tests, information on liver transplants and deaths, concomitant medications, primary and secondary efficacy endpoints, and adverse events.

The data from the active patients and the historical controls appear to have been collected adequately at this site and the data generated by this site may be used in support of the respective indication

3. Dr. Kara L. Calkins

UCLA Mattel Children's Hospital, 10833 Le Conte, Los Angeles, CA 90095

Note: Observations below for this clinical investigator (CI) inspection are based on communications with the FDA field investigator. An inspection summary addendum will be issued if conclusions change upon review of the final (EIR).

At this site, 67 subjects were screened and 18 subjects were considered eligible to be used in the computer algorithm for matched pairing with subjects from either study. A total of 11 records were pair matched, 6 with subjects from Boston for the OMEG-034-IP3 study and 5 with subjects at Texas Children's Hospital for the OMEG-035-IP3 study. Seven records were not matched. The FDA investigator performed a detailed review of all 11 matched clinical research charts and a review of the 7 unmatched clinical research charts. This included review of inclusion/exclusion criteria, demographics, medical history, laboratory test results, liver function tests, evolution of direct bilirubin, administration of comparator product (Intralipid), development and growth of subjects, outcome of assessments and tests, information on liver transplants and deaths, concomitant medications, primary and secondary efficacy endpoints, and adverse events.

The data from the source documents of the historical controls appear to have been collected adequately at this site and the data generated by this site may be used in support of the respective indication.

4. Fresenius Kabi

Borkenberg 14, Germany

This inspection is planned for April 23 to 27, 2018. An addendum to this report will be submitted when the report is available.

{See appended electronic signature page}

Susan Leibenhaut, M.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

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OSI/DCCE/GCP Reviewer/ Susan Leibenhaut  
OSI/ GCP Program Analysts/ Joseph Peacock/Yolanda Patague  
OSI/Database PM/Dana Walters

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/s/  
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SUSAN LEIBENHAUT  
03/26/2018

SUSAN D THOMPSON  
03/26/2018