DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 210589

NDA APPROVAL

Fresenius Kabi USA LLC
Attention: Aparna Dagar, Ph.D., RAC
Director, Regulatory Affairs
3 Corporate Drive
Lake Zurick, IL 60047

Dear Dr. Dagar:

Please refer to your New Drug Application (NDA) dated and received December 1, 2017, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Omegaven (fish oil triglycerides) injectable emulsion.

We also refer to our approval letter dated July 27, 2018, and the attached Prescribing Information which did not contain the following (underline):

2 DOSAGE AND ADMINISTRATION

2.2 Admixing Instructions

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

This replacement approval letter incorporates the correction of the error. The effective approval date will remain July 27, 2018, the date of the original approval letter.

This new drug application provides for the use of Omegaven (fish oil triglycerides) injectable emulsion indicated as a source of calories and fatty acids in pediatric patients with parenteral nutrition-associated cholestasis.

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

<u>CONTENT OF LABELING</u>

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL*

Standard for Content of Labeling Technical Qs and As, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3).* For administrative purposes, designate this submission "**Final Printed Carton and Container Labels for approved NDA 210589**." Approval of this submission by FDA is not required before the labeling is used.

ADVISORY COMMITTEE

Your application for Omegaven was not referred to an FDA advisory committee because outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of essential fatty acid deficiency or EFAD (serious bleeding events, neurological developmental delay), or life-threatening pleural and pericardial effusions related to the use of Omegaven (fish oil triglycerides) injectable emulsion, for intravenous use.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3445-1 A prospective, longitudinal cohort study with an external control to assess the long-term safety (defined as patient monitoring for ≥ 1 year of continuous treatment) of Omegaven (fish oil triglycerides) injectable emulsion, for intravenous use in pediatric patients with PNAC, evaluating the potential for essential fatty acid deficiency (EFAD) by measuring:
1. long-chain polyunsaturated fatty acid (LCPUFA) profiles with prespecified thresholds to assess EFAD during Omegaven infusion and at 4 weeks after discontinuation of Omegaven, and
2. the occurrence of serious bleeding events during Omegaven infusion and at 4 weeks after discontinuation of Omegaven, and
3. neurodevelopmental delays assessed later in life to include at least the baseline Bayley assessments at 6 months, 12 months and 2 years; and age appropriate assessment at 5 years of age.

In addition, life-threatening pleural and pericardial effusions will also be reported during Omegaven infusion and 4 weeks after discontinuation of Omegaven. Clinical narratives will be assessed to determine whether the pleural/pericardial effusions are clinically related to the infusions.

The timetable you submitted on July 26, 2018 (eCTD SN 0038) states that you will conduct this study according to the following schedule:

Draft Protocol Submission: 05/2019
Final Protocol Submission: 11/2019
Interim Report #1: 12/2021
Interim Report #2: 12/2022
Interim Report #3: 12/2024
Study Completion: 07/2026
Final Report: 06/2027

3445-2 A study to show that the levels of the elemental impurities, (b) (4) are controlled in Omegaven (fish oil triglycerides) injectable emulsion, for intravenous use.

This study should include a risk assessment and screening of the finished product for the elemental impurities as stated above including analysis of at least three batches of the product. Develop and validate a detailed rationale for the calculation of control thresholds and acceptance criteria for all elements stated

above, with consideration of the amount of each element that may be intentionally added to TPN.

The timetable you submitted on July 24, 2018 (eCTD SN 0037) states that you will conduct this study according to the following schedule:

Interim Report Submission: 12/2018
Final Report Submission: 06/2019

Submit clinical protocol(s) to your IND 114141 with a cross-reference letter to this NDA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your NDA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate:
Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).

Submission of the protocol(s) for required postmarketing observational studies to your IND is for purposes of administrative tracking only. These studies do not constitute clinical investigations pursuant to 21 CFR 312.3(b) and therefore are not subject to the IND requirements under 21 CFR part 312 or FDA's regulations under 21 CFR parts 50 (Protection of Human Subjects) and 56 (Institutional Review Boards).

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 314.81(b)(2)(vii) requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 314.81(b)(2)(vii) to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 314.81(b)(2)(vii). We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the prescribing information, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the prescribing information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

We request that for a period of 2 years from the U.S. approval date, you submit all cases of serious hemorrhage, pleural effusion, pericardial effusion, and fat overload syndrome reported with Omegaven (fish oil triglycerides) injectable emulsion, for intravenous use, as 15-day Alert reports (as described under 21 CFR 314.80(c)(1)), and that you provide detailed analyses of events of serious hemorrhage, pleural effusion, pericardial effusion, and fat overload syndrome reported from clinical study and post-marketing reports in your periodic safety report (i.e., the Periodic Adverse Drug Experience Report [PADER] required under 21 CFR 314.80(c)(2) or the ICH E2C Periodic Benefit-Risk Evaluation Report [PBRER] format). These analyses should show cumulative data relative to the date of approval of Omegaven (fish oil triglycerides) injectable emulsion, for intravenous use, as well as relative to prior periodic safety reports. Medical literature reviews for case reports/case series of serious hemorrhage, pleural effusion, pericardial effusion, and fat overload syndrome reported with Omegaven (fish oil triglycerides) injectable emulsion, for intravenous use, should also be provided in the periodic safety report.

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call CAPT Mimi Phan, Regulatory Project Manager, at (301) 796-5408.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JULIE G BEITZ
07/27/2018