Omegaven

Intermediate Size Patient Population IND Packet

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A. Omegaven Background

Omegaven 10% Emulsion is a fish oil emulsion administered intravenously in patients who require parenteral nutrition lipid supplementation and cannot tolerate available lipid emulsions. Omegaven is not approved for marketing in the United States but is approved in Germany. Fresenius Kabi, the manufacturer, has been supplying it for expanded access in the United States. Physicians interested in obtaining expanded access for Omegaven must submit an investigational new drug application (IND). An IND is a request for FDA authorization to administer an investigational new drug (e.g., Omegaven) to humans. Such authorization would allow the importation, interstate shipment, and administration of the drug even though it is not approved for sale in the U.S.

B. Obtaining an IND

FDA currently allows patients to receive Omegaven through the Expanded Access to Investigational Drugs program which facilitates availability of investigational drugs (such as Omegaven) to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

To help facilitate the IND process, FDA has developed this packet, which includes instructions, templates, checklists, a protocol outlining the treatment plan, and summary of regulatory requirements. As sponsors of an active IND, physicians can prescribe Omegaven to qualifying patients.

C. Application Process

A physician may open an IND for a single patient or for multiple patients. For those physicians treating only one patient, please download the Omegaven Single Patient Packet from our website. Physicians anticipating treatment of more than one patient in one year are advised to submit an Intermediate Size Patient Population (multi-patient) IND. Multi-patient INDs allow for consolidated reporting and reduced administrative paperwork in the long-run.

Application Checklist:

- Cover letter (see Appendix 1)
- Form 1571 (see Appendix 2)
- Form 1572 (see Appendix 2)
- Clinical Protocol (see Section H)
- Copy of the Informed Consent document planned for use (see Section G)

Mailing Address:

Food and Drug Administration

Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
Central Document Room
5901B Ammendale Road
Beltsville, MD 20705-1266

Upon receipt of the IND by FDA, an IND number will be assigned, and the application will be forwarded to the Division of Gastroenterology and Inborn Errors Products (DGIEP). **It is imperative that you are available during our review of your application in the event that we have questions. Unresolved issues may lead to a clinical hold.** The reviewing division will send an acknowledgement letter to you (the Sponsor-Investigator) providing notification of the IND number assigned, contact information for the FDA Division and regulatory project manager, and reporting requirements. Normally, you cannot initiate any studies (i.e., administer the investigational drug) until 30 days after the date FDA receives the IND. However, the acknowledgement letter usually contains language notifying you that studies may begin upon receipt of the letter.

Secure Email
Secure email between FDA and sponsors is useful for informal communications when confidential information may be included in the message (e.g., confidential patient information). Parties who would like to establish secure email with FDA should email a request to SecureEmail@fda.hhs.gov.

D. Regulatory Responsibilities as a Sponsor

Your ongoing responsibilities as the Sponsor-Investigator of an IND include:

- Obtaining informed consent of patients to be treated under the IND
- Monitoring patients treated under the IND
- Maintaining control of and keeping records on the drug dispensed under the IND
- Notifying FDA of any changes made to the IND (e.g., changes to the protocol, a change in drug supplier)
- Reporting to FDA serious, fatal, and/or life-threatening adverse events that are associated with use of the drug (see Attachment C)
- Submitting an annual report to the IND (see Attachment C) within 60 days of the anniversary date you are permitted to initiate studies (i.e., begin administering the investigational drug), which is usually 30 days after FDA receives the application.
- Regularly visiting the FDA Website for important updates to this packet, e.g., regarding drug interactions or protocol changes.

E. Ordering Omegaven

You may begin arranging a supply of Omegaven prior to requesting an IND from the FDA. Once you are granted an IND number, you would provide it to your supplier and they will ship Omegaven to you or an infusion pharmacy if you have this type of

arrangement. Pharmacy International in Hamburg, Germany currently supplies Omegaven (email: wholesale@pharmacy-international.de).

F. Financial Responsibility

U.S. regulations prohibit charging a patient for an investigational drug unless FDA gives authorization to do so (see 21 CFR 312.8). **A request to charge must be made if the sponsor or pharmacy plan to charge the patient or health insurance provider for the cost of the drug.** In this case, cost recovery would extend only to the cost of the drug and associated shipping costs. Commercialization of an investigational drug is prohibited.

Sponsors can request to charge in the IND application by checking **Charge Request** in box # 12 of the 1571 and by checking the box next to appropriate box in the cover letter provided in this packet. The FDA will respond in writing with the authorization to charge as part of the Acknowledgement letter for the IND. Note that under 21 CFR 312.8, the price charged may not be larger than necessary to recover direct costs; and that under 21 CFR 312.8, authorization to charge for an investigational drug may be withdrawn by FDA if we find that the conditions underlying the authorization are no longer satisfied.

G. Human Protection

Contacting your IRB

An Institutional Review Board (IRB) is a group formally designated by an institution to review, approve the initiation of, and conduct periodic review of biomedical research involving human subjects. The primary purpose of IRB review is to assure that the rights and welfare of human subjects are protected, and to determine that informed consent is obtained in accordance with and to the extent required by Federal requirements.

Under the IND regulations (21 CFR 312), you must ensure that an IRB that complies with FDA regulations (21 CFR 56) will be responsible for the initial and continuing review and approval of the proposed clinical protocol. You must also assure that you will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects and that you will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

You must provide the name and address of the IRB that will be responsible for the review of your proposed clinical protocol on form FDA 1572 "Statement of Investigator." If using the form FDA 3926, the Certification statement in box #11 contains this information.

Many institutions have their own IRB to oversee human subjects research conducted within the institution or by its staff. If you do not have access to a local IRB, an

independent IRB may be used. The Department of Health & Human Services' Office for Human Research Protections maintains a database of registered IRBs. Go to http://ohrp.cit.nih.gov/search/irbsearch.aspx?styp=bsc and click on "Advanced Search." Enter your state to find registered IRBs in your area.

For questions about locating an IRB, you may email FDA's Office of Scientific Investigations at CDER-OSI-GCPReferrals@fda.hhs.gov, or contact Quynh-Van Tran at 301-796-0185.

Informed Consent Documents
Your IRB may have an Informed Consent Document that they prefer you use. When creating an Informed Consent, please consult the elements of informed consent: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25

In the content of your Informed Consent Document, you must at a minimum address the following risks in addition to ensuring that all requirements of 21 CFR 50 are met: the risk of bleeding, hypertriglyceridemia, allergic reactions and additional unknown risks from the use of Omegaven.

H. Protocol

1. INTRODUCTION

TITLE: Intermediate Size Patient Population IND for Omega-3 lipid emulsion (Omegaven™ parenteral infusion) for providing parenteral nutritional (PN) support to patients with Parenteral Nutrition Associated Cholestasis (PNAC).

PROTOCOL SYNOPSIS:
[Sponsor to summarize]

[Sponsor to provide background on PNAC and a rationale for the use of Omegaven]

2. STUDY OBJECTIVES

Primary Objective
To assess the safety of Omegaven™ as a source of lipids in PN-dependent patients who have developed PNAC while on standard soybean-based lipid emulsions.

Secondary Objectives
- characterize the changes in liver biochemical enzymes relative to baseline
- characterize progression or reversal of cholestasis associated with use of Omegaven in pediatric patients with PNAC/PNAC

- evaluate if Omegaven has an impact on age-specific morbidities (e.g., bronchopulmonary dysplasia, retinopathy of prematurity etc.) and mortality in pediatric patients with PNAC
- characterize if there is an impact on liver transplantation (combined liver and intestinal or multivisceral transplant) when Omegaven™ is used in pediatric patients with PNAC
- characterize PN-related morbidities (e.g., infection rate), short-term and long-term effects on growth in children and weight in adults), and essential fatty acid deficiency associated with use of Omegaven™ in patients with PNAC

3. INVESTIGATIONAL PLAN

Overall Study Design

This is a prospective, non-randomized, open-label study of PN-dependent patients who have developed PNAC. PNAC is defined as serum direct bilirubin ≥2 mg/dL, that occurs in the absence of sepsis, after ≥14 days of exposure to standard intravenous lipid emulsions. Expected enrollment is XX patients (investigator to fill in) per year. Enrollment is for XX years (Investigator to fill in).

Rationale

The rationale for this study is to:

- collect consistent safety data in patients with PNAC on Omegaven
- collect natural history of PNAC clinical course in patients on Omegaven
- understand better the potential role of Omegaven in the treatment of patients with PNAC

4. STUDY POPULATION

This cohort is comprised of PN-dependent patients with PNAC, who have failed standard/conventional therapy, and meet the following inclusion and none of the exclusion criteria (below).

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Patients must have a diagnosis of PNAC defined as a conjugated or direct bilirubin of ≥2 mg/dL on the last two consecutive measurements at least 2 weeks apart (provide the most recent values).
- Patients with intestinal failure must have a conjugated or direct bilirubin of ≥2 mg/dL on the last two consecutive measurements at least 48 hours apart in absence of absence of sepsis (provide the most recent values))

In addition, all patients:

- Must be PN-dependent (unable to meet nutritional needs by enteral nutrition)
- Must have failed therapies to prevent progression of PNAC (e.g., cyclic PN/Intralipids, reduction/removal of copper and manganese from PN, advancement of enteral feeding, use of ursodiol (i.e. Actigall))
- Must have a signed informed consent

Exclusion Criteria (patient meets none of the following criteria)

- Abnormal liver enzymes (serum AST, ALT, T. bili, D. bili, Alk Phos, gamma-GTP) that can be attributed to non-PNAC liver disease (e.g. cystic fibrosis, biliary atresia, alpha 1 anti-trypsin deficiency, manganese toxicity, biliary obstruction)
- Sepsis
- Known allergy to eggs and/or shellfish
- Drug toxicity leading to liver injury
- Evidence of viral hepatitis (hepatitis B, C, EBV, CMV) which may cause elevation of liver enzymes
- Hemorrhagic disorder with active bleeding, and unexplained bleeding
- Preterm infants <2 weeks of age (high risk of intra-ventricular hemorrhage)
- Concomitant medications or conditions that, in the opinion of the investigator, would preclude participation in a trial of an experimental drug

5. TREATMENT

Identification of Investigational Product/Description of Investigational Product
The intravenous formulation of the investigational product is provided as a white, homogenous emulsion that contains highly refined fish oil.

Dose and Administration of Investigational Product
Prior to study initiation, clinical staff and patient/family will complete orientation and training.

Infants and children: 0.5 -1 g/kg/day (expressed in grams of the fish oil component) infused over 12-24 hours. Omegaven can be infused intravenously through a central or peripheral venous catheter, or piggy-backed with other compatible parenteral nutrition products. If tolerated, the dose may be increased not to exceed 2.5 g/kg/day.

Adults: Omegaven can be administered 0.1 g/kg/day up to 2 g/kg/day .
If additional parenteral calories from lipids to supplement Omegaven are needed to satisfy nutritional requirements in pediatric and adult subjects, another source of lipids may be administered.

Dose Adjustment

If hypertriglyceridemia[1] (200 – 400 mg/dL) develops, the following actions will be taken if considered clinically appropriate:

- Repeat the serum triglyceride levels 4 hours after discontinuing the Omegaven (triglyceride levels drawn while the patient is on a continuous 24-hour infusion of Omegaven, may lead to falsely high TGA).
- Omegaven infusion duration should be shortened and the dose should be reduced by 25%.
    - If the triglycerides levels do not improve or normalize, Omegaven should be discontinued.
- If there are other known causes of lipid intolerance, such as sepsis or renal disease that may affect fatty acid clearance, consider reducing or discontinuing Omegaven until resolution of the intercurrent illness.

Product Discontinuation

Omegaven Discontinuation

Omegaven will be permanently discontinued for any of the following reasons:

- patient or patient's guardian request withdrawal from the study
- withdrawal of consent/assent
- severe bleeding from any cause
- severe and persistent hypertriglyceridemia[2]
- anaphylaxis associated with use of Omegaven
- investigator or sponsor deems that it is not in the patient's best interest to continue Omegaven
- noncompliance with study procedures, which investigator or sponsor feels might jeopardize the patient's safety
- imminent organ transplant, i.e., liver, intestinal or both

Drug Accountability

Investigational products are to be dispensed only for those patients formally entered into the study. The actual dosing time of the investigational product is to be properly documented in the hospital medication administration record. At the end of the study, these records should be used to account for all the investigational product.

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[1] Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, Grunberger G, Guerin CK, Bell DSH, Mechanick JI, Pessah-Pollack R, Wyne K, Smith D, Brinton EA, Fazio S, Davidson M, Zangeneh F, Bush MA. American Association of Clinical Endocrinologist and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular diseases. Endocr Pract. 2017 Apr 2;23(4):479-497.

[2] In this protocol, the triglyceride level for a diagnosis of hypertriglyceridemia is based on clinical judgment and varies with gestational age, age, diagnosis, concomitant medications, and other factors.

Storage
Investigational product is to be shipped to and stored in the hospital pharmacy, and the pharmacist or designee should keep detailed disposition records of all investigational product.

6. Informed Consent Document (ICD)

Prior to initiating the study, the institutional IRB must have allowed the study to proceed. Once it has been decided that the patient qualifies for enrollment, informed consent will be obtained prior to starting Omegaven™. Your IRB may have an ICD that they prefer you use. When creating an Informed Consent, please consult the elements of informed consent:
http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.25
The ICD should adequately address the potential risks associated with Omegaven and should specifically communicate the following, which are not inclusive: the risk of bleeding, hypertriglyceridemia, hypersensitivity reactions (difficulty breathing, high or low blood pressure, hives, or rash, etc.) and additional unknown risks from the use of Omegaven. Please refer to the available product information for Omegaven for a full listing of possible adverse reactions.

7. Study Procedures

It is preferred that initiation of therapy takes place in a hospital setting, especially in pediatric patients. Patients may be transitioned to outpatient treatment with the following recommended monitoring:

Table 1 Schedule of Assessment

Parameter	Baseline	Initiation	Critical Illness (Inpatient)	Stable Inpatient	Stable at Home
CBC with differential	✓		Weekly	Weekly	Every other week for 1-3 months then every month and then as needed
Serum chemistries (Na, K, Cl, CO2 , serum urea nitrogen, creatinine, ionized calcium, magnesium, phosphorus, serum glucose)	✓	Daily for 3 consecutive days	Daily	1-2 times per week	Every other week for 1-3 months then every month and then as needed

ALT, AST, ALP, total bilirubin	✓	Day 1	Weekly	Monthly	Every other week for 1-3 months then every month and then as needed
Serum triglycerides	✓	Day 1	Weekly	Weekly	Every other week for 1–3 months, then monthly, therapy >6 months every 6–12 months
PT/INR	✓	Day 1	Weekly	As needed[3]	As needed[3]
Capillary glucose[4]	✓	As needed	Every 1-6 hours	As needed	When ill or at risk of glucose intolerance
Weight	✓	Daily	Daily	2-3 times per week	Daily, same time and same scale until fluid status stable, then weekly to monthly
Vital signs	✓	As needed	As needed	2-3 times a day	Daily
Catheter site inspection	✓	Daily	Daily	Daily	Daily
Fat soluble vitamin levels	✓	As needed	As needed	Every 2-3 months	Every 2-3 months
Trace elements (copper, manganese, chromium, zinc, selenium, iron)			Every 2-3 months or sooner if patient is symptomatic		
Essential Fatty Acids (linoleic			Every 2-3 months or sooner if patient is symptomatic		

[3] Monitor closely in the event of worsening of liver enzymes

[4] Monitoring frequency may be adjusted or discontinued based on antidiabetic medication use and glycemic target achievement

acid and α-linolenic acid)			
Vitamins (Folate, Vitamin B12)			Every 2-3 months or sooner if patient is symptomatic
Fat soluble vitamins (A, D, E and PT/INR)			Every 2-3 months or sooner if patient is symptomatic

Source: http://ncp.sagepub.com/content/early/2016/07/20/0884533616657650.full.pdf+html

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBC, complete blood count; Cl, chloride; CO2 , bicarbonate or total carbon dioxide; INR, international normalized ratio; K, potassium; Na, sodium; PT, prothrombin time.

Growth Assessments and Laboratory Tests: The schedule of laboratory tests and growth assessments appears in Table 2. The Baseline visit is the visit closest to but prior to initiation of Omegaven. Repeat measurements should be collected 30 days after discontinuation of Omegaven.

Table 2 Scheduled Study Procedures for infants and children*

Parameter	Baseline	Initiation	Critical illness	Stable Inpatient	Stable at Home
Length/Height	✓	✓	Weekly	Once every 2 weeks	Monthly
Weight	✓	✓	Weekly	Once every 2 weeks	Monthly
Head circumference (when applicable)	✓	✓	Weekly	Once every 2 weeks	Monthly

*Frequency of assessments in children should be adjusted as age appropriate.

Due to the need to obtain data on the safety profile of Omegaven™, which is currently not approved in the United States, additional laboratory blood tests (research blood draws) beyond those required for PN administration will be obtained under this protocol (e.g., free fatty acids and coagulation tests (PT/PTT, INR, fibrinogen)).

Caretakers and home health care providers of infants who will be transitioned to receive outpatient Omegaven infusions must be educated to recognize AEs that may occur with Omegaven (e.g., bleeding, bruising), and instructed when to contact the investigator. Besides recording of AEs, safety monitoring will include routine monitoring of vital signs, laboratory data and physical exam.

8. SAFETY ASSESSMENT

Safety assessment will be performed for the duration of this study and for at least 30 days following discontinuation of Omegaven™. Investigators will be responsible for identification and documentation of adverse drug experiences.

Definitions of Adverse Event and Serious Adverse Event

Definition of Adverse Event (AE) An adverse event is any untoward medical occurrence (any unfavorable or unintended sign, symptom, disease, or test result) in a patient, which is temporally associated with the use of Omegaven™, whether or not considered related to Omegaven™.

All AEs, regardless of seriousness or relationship to Omegaven, will be recorded on an AE Case Report Form (CRF). All adverse events should be categorized by seriousness and severity.

Definition of Serious Adverse Event (SAE) A serious adverse event is any untoward medical occurrence that, at any dose, results in any of the following outcomes[5]:

a) death
b) a life-threatening adverse drug experience
c) inpatient hospitalization or prolongation of existing hospitalization
d) persistent or significant disability/incapacity
e) a congenital anomaly/birth defect

Abnormal laboratory findings (e.g., clinical chemistry, hematology) or other abnormal assessments (e.g., abdominal ultrasound, vital signs) that are judged by the investigator as clinically significant should be recorded as AEs or SAEs if they met the definition of an AE or SAE (see above).

Recording, Evaluation, and Reporting of Adverse Events and Serious Adverse Events

Recording of Adverse Events

All adverse events during the study (Baseline to End-of-Study) will be recorded for each patient on a CRF[6]. A good faith effort will be made to complete the AE CRF in its entirety and until no more information is reasonably available or possible to obtain about the AE. For all adverse events, dates and times of onset and resolution will be recorded on the AE CRF as well as patient ID information in addition to the evaluations below.

Evaluation of Adverse Events

Seriousness See definitions. The seriousness of the AE will be recorded on the AE CRF.

Severity In addition to seriousness, each AE will be rated by the investigator as to its severity (mild, moderate, or severe) based on clinical judgment. The severity of the AE will be recorded on the AE CRF.

[5] Reference: 21 CFR 312.32

[6] See: https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

Relationship of AE to Omegaven Each AE will be evaluated by the investigator on its relationship to Omegaven as:

- Unlikely: The investigator makes a judgment that the AE bears little or no relationship to Omegaven
- Possible: The investigator makes a judgment that the AE can reasonably be attributed to other factors as well as Omegaven
- Probable: The investigator makes a judgment that the AE is more likely related to Omegaven than any other factors

The relationship to Omegaven will be recorded on the AE CRF.

Resolution Status The resolution status of all AEs will be recorded as 'resolved' or 'not resolved'. The resolution status on the AE CRF will be completed when it becomes known that:

- the AE is resolved
- the AE is permanent
- it is end-of-study
- a time point has been reached in the study when it is clear that no more information will be available to assess resolution

Actions Taken Any actions taken to resolve the AE (e.g., transfusion) will be recorded on the AE CRF. These actions can include discontinuation of Omegaven, withdrawal from study, initiation of other treatments, antibiotics, surgery, dialysis, and/or other treatments.

Outpatients For outpatients on Omegaven, patients and/or their caretakers/parents will be queried at each clinic follow-up visit about intercurrent illness or healthcare provider contact since the last visit. This information will be used to decide if any previously unknown AEs occurred. If so, they will be reported on AE CRFs (one CRF per AE).

Reporting of Adverse Events (Expedited Reporting)

All adverse events will be reported in the 60-day and annual reports (see Attachment C). Some AEs (fatal, life-threatening, and both serious and unexpected) will require expedited reporting. You are responsible for reporting any unexpected fatal or life-threatening suspected adverse reactions to this Division no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)]. You are also responsible for reporting any (1) serious, unexpected suspected adverse reactions, (2) findings from other clinical, animal, or in-vitro studies that suggest significant human risk, and (3) a clinically important increase in the rate of a serious suspected adverse reaction to this Division and to all investigators no later than 15 calendar days after determining that the information qualifies for reporting [21 CFR 312.32(c)(1)].

Withdrawal from Study

A patient will be withdrawn from the study if he/she meets any of the following criteria:

- lost to follow-up
- patient or guardian withdraws consent
- patient or guardian wishes to withdraw from the study for any reason
- investigator withdraws the patient because it is in the best interest of the patient.

In the event of study withdrawal or Omegaven discontinuation, standard/conventional clinical care will be rendered without prejudice or bias. At the time of study withdrawal, study staff will document date of withdrawal, reasons, and all safety and efficacy measurements up to date of withdrawal. Additionally, safety data collection will be encouraged for as long as possible for up to six months following Omegaven discontinuation.

STATISTICAL CONSIDERATIONS (for Intermediate Size Patient Population INDs)

Endpoints

The primary objective of this study is to evaluate the safety of Omegaven. To assess the primary objective, safety data will be collected which include, but are not limited to, adverse events, safety laboratory assessments such as CBC, LFT's, coagulation time, essential fatty acids, TG's, chemistries (see Table 1), overall survival, major liver events such as portal hypertension, hepatic decompensations (variceal bleeding, ascites, hepato-renal syndrome etc.), liver or combined liver and small intestine transplant, catheter related infection(s), sepsis, growth in children and weight in adults.

Secondary endpoints will be assessed using study data on laboratory tests and other clinical outcomes, and include:

- Proportion of patients in whom PNAC resolves while on Omegaven at prespecified intervals (e.g. monthly and by End-of-Study)
- Time to first direct bilirubin (D. bili) <2mg/dL
- Time to PNAC resolution (defined as two consecutive D. bili<2mg/dL, at least two weeks apart)
- Growth (weight, head circumference, length) in infants and children
- Time to transplantation
- Time to discontinuation of Omegaven due to efficacy or futility
- Time to death
- Time to weaning off PN

Data Analysis

Demographics will be summarized by age, gender, race, and possibly other variables. Baseline characteristics will be summarized, including baseline growth parameters, liver enzymes, total and direct bilirubin, diagnosis, amount of residual bowel, gestational age, and other factors. Patients who received any intravenous Omegaven will be included in the safety analysis population. For safety characterization, the prevalence and

proportions of adverse events (AEs) in this study will be summarized by body system, type of AE (e.g., anemia), seriousness, and clinically significant laboratory AEs. Additionally, AEs may also be summarized by demographics, infection, disease, gestational age, seriousness, or other variables. Due to the possible effect of Omegaven on coagulation, AEs may also be summarized by changes and trends in coagulation parameters and free fatty acid profiles (e.g., triene:tetraene ratio). Additional exploratory analyses may also be conducted. Reporting of the adverse event can be done using common terminology criteria for adverse event (CTCAE) in adults. We advise that you use the latest version of CTCAE available online. A link to the current version (6-13-2017) can be found at https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Appendix A – Cover Letter Template

Please edit directly to suit your needs

[Date]

Dragos Roman, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products
Central Document Room 5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

Subject: New Intermediate Size Patient Population IND Application for Omegaven

Dear Dr. Roman,

I am hereby submitting an Investigational New Drug application (IND) under section 505(i) of the Federal Food, Drug, and Cosmetic Act and in accord with 21 CFR 312 for Omegaven.

This application contains the following (*please check all that apply*):

☐ Form 1571,
☐ Form 1572
☐ Clinical Protocol
☐ Copy of Informed Consent planned for use

You must check the following box if you are requesting to charge for Omegaven:
☐ Permission is requested, under 21 CFR 312.8, to charge for the investigational drug used in this IND.
☐ I have included justification for the cost to be recovered or will submit documentation after purchase, which is consistent with 21 CFR 312.8 and agree not to profit

I plan to provide Omegaven prescriptions to approximately _____ (#) patients under this IND.

The name of the supplier of Omegaven to be administered under this IND is _____.

I claim a categorical exclusion from environmental assessment requirements (under 21 CFR 25.31[e]) for this IND. To my knowledge, no extraordinary circumstances exist.

Sincerely,

Attachment B – FDA 1571 and 1572 Forms

Fillable Forms FDA 1571 and 1572 and corresponding instructions can be found at:
https://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm
More specific instructions are listed below (numbers correspond to numbered boxes on form):

FDA 1571

1. Insert the name of the Sponsor-Investigator (physician).
7. Indication is **to provide lipid support in patients on parenteral nutrition who have Parenteral Nutrition Associated Cholestasis (PNAC).**
8-10 Leave blank
11. Check **Initial Investigational New Drug Application (IND)**
12. Check **Charge Request, 21 CFR 312.8** if the sponsor or pharmacy plans to charge the patient. Check **Intermediate Size Patient Population, 21 CFR 312.315** for multi-patient
13. Contents of the Application:
    Items 2, 3, 4:
        May be briefly addressed in the cover letter or in a summary
    Item 5:
        Because Omegaven is approved for use in another country, the approved professional labeling (in English) can be submitted in lieu of the Investigator's Brochure.
    Item 6a:
        See Attachment C (Protocol)
    Items 6b, 6c, 6d:
        Included in Form FDA 1572
    Items 7, 8:
        If using a Fresenius Kabi product, no additional information needs to be submitted for items 7 or 8.
15-16. Note there are certain important commitments that the Sponsor-Investigator makes by signing the form FDA 1571, which are listed below box 15.
17-25. Original signature by the Sponsor-Investigator

FDA 1572

Form FDA 1572 with its attachments may satisfy Form FDA 1571, box 12, items 6 b-d. Information can be supplied in the form of attachments (such as a curriculum vitae) rather than entering that information directly onto the form, but this should be so noted under the relevant section numbers.

3-4. Name and address of facility where the clinical investigation(s) will be conducted and any clinical laboratory to be used

5. Insert the name and address of your Institutional Review Board (IRB) (see section G)
6. List any residents, fellows, research nurses, or others assisting the physician
7-8. N/A

Attachment C - Adverse Event and Annual Reporting

Adverse Event Reporting

As sponsor of this IND, you are responsible for compliance with the Federal Food, Drug, and Cosmetic Act, and the implementing regulations [Title 21 of the Code of Federal Regulations (CFR)]. Your responsibilities include the following.

- Communicating any unexpected fatal or immediately life-threatening reactions associated with use of this product, either by telephone (301-796-1413) or fax (301-796-9904) no later than 7 calendar days after initial receipt of the information.
- Submitting all serious, unexpected adverse experiences as well as results from animal studies that suggest significant clinical risk within 15 calendar days after initial receipt of this information [21 CFR 312.32]. You may submit your safety report using FDA Form 3500 or in narrative format with the title "IND Safety Report".

Definitions

"Associated with the use of the drug"- There is a reasonable possibility that the experience may have been caused by the drug.
"Disability" - A substantial disruption of a person's ability to conduct normal life functions.
"Life-threatening adverse drug experience"- Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred.
"Serious adverse drug experience"- Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.
"Unexpected adverse drug experience"- Any adverse drug experience, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Annual Reporting

As sponsor of this IND, you are responsible for submitting written progress reports, which are required at intervals not exceeding one year and are due within 60 days of the application anniversary date (i.e., the date you were allowed to proceed with treatment under your IND number). Please include:

- A brief summary of the status of each patient enrolled in the protocol as it relates to their use of Omegaven. If there is more than one protocol, identify the protocol.
- The total number of subjects you plan to treat under the protocol; the number

entered into treatment to date, and the number who dropped out of the study for any reason.
- A summary of all adverse events
- A description of the general investigational plan for the coming year

A draft letter is provided for your convenience:

Date **IND #**

Annual Report

Dragos Roman, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastroenterology and Inborn Errors Products, HFD-180
Central Document Room
5901B Ammendale Road
Beltsville, Maryland 20705-1266

Dear Dr. Roman,

In compliance with 21 CFR 312.33, I am submitting an annual report to IND (insert #) for Omegaven submitted on (insert original IND submission date).

This annual report covers the time period from (insert date FDA permitted you to administer Omegaven) to (the ending date of your summary of treatment).

Title of protocol:
Status of each patient studied:
Number of patients planned for enrollment:
Number of patients enrolled to date:
Number of patients who dropped out:
Numbers of deaths and brief narrative for each:
Demographics (counts by age, gender, race, and other):
Numbers of adverse events:
Narratives of serious adverse events related to Omegaven treatment:
General investigational plan for coming year:

If you have any questions, you may reach me at (provide phone number and email).

Sincerely,