

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205060Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 205060

SUPPL #

HFD # 180

Trade Name Epanova

Generic Name omega-3-carboxylic acids

Applicant Name AstraZeneca Pharmaceuticals LP

Approval Date, If Known May 5, 2014

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES X NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES X NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

c) Did the applicant request exclusivity?

YES X NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO X

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO X

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO X

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: Kati Johnson
Title: Senior Regulatory Project Manager
Date: June 9, 2016

Name of Office/Division Director signing form: James P. Smith, MD, MS
Title: Deputy Director, Division of Metabolism and Endocrinology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATI JOHNSON
06/15/2016

JAMES P SMITH
06/15/2016

ACTION PACKAGE CHECKLIST

| APPLICATION INFORMATION ¹ | | |
|--|--------------------------------------|---|
| NDA # 205060 BLA # | NDA Supplement # BLA Supplement # | If NDA, Efficacy Supplement Type: |
| Proprietary Name: Epanova Established/Proper Name: omega-3-carboxylic acid Dosage Form: capsules | | Applicant: Astra Zeneca Pharmaceuticals LP Agent for Applicant (if applicable): Omthera Pharmaceuticals |
| RPM: Kati Johnson | | Division: Division of Metabolism and Endocrinology Products |
| <p><u>NDA and NDA Efficacy Supplements:</u></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(For additional information regarding 505(b)(2)s, please refer to http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/RegulatoryAffairsTeam/ucm027499.htm)</p> | | <p><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug. <input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> This application relies on (explain)</p> <p><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> |
| ❖ Actions | | |
| <ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>May 5, 2014</u> | | X AP <input type="checkbox"/> TA <input type="checkbox"/> CR |
| <ul style="list-style-type: none"> • Previous actions (<i>specify type and date for each action taken</i>) | | X None |

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

² For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

| | |
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| <p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____</p> | <input type="checkbox"/> Received |
| <p>❖ Application Characteristics ³</p> | |
| <p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <p> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC <input type="checkbox"/> Breakthrough Therapy designation </p> <p> NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies </p> <p> <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request </p> <p> BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies </p> <p> REMS: <input type="checkbox"/> MedGuide <input type="checkbox"/> Communication Plan <input type="checkbox"/> ETASU <input type="checkbox"/> MedGuide w/o REMS <input type="checkbox"/> REMS not required </p> <p>Comments:</p> | |
| <p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p> | <input type="checkbox"/> Yes, dates |
| <p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p> | <input type="checkbox"/> Yes <input type="checkbox"/> No |
| <p>❖ Public communications (<i>approvals only</i>)</p> | |
| <ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> Press Office notified of action (by OEP) | <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No |
| <ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated | <input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other |

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

| ❖ Exclusivity | |
|--|---|
| <ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes |
| <ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____ |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____ |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____ |
| <ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____ |
| <ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> | <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____ |
| ❖ Patent Information (NDAs only) | |
| <ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. | <input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic. |
| <ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. | 21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) |
| <ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). | <input type="checkbox"/> No paragraph III certification Date patent will expire _____ |
| <ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> | <input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified |

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

| | |
|---|--|
| <p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p> | <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p> |
|---|--|

CONTENTS OF ACTION PACKAGE

| | |
|---|-----------------------------------|
| ❖ Copy of this Action Package Checklist ⁴ | X |
| Officer/Employee List | |
| ❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>) | X Included |
| Documentation of consent/non-consent by officers/employees | X Included |
| Action Letters | |
| ❖ Copies of all action letters (<i>including approval letter with final labeling</i>) | Action(s) and date(s) 5/5/2014 AP |
| Labeling | |
| ❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>) | |
| <ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling | |
| <ul style="list-style-type: none"> • Example of class labeling, if applicable | |

⁴ Fill in blanks with dates of reviews, letters, etc.

| | |
|--|---|
| <ul style="list-style-type: none"> ❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>) | <input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None |
| <ul style="list-style-type: none"> • Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. | |
| <ul style="list-style-type: none"> • Original applicant-proposed labeling | |
| <ul style="list-style-type: none"> • Example of class labeling, if applicable | |
| <ul style="list-style-type: none"> ❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>) | |
| <ul style="list-style-type: none"> • Most-recent draft labeling | See approval letter |
| <ul style="list-style-type: none"> ❖ Proprietary Name <ul style="list-style-type: none"> • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) • Review(s) (<i>indicate date(s)</i>) • Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. | Letter dated 9/19/2013 Review dated 9/18/2013 |
| <ul style="list-style-type: none"> ❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>) | <input type="checkbox"/> RPM 2/19/14 <input type="checkbox"/> DMEPA 1/30/2014 <input type="checkbox"/> DMPP/PLT (DRISK) 4/14/2014 <input type="checkbox"/> OPDP (DDMAC) 4/8/2014 <input type="checkbox"/> SEALD N/A <input type="checkbox"/> CSS N/A <input type="checkbox"/> Other reviews N/A |
| Administrative / Regulatory Documents | |
| <ul style="list-style-type: none"> ❖ Administrative Reviews (<i>e.g., RPM Filing Review⁵/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>) | RPM review-9/12/2013 |
| <ul style="list-style-type: none"> ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte | X Not a (b)(2) |
| <ul style="list-style-type: none"> ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>) | X Not a (b)(2) |
| <ul style="list-style-type: none"> ❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)-to be filled out later | <input type="checkbox"/> Included |
| <ul style="list-style-type: none"> ❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm | |
| <ul style="list-style-type: none"> • Applicant is on the AIP | <input type="checkbox"/> Yes X No |
| <ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) | <input type="checkbox"/> Yes X No <input type="checkbox"/> Not an AP action |
| <ul style="list-style-type: none"> ❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>5/21/2014</u> If PeRC review not necessary, explain: _____ • Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) | <input type="checkbox"/> Included |

⁵ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

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|--|---|
| ❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent <i>(include certification)</i> | X Verified, statement is acceptable |
| ❖ Outgoing communications <i>(letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons)</i> | X |
| ❖ Internal memoranda, telecons, etc. | N/A |
| ❖ Minutes of Meetings | |
| • Regulatory Briefing <i>(indicate date of mtg)</i> | X No mtg |
| • If not the first review cycle, any end-of-review meeting <i>(indicate date of mtg)</i> | X N/A or no mtg |
| • Pre-NDA/BLA meeting <i>(indicate date of mtg)</i> | <input type="checkbox"/> No mtg 11/14/2012 |
| • EOP2 meeting <i>(indicate date of mtg)</i> | <input type="checkbox"/> No mtg 6/2/2010 |
| • Other milestone meetings (e.g., EOP2a, CMC pilots) <i>(indicate dates of mtgs)</i> | Biopharm meeting 11/6/2013 |
| ❖ Advisory Committee Meeting(s) | X No AC meeting |
| • Date(s) of Meeting(s) | |
| • 48-hour alert or minutes, if available <i>(do not include transcript)</i> | |
| Decisional and Summary Memos | |
| ❖ Office Director Decisional Memo <i>(indicate date for each review)</i> | X None |
| Division Director Summary Review <i>(indicate date for each review)</i> | <input type="checkbox"/> None 5/5/2014 |
| Cross-Discipline Team Leader Review <i>(indicate date for each review)</i> | <input type="checkbox"/> None 5/5/2014 |
| PMR/PMC Development Templates <i>(indicate total number)</i> | <input type="checkbox"/> None |
| Clinical Information⁶ | |
| ❖ Clinical Reviews | |
| • Clinical Team Leader Review(s) <i>(indicate date for each review)</i> | N/A |
| • Clinical review(s) <i>(indicate date for each review)</i> | 5/3/2014 (efficacy), 5/2/2014 (safety), 9/3/2013 |
| • Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i> | X None |
| ❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i> | Page 15 of 5/3/2014 review |
| ❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i> | X None |
| ❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i> | X Not applicable |
| ❖ Risk Management | |
| • REMS Documents and REMS Supporting Document <i>(indicate date(s) of submission(s))</i> | |
| • REMS Memo(s) and letter(s) <i>(indicate date(s))</i> | |
| • Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i> | X None |

⁶ Filing reviews should be filed with the discipline reviews.

| | |
|--|--|
| ❖ OSI Clinical Inspection Review Summary(ies) (include copies of OSI letters to investigators) | <input type="checkbox"/> None requested 4/10/2014 |
| Clinical Microbiology X None | |
| ❖ Clinical Microbiology Team Leader Review(s) (indicate date for each review) | <input type="checkbox"/> None |
| Clinical Microbiology Review(s) (indicate date for each review) | <input type="checkbox"/> None |
| Biostatistics <input type="checkbox"/> None | |
| ❖ Statistical Division Director Review(s) (indicate date for each review) | X None |
| Statistical Team Leader Review(s) (indicate date for each review) | X None |
| Statistical Review(s) (indicate date for each review) | <input type="checkbox"/> None 4/16/2014, 8/30/2013 |
| Clinical Pharmacology <input type="checkbox"/> None | |
| ❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review) | X None |
| Clinical Pharmacology Team Leader Review(s) (indicate date for each review) | X None |
| Clinical Pharmacology review(s) (indicate date for each review) | <input type="checkbox"/> None 3/27/2014, 9/4/2013 |
| ❖ DSI Clinical Pharmacology Inspection Review Summary (include copies of OSI letters) | X None |
| Nonclinical <input type="checkbox"/> None | |
| ❖ Pharmacology/Toxicology Discipline Reviews | |
| • ADP/T Review(s) (indicate date for each review) | X None |
| • Supervisory Review(s) (indicate date for each review) | X None |
| • Pharm/tox review(s), including referenced IND reviews (indicate date for each review) | <input type="checkbox"/> None 3/28/2014, 8/8/2013 |
| ❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review) | X None |
| ❖ Statistical review(s) of carcinogenicity studies (indicate date for each review) | X No carc |
| ❖ ECAC/CAC report/memo of meeting | <input type="checkbox"/> None Included in P/T review, page 66 |
| ❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters) | <input type="checkbox"/> None requested |
| Product Quality <input type="checkbox"/> None | |
| ❖ Product Quality Discipline Reviews | |
| • ONDQA/OBP Division Director Review(s) (indicate date for each review) | X None |
| • Branch Chief/Team Leader Review(s) (indicate date for each review) | X None |
| • Product quality review(s) including ONDQA biopharmaceutics reviews (indicate date for each review) | <input type="checkbox"/> None 3/27/2014, 8/20/2013 |
| ❖ Microbiology Reviews | <input type="checkbox"/> Not needed 7/19/2013 |
| <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) (indicate date of each review) | |
| <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) (indicate date of each review) | |
| ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date of each review) | Biopharmaceutics- reviews dated 3/26/2014 and 9/10/2013 |

| | |
|---|--|
| ❖ Environmental Assessment (check one) (original and supplemental applications) | |
| <input type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>)(<i>all original applications and all efficacy supplements that could increase the patient population</i>) | Page 132 of 3/27/2014 review |
| <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) | |
| <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) | |
| ❖ Facilities Review/Inspection | |
| <input type="checkbox"/> NDAs: Facilities inspections (include EER printout or EER Summary Report only; do NOT include EER Detailed Report) (<i>date completed must be within 2 years of action date</i>) (<i>only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁷</i>) | Date completed: 4/24/2014 X Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable |
| <input type="checkbox"/> BLAs: TB-EER (<i>date of most recent TB-EER must be within 30 days of action date</i>) (<i>original and supplemental BLAs</i>) | Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation |
| ❖ NDAs: Methods Validation (<i>check box only, do not include documents</i>) | <input type="checkbox"/> Completed <input type="checkbox"/> Requested X Not yet requested <input type="checkbox"/> Not needed (per review) |

⁷ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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/s/

KATI JOHNSON
05/07/2014

Executive CAC

Date of Meeting: February 11, 2014

Committee: David Jacobson-Kram, Ph.D., OND-IO, Chair
Abigail Jacobs, Ph.D., OND-IO, Member
Paul Brown, Ph.D., OND- IO, Member
Todd Palmby, Ph.D., DHOT, Alternate Member
Karen Davis Bruno, Ph.D., DMEP, Supervisor
Parvaneh Espandiari, Ph.D., DMEP, Presenting Reviewer

Author of Draft: Parvaneh Espandiari

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA # 205-060

Drug Name: Epanova (omega-3 carboxylic acid) capsules

Sponsor: Omthera Pharmaceuticals, Inc.

Background

Epanova soft gelatin capsules contain 1,000 mg of omega-3 carboxylic acid, a complex drug substance mixture consisting of a mixture of polyunsaturated free fatty acids (PUFAs) derived from fish oils and includes multiple long-chain omega-3 and omega-6 fatty acids, with eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and other fatty acids . Epanova is being developed for the treatment of hypertriglyceridemia. (b) (4)

(b) (4) The proposed clinical dose is for 2 g/day (2 capsules) and (b) (4) up to 4 g/day (4 capsules) (b) (4). The sponsor submitted results of two carcinogenicity studies. The test material in the carcinogenicity studies was extracted from Epanova capsules.

Tg.rasH2 Mouse Carcinogenicity Study:

A 26-week daily oral (gavage) study in Tg.rasH2 mice was conducted with omega-3 carboxylic acid at 0 (water), 500, 1000, 2000 and 4000 mg/kg/day or 4.4 (Water), 0.55, 1.1, 2.2 and 4.4 mL/kg/day, respectively. The protocol was previously reviewed by ECAC. Mortality in this study was statistically significantly increased in all dose groups for both genders. The high dose (4000mg/kg/day) animals were removed from the study on Day 73 (Week 10), with 50% surviving. The cause of death was considered to be pathological findings in the respiratory system. No drug-related neoplasms were found.

Rat Carcinogenicity Study:

A 104-week daily oral (gavage) carcinogenicity study in Sprague-Dawley rats was conducted with omega-3 carboxylic acid at 0 (corn oil), 100, 600, or 2000 mg/kg/day or 2.2, 0.11, 0.65, or 2.2 mL/kg/day, respectively. The proposed dose selection was not submitted to the ECAC by the sponsor but was based on the MTD from the 13-week oral repeat toxicity study in rats. There were deviations from the protocol regarding the early discontinuation of dosing and termination of all groups (with ECAC consultation). Increased mortality was statistically significant in all dose groups. The cause of death was considered to be non-neoplastic pathological findings in the respiratory system. Benign sex cord stromal tumors of the ovaries in the high dose (2000mg/kg/day) females were statistically significant both by trend (P=0.0005) and pairwise comparison (P=0.0054):(control, 5/64; low dose, 4/62; mid dose, 6/62; and high dose, 11/64).

Executive CAC Conclusions:

Tg.rasH2 mouse:

- The Committee concurred that the study was adequate.
- The Committee concurred that there were no drug-related neoplasms in the study.

Rat:

- The Committee concurred that the study was acceptable despite being suboptimal.
- The Committee concurred that benign ovarian sex cord stromal tumors in female rats were drug related at a dose that exceeded the MTD, based on non-neoplastic respiratory tract lesions. The Committee noted that the study design was problematic in comparing the effect of undiluted omega-3 carboxylic acid to the corn oil control.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/NDA205060, DMEP
/Karen Davis-Bruno, DMEP
/Parvaneh Espandiari, DMEP
/Kati Johnson, DMEP
/ASeifried, OND-IO

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/s/

ADELE S SEIFRIED
02/13/2014

DAVID JACOBSON KRAM
02/13/2014



NDA 205060

MEETING MINUTES

Omthera Pharmaceuticals, Inc.
Attention: Samia Siddiqui, PhD
Director, Regulatory Affairs
707 State Road
Princeton, NJ 08540

Dear Dr. Siddiqui:

Please refer to your New Drug Application (NDA) dated July 3, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Epanova (omega-3-carboxylic acids) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on November 6, 2013. The purpose of the meeting was to discuss the Biopharmaceutics comments contained in the September 16, 2013 "Filing Review Issues Identified" letter.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: C
Meeting Category: Guidance
Meeting Date and Time: November 6, 2013, 2:00 – 3:00 pm
Meeting Location: FDA, White Oak Campus
Building 22, Conference Room 1315
Silver Spring, MD 20903
Application Number: NDA 205060
Product Name: Epanova (omega-3 carboxylic acid) Capsules
Indication: Treatment of severe hypertriglyceridemia
Sponsor/Applicant Name: Omthera Pharmaceuticals, Inc.
Meeting Chair: Houda Mahayni, PhD
Meeting Recorder: Kati Johnson, Senior Regulatory Project Manager

FDA ATTENDEES

Office of New Drug Quality Assessment

Angelica Dorantes, PhD-Biopharmaceutics Team Leader
Sandra Suarez, PhD-Biopharmaceutics Reviewer
Houda Mahayni, PhD-Biopharmaceutics Reviewer

Division of Metabolism and Endocrinology Products

Kati Johnson-Senior Regulatory Project Manager

SPONSOR ATTENDEES

Omthera Pharmaceuticals

Doug Kling, VP, Clinical Development and Project Management
Timothy Maines, VP, Quality
Bharat Mehta, PhD, VP, CMC/Manufacturing

(b) (4), President, (b) (4)

Samia Siddiqui, PhD, Director Regulatory Affairs

(b) (4) Regulatory consultant, (b) (4)

BACKGROUND

NDA 205060 was submitted July 3, 2013 and proposed to market Epanova for the treatment of severe hypertriglyceridemia. On September 3, 2013 the application was considered sufficiently complete to review, so the application was filed. However, a 74-day letter was issued September 16, 2013 which identified some potential review issues with the Biopharmaceutics portion of the application.

On October 22, 2013, the firm submitted a meeting request, accompanied by the background package to discuss these issues. The meeting was granted on November 3, 2013.

NOTE: this product was previously called omefas. "Omega-3-carboxylic acids" is the recently approved USAN name.

1.0 DISCUSSION

FDA comments in the September 16, 2013, letter is in **bolded** text, followed by the firm's response in regular text. Any meeting discussion is in *italicized* text.

Question 1. We do not agree with your "Immediate Release" claim for your proposed drug product.

In addition, in your submission you clearly state that (b) (4)
. Therefore, the (b) (4)
and your statement indicate that the (b) (4).

Firm's Response:

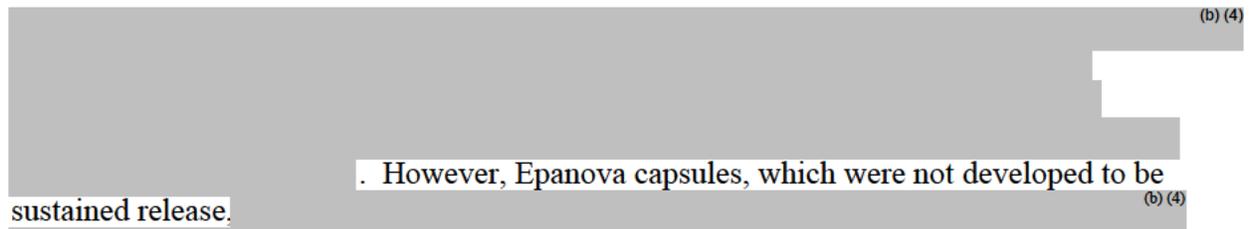
(b) (4)

(b) (4)



(b) (4)

sustained release. . However, Epanova capsules, which were not developed to be (b) (4)



(b) (4)



(b) (4)



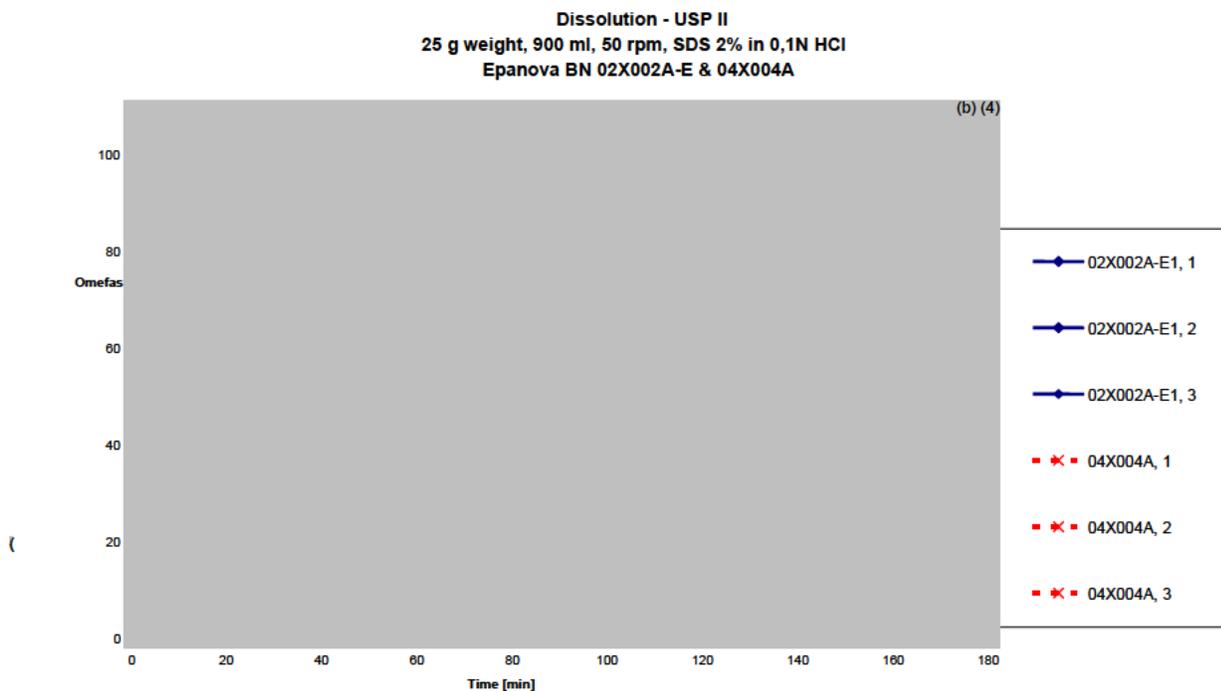


Figure 1. Omefas release profile from Epanova capsules BN04X004A (dotted lines) and BN02X002A-E1 (solid lines) in 2% SDS in 0.1N HCl. Each line represents the profile from a single capsule.

(b) (4)

release of omefas from the capsules likely begins in the stomach. This formulation design was considered optimal for Epanova capsules. Clinical study OM-EPA-001 compared the bioavailability of 4g of Epanova vs. 4g of Lovaza® (uncoated capsules containing omega-3-acid ethyl esters); (*Section 5.3.3.1, Study OM-EPA-001: Bioavailability of Epanova and Lovaza After Low-Fat and High-Fat Meals*). In this study, the Tmax for Epanova was reported to be not different from the uncoated Lovaza capsules (6.20 hr vs. 5.98 hr). As shown in @@Figure 2, the shape of the mean plasma concentration-time curves of total EPA+DHA for Epanova and the uncoated Lovaza capsules are similar. These data support the premise that Epanova does not act as a delayed release dosage form.

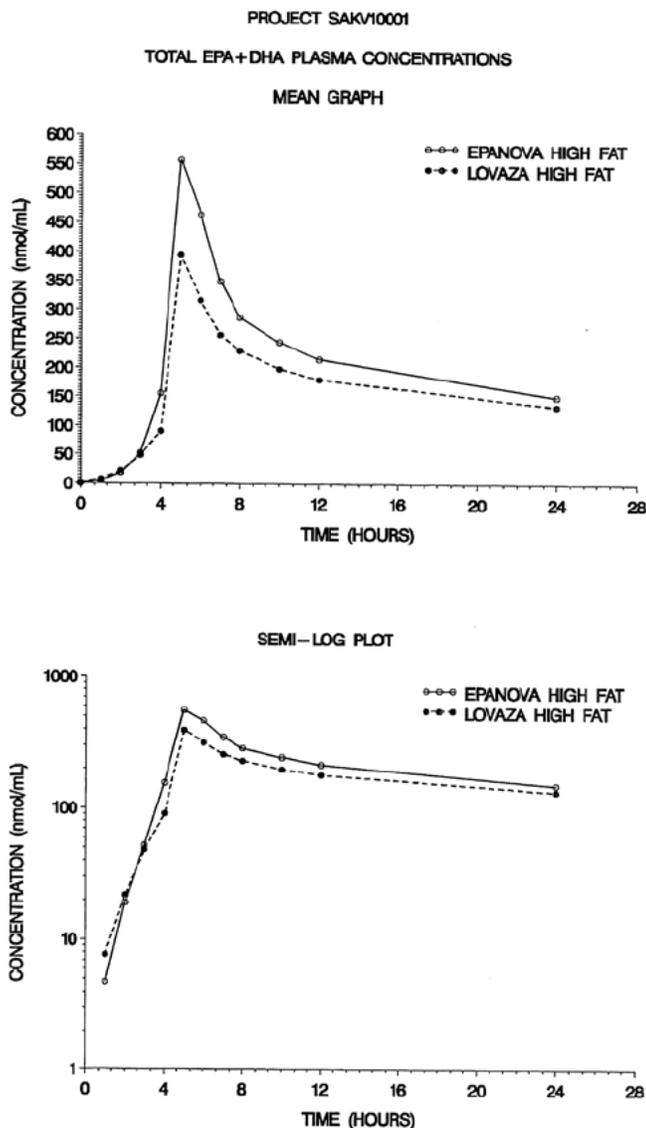


Figure 2. Total EPA + DHA plasma concentrations vs. time following administration of Epanova or Lovaza following a high fat meal. From @@ Clinical Study Report OM-EPA-001; Section 5.3.3.1.

The design of Epanova capsules was based on a non-standard approach to [REDACTED] (b) (4). Thus, the terminology used throughout NDA 205060 in describing formulations, testing methodology and evaluation of results may appear somewhat inconsistent. However, from the supporting evidence presented, Epanova capsules were not designed to be, and do not behave as an enteric coated delayed release dosage form.

Meeting Discussion: *The background package contained Figure 1 which provided the release profile of two batches of Epanova in 0.1N HCl with 2% SDS, and showed that the product would not meet the USP<711> requirement for delayed release dosage forms. Figure 2 provided the Tmax PK for Epanova compared to Lovaza and they were similar, and according to the firm, provided additional evidence that Epanova did not behave like a delayed-release dosage form in-vivo. The firm also stated that they do not plan to make any claims related to delayed release in the proposed labeling.*

FDA agreed that Epanova behaves like an immediate release dosage form and agreed that the product can be classified as an immediate-release dosage form.

FDA expressed its concern with the large variability in the in-vitro release profiles in Figure 1. FDA inquired if the product has (b) (4). The firm stated that the (b) (4). FDA asked if the surfactant concentration at 2% in Figure 1 may be the reason why there is release in acidic media and not because (b) (4). FDA recommended the firm to provide data showing the same release behavior is maintained in the absence of surfactant.

FDA stated that it is imperative that the firm determine the source of the variability and its clinical relevance and to take the appropriate measures to control it; or to justify the lack of clinical impact resulting from such high variability, as it may affect the safety or efficacy profiles of the drug product.

FDA asked if the profiles in Figure 1 are of the three active components. The firm stated that Figure 1 shows the profiles of three capsules from two batches for one of the three components.

The firm clarified that the Epanova lots depicted in Figure 1 were early batches and were not used in the clinical trial. FDA said that it would be helpful to have the release profile for lots used in the pivotal study. FDA added that this figure does show a lot of variability in the release patterns, and reiterated that this variability should either be minimized or information needs to be provided demonstrating the lack of clinical impact.

The firm stated that the high variability may be due to the use of inappropriate media. Also, the firm later affirmed that the batches in Figure 1 were tested in clinical studies.

In summary, there was agreement that Epanova will be classified as an immediate release dosage form. The acceptability of the dissolution method is a review issue, and additional questions/comments may be forthcoming as the review proceeds.

Question 2:

(b) (4)

B). Therefore, revise the dissolution method as appropriate by implementing an “Acid Stage” followed by a “Buffer Stage” testing.

Firm’s Response:

Given that Epanova capsules and the *in-vitro* release characteristics do not match well with the definition of enteric coating/delayed release formulations as provided in the regulatory guidances, use of the USP dissolution method for delayed release dosage forms was considered to be not fully applicable for the following reasons:

- The low solubility of omefas in 0.1N HCl (0.002mg/ml) precludes its use as a dissolution media.
- Omefas oil does not disperse or dissolve in 0.1N HCl making it impossible to achieve sink conditions without the addition of a surfactant.
- The release of omefas from the coated capsules at 120 minutes in 0.1N HCl containing 2% SDS ranged from (b) (4) % to (b) (4) % (Figure 1). The capsules were not designed to totally eliminate release in the stomach and therefore would not pass the USP<711> acceptance criteria of no individual value exceeding (b) (4) % after 120 minutes in 0.1N HCl.

The ethyl acrylate and methyl methacrylate copolymer coating used to (b) (4) Thus, for quality control purposes, a method incorporating an acid stage and a buffer stage was not considered appropriate or feasible and therefore a time-dependent two-stage evaluation of omefas release from Epanova capsules was incorporated in method OP 6.1083 (*Section 3.2.P.5.2*) which is considered a quantitative capsule rupture test.

(b) (4)



Figure 3. Omefas release profiles from Epanova capsules Batch 02X002A-E (solid line) and Batch 04X004A (dotted line) using a two-stage test.

Since the (b) (4) coating on Epanova capsules is (b) (4), and capsule rupture and release of the capsule contents does takes place in acid media, use of a two-stage acid/buffer release method does not seem appropriate or feasible. The developed method, which is a two-stage time-based procedure, is the most appropriate since it is designed to assess the delay in capsule rupture (b) (4).

The components and parameters of the omefas release method (OP 6.1083) which were evaluated during method development, and the method validation parameters that were evaluated were summarized in the briefing document submitted for the pre-NDA CMC meeting (*IND 107616, SN 0038*). Since the draft guidance on Omega-3-Acid Ethyl Esters recommends the use of USP Apparatus 4 for the quantitative capsule rupture test for those products, the rationale for using Apparatus 2 with a special sinker device in the omefas release method is described here.

(b) (4)

(b) (4) (b) (4)

The developed method was found to be suitable for assessing and ensuring consistent batch-to-batch quality and drug product performance at release and during shelf life stability monitoring, and is able to detect relevant drug product manufacturing changes.

Meeting Discussion: Since it has been determined that Epanova is not a delayed-release dosage form, the development of a new dissolution testing method is no longer necessary.

Question 3: Also, revise the dissolution acceptance criteria as appropriate and provide your proposal and the supportive data. Note that for delayed-release products, specifications should be established in both acid stage and buffer stage as per USP. You should use the dissolution profile data from the biobatches (PK and clinical) and stability-registration batches to set the acceptance criteria.

- **Acid Stage:** No individual tablet exceeds (b) (4) % dissolved at 2 hours.
- **Buffer Stage:** The dissolution acceptance criteria for your product should be based on the following:
 - The **in vitro** dissolution profile should encompass the timeframe over which at least (b) (4) % of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
 - The selection of the specification time point should be where $Q = (b) (4) \%$ dissolution occurs. However, if you have a slowly dissolving product in the buffer stage, a two point specifications option may be adequate for your product. The first time point should be during the initial dissolution phase (i.e., 15-20 minutes) and the second time point should be where $Q = (b) (4) \%$ dissolution occurs.
 - The dissolution acceptance criterion should be based on average in-vitro dissolution data (n=12).

Firm's Response:

The acceptance criteria for the omefas release method OP 6.1083 were based upon quality control test results from the development batches used in the Phase 1-3 trials that support the proposed indication (Section 3.2.P.2.2.1.3) and the stability studies performed on the 3 registration batches (Section 3.2.P.8.1). The dissolution acceptance criteria were confirmed in the method validation studies based on average *in-vitro* dissolution data from 12 units at the (b) (4) min. time points. However, based upon the data obtained from stability studies, meeting the criteria of not less than (b) (4) % Q at (b) (4) min. was considered (b) (4). Therefore, the 30 min. and 120 min. time points were selected for the acceptance criteria.

Since a change to the method incorporating an acid-stage would provide no additional control of quality for the product and would likely make the method less discriminating, we are proposing to maintain the current test method and acceptance criteria.

Meeting Discussion: *Figure 1 provides the release profile from capsules in 0.1N HCl with 2% SDS. FDA questioned whether the SDS in the medium impacts the capsule rupture, so that it may be a confounding factor in the interpretation of the results. FDA requested the profile of the three components of Epanova capsules in 0.1N HCl in the absence of SDS. The data are needed to support the IR properties of the proposed product. According to the firm, SDS was added to achieve sink conditions, and without these conditions, the sampling is not representative, as the oil will not disperse well in the media. FDA said that the collection of samples during the dissolution testing should be properly done to sample what is dissolved in the medium and not to the intact droplets with un-dissolved drug that are floating on top of the medium.*

The firm agreed to submit 2 hour release data for the clinical lots of Epanova in 0.1N HCl with and without 2% SDS.

Question 4:

(b) (4)

(b) (4)

Firm's Response:

(b) (4)

Meeting Discussion: *None.*

Since the product is been considered as an immediate release dosage form, this information is no longer needed.

Question 5: As per SUPAC-MR Level 3, data from a bioequivalence study are needed to support the approval of the proposed [REDACTED] (b) (4) for your [REDACTED] (b) (4) product. Revise the drug product [REDACTED] (b) (4) comparability protocol as appropriate to include this assessment.

Firm's Response:

We will be prepared to provide additional information pending feedback from the FDA on Questions 1 – 4.

Meeting Discussion: None.

Since the dosage form is an immediate release dosage form, a discussion for this question was no longer needed.

Question 6: Provide additional stability data using the revised dissolution method.

Firm's Response:

We will be prepared to provide additional information pending feedback from the FDA on Questions 1 – 4.

Meeting Discussion: None.

The requested data are no longer needed, because the proposed dosage form has been categorized as an immediate release dosage form.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

4.0 ACTION ITEMS

For the sponsor:

1. The firm agreed to submit 2 hour release data for the clinical lots of the three components of Epanova in 0.1N HCl with and without 2% SDS.
2. The firm agreed to provide PK data similar to the data presented in Figure 2, if available, for the lots noted in Figure 1 in the briefing document or for more recent lots that are presented in the pending NDA.

NOTE-The sponsor provided this requested information in an amendment dated January 3, 2014.

5.0 ATTACHMENTS AND HANDOUTS

Omthera's slide deck provided to the FDA at the meeting.

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/s/

KATI JOHNSON
01/23/2014



NDA 205060

MEETING REQUEST GRANTED

Omthera Pharmaceuticals
Attention: Samia Siddiqui, PhD
Director, Regulatory Affairs
707 State Road
Princeton NJ 08540

Dear Dr. Siddiqui:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Epanova (omega-3-carboxyl acids) Capsules.

We also refer to your October 22, 2013, correspondence requesting a meeting to discuss the Biopharmaceutics issues contained in the September 16, 2013, filing communication. Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting.

The meeting is scheduled as follows:

Date: Wednesday, November 6, 2013
Time: 2:00 to 3:00 pm
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Invited CDER Participants:

Office of New Drug Quality Assessment

Angelica Dorantes, PhD-Biopharmaceutics Team Leader
Sandra Suarez, PhD-Biopharmaceutics Reviewer
Houda Mahayni, PhD-Biopharmaceutics Reviewer
Xavier Ysern, PhD-Reviewing Chemist

Division of Metabolism and Endocrinology Products

Kati Johnson-Senior Regulatory Project Manager

Please e-mail me any updates to your attendees at Kati.Johnson@fda.hhs.gov, at least one day prior to the meeting. For each foreign visitor, complete and email me the enclosed Foreign Visitor Data Request Form, at least two weeks prior to the meeting. A foreign visitor is any non-U.S. citizen who does not have Permanent Resident Status or a valid U.S. Federal Government

Agency issued Security Identification Access Badge. If we do not receive the above requested information in a timely manner, attendees may be denied access.

A few days before the meeting, you may receive an email with a barcode generated by FDA's Lobbyguard system. If you receive this email, bring it with you to expedite your group's admission to the building. Ensure that the barcode is printed at 100% resolution to avoid potential barcode reading errors.

Please have all attendees bring valid photo identification and allow 15-30 minutes to complete security clearance. Upon arrival at FDA, provide the guards with either of the following numbers to request an escort to the conference room: Kati Johnson, 301-796-1234.

We note that the background package was submitted with the meeting request.

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Senior Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

KATI JOHNSON
11/03/2013



NDA 205060

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Omthera Pharmaceuticals, Inc.
707 State Road
Princeton, NJ 08540

Attention: Samia M. Siddiqui, Ph.D.
Director, Regulatory Affairs

Dear Dr. Siddiqui:

Please refer to your July 3, 2013, New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for (b)(4) Capsules, 1 gram.

We also refer to your correspondence, dated and received July 17, 2013, requesting review of your proposed proprietary name, Epanova. We have completed our review of the proposed proprietary name and have concluded that it is acceptable.

The proposed proprietary name, Epanova, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If any of the proposed product characteristics as stated in your July 17, 2013, submission are altered prior to approval of this application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Margarita Tossa, Safety Regulatory Project Manger in the Office of Surveillance and Epidemiology, at (301) 796-4053. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Kati Johnson at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
09/19/2013



NDA 205060

**FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED**

Omthera Pharmaceuticals, Inc.
Attention: Samia M. Siddiqui, PhD
Director, Regulatory Affairs
707 State Road
Princeton, NJ 08540

Dear Dr. Siddiqui:

Please refer to your New Drug Application (NDA) dated July 3, 2013, received July 5, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for Epanova (omefas) Capsules 1 gram.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is **May 5, 2014**.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests **April 11, 2014**.

During our filing review of your application, we identified the following potential review issues:

Clinical

Submit a rationale for assuming the applicability of foreign data in the submission to the US population.

Product Quality

Chemistry, Manufacturing and Controls (CMC):

Provide a copy of your application for a US Adopted Name (USAN) for your drug substance (reference is made to the US Pharmacopeia Dictionary for details) and advise us of the progress of your application.

Biopharmaceutics:

1.  (b) (4)

2.  (b) (4)

herefore, revise the dissolution method as appropriate by implementing an “Acid Stage” followed by a “Buffer Stage” testing.

3. Also, revise the dissolution acceptance criteria as appropriate and provide your proposal and the supportive data. Note that for delayed-release products, specifications should be established in both acid stage and buffer stage as per USP. You should use the dissolution profile data from the biobatches (PK and clinical) and stability-registration batches to set the acceptance criteria.
 - Acid Stage: No individual tablet exceeds (b) (4) % dissolved at 2 hours.
 - Buffer Stage: The dissolution acceptance criteria for your product should be based on the following:
 - o The in vitro dissolution profile should encompass the timeframe over which at least (b) (4) % of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
 - o The selection of the specification time point should be where $Q = (b) (4) \%$ dissolution occurs. However, if you have a slowly dissolving product in the buffer stage, a two-point specifications option may be adequate for your product. The first time point should be during the initial dissolution phase (i.e., 15-20 minutes) and the second time point should be where $Q = (b) (4) \%$ dissolution occurs.
 - o The dissolution acceptance criterion should be based on average in-vitro dissolution data (n=12).

4.  (b) (4)



5. As per SUPAC-MR Level 3, data from a bioequivalence study are needed to support the approval of the proposed (b) (4) for your (b) (4) product. Revise the drug product (b) (4) comparability protocol as appropriate to include this assessment.
6. Provide additional stability data using the revised dissolution method.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

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

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), Medication Guide, and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Jean-Marc Guettier, MD
Director (Acting)
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KATI JOHNSON

09/16/2013

signing for Jean-Marc Guettier



NDA 205060

NDA ACKNOWLEDGMENT

Omthera Pharmaceuticals, Inc.
Attention: Samia M. Siddiqui, PhD
Director, Regulatory Affairs
707 State Road
Princeton, NJ 08540

Dear Dr. Siddiqui:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Epanova (omefas) Capsules

Date of Application: July 3, 2013

Date of Receipt: July 5, 2013

Our Reference Number: NDA 205060

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 3, 2013, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolism and Endocrinology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call Kati Johnson, Regulatory Project Manager, at (301) 796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Senior Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

KATI JOHNSON
07/08/2013



IND 107616

MEETING MINUTES

Omthera Pharmaceuticals, Inc.
Attention: Samia M. Siddiqui, PhD
Director, Regulatory Affairs
707 State Street
Princeton, NJ 08540

Dear Dr. Siddiqui:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Epanova (omefas) Capsules.

We also refer to the meeting between representatives of your firm and the FDA on November 14, 2012. The purpose of the meeting was to discuss your to-be-submitted NDA for the treatment of severe hypertriglyceridemia (≥ 500 mg/dL).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

IND 107616
Meeting Minutes
PNDA (clinical) Meeting

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA (clinical)
Meeting Date and Time: Wednesday, November 14, 2012
Meeting Location: FDA White Oak
Building 22, Conference Room 1313

Application Number: IND 107616
Product Name: Epanova (omefas) Capsules
Indication: Treatment of severe hypertriglyceridemia (≥ 500 mg/dL)
Sponsor/Applicant Name: Omthera Pharmaceuticals, Inc.

Meeting Chair: Iffat Chowdhury, MD
Meeting Recorder: Kati Johnson

FDA ATTENDEES

Division of Metabolism and Endocrinology Products

Mary Parks, MD-Director
Eric Colman, MD-Deputy Director
Iffat Chowdhury, MD-Clinical Reviewer
Karen Davis Bruno, PhD-Supervisory Pharmacologist
Parvaneh Espandari, PhD-Nonclinical Reviewer

Division of Biometrics II (OBII)

Todd Sahlroot, PhD-Deputy Director
Japo Choudhury, PhD-Statistical Reviewer

Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology II (DCPII)

Immo Zadezensky, PhD-Clinical Pharmacology Team Leader
S.W. Johnny Lau, PhD-Clinical Pharmacology Reviewer

Office of Scientific Investigations, Division of Good Clinical Practice, Good Clinical Practice Assessment Branch

Cynthia Kleppinger, MD-Senior Medical Officer

Office of Surveillance and Epidemiology

Margarita Tossa-Project Manager

Division of Risk Management

Cynthia LaCivita, PharmD-Team Leader, Risk Management Analyst

Division of Medication Error Prevention and Analysis

Reasol Agustin, PharmD-Labeling Reviewer

Division of Epidemiology I

Christian Hampp, PhD-Visiting Associate/Epidemiologist

SPONSOR ATTENDEES

Jerry Wisler, Chief Executive Officer, Omthera

Michael Davidson, MD, Executive VP & Chief Medical Officer, Omthera

Douglas Kling, VP, Clinical Development & Project Management, Omthera

Samia Siddiqui, PhD, Director, Regulatory Affairs, Omthera

Judith Johnson, Director, Project Management, Omthera

(b) (4), Clinical Regulatory Consultant, (b) (4)
(b) (4), Toxicology Consultant, (b) (4)
(b) (4), Clinical Regulatory Consultant, (b) (4)

1.0 BACKGROUND

IND 107616 was submitted March 25, 2010, and included an End-of-Phase 2 (EOP2) meeting request to discuss the applicant's plan to develop this compound as an adjunct to diet for the treatment of severe hypertriglyceridemia (≥ 500 mg/dL). According to the sponsor, Epanova is 20% DHA and 55% EPA (extracted from fish oil) in their free fatty acid forms and has the potential advantage of greater bioavailability than existing omega-3-fatty acid alternatives.

Epanova was previously investigated in the Division of Gastrointestinal and Inborn Errors Products for the treatment of Crohn's Disease (IND (b) (4) (EPIC studies). The sponsor of that application was Tillots Pharma AG, and ownership of the application was transferred to Omthera on December 8, 2009.

An EOP2 meeting was held on June 2, 2010, and, at that meeting, the firm was notified that an indication involving an add-on to statin therapy would require a CV outcomes trial be underway with approximately 50% of the patients enrolled at the time of NDA/supplement submission. During drug development, the following protocols were reviewed under the Special Protocol Assessment program:

1. OM-EPA-003 (later called EVOLVE): *Efficacy and Safety of Epanova® in Severe Hypertriglyceridemia*. An "agreement" letter issued October 22, 2010.
2. OM-EPA-004 (later called ESPRIT): *A 6-Week, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Add-on Epanova to Statin Therapy in High-Risk Subjects with Persistent Hypertriglyceridemia*. An "agreement" letter issued May 31, 2011.
3. OM-EPA-005 (STRENGTH): *A Phase III, Double-Blind, Long-Term Outcomes Study to Assess Statin Residual Risk Reduction with Epanova in High Cardiovascular Risk Patients with Hypertriglyceridemia*. An "agreement" letter issued March 16, 2012.

In a February 29, 2012 submission, the applicant requested a pre-NDA meeting, however, that request was eventually withdrawn.

On April 25, 2012, the applicant requested agency concurrence on the proposal to, in lieu of conducting a thorough QTc study, assess ECGs recorded pre-dose and during periods of trough levels after dosing with dosing with Epanova for multiple days in the EVOLVE study. This proposal was found acceptable on October 3, 2012.

The firm is proposing to submit a 505(b)(1) application for the treatment of severe hypertriglyceridemia, based on the EVOLVE study.

Following approval, the applicant is proposing to pursue an additional indication based on the ESPRIT study: adjunct to statin therapy to reduce non-HDL-C, TG and increase HDL-C in patients with mixed dyslipidemia and coronary heart disease (CHD) or CHD equivalents. The initial NDA application will include the results from ESPRIT to further support the safety and efficacy of Epanova, however, the supplement for that indication will not be submitted until there is approximately 50% enrollment in the CV outcomes trial (STRENGTH).

Pending completion of STRENGTH, the applicant will pursue an indication as an adjunct to statin therapy and diet in high-risk patients for the prevention and reduction of major adverse cardiovascular events.

2. DISCUSSION

Any background information and the firm's questions are in regular text, preliminary responses are in **bolded** text, any meeting text is in *italicized* text. Post-meeting comments are in underlined text.

Nonclinical

Question #1

Background

The Sponsor considers the toxicology studies conducted with EPANOVA and the published pharmacology and ADME literature for the GRAS substances EPA and DHA provide a comprehensive ICH M3 compliant package of preclinical information that can be used to assess the pharmacology, ADME and safety of EPANOVA and thus support the filing of the NDA.

Table 3 of the background package lists the toxicology studies performed with EPANOVA and key noteworthy findings from these studies. These studies demonstrated no safety concerns or signals and a benign safety profile similar to other fish oils. These study reports will be submitted and results summarized in the NDA. Additionally the pharmacology and ADME of EPA and DHA will be summarized from the literature and submitted in the NDA.

No formal safety pharmacology and ADME studies have been conducted with EPANOVA as the general pharmacology and details regarding metabolism and excretion of EPA and DHA in animals and humans are well established in the published literature. Based on the secondary pharmacodynamic studies in the cardiovascular system and coagulation system published in the literature, there was no cause for cardiovascular safety concerns for the proposed clinical indication of hypertriglyceridemia. Although stand alone safety pharmacology studies have not been conducted with EPANOVA, a comprehensive review of the general toxicology data in mice (up to 4 weeks), rats (up to 26 weeks) and dogs (up to 39 weeks) as well as reproductive

toxicology in rats and rabbits and carcinogenicity data in transgenic mice (26 weeks) does not indicate any safety concerns in the cardiovascular, renal, respiratory, gastrointestinal (GI), or neurological systems.

Does the Agency agree that the nonclinical information available for EPANOVA is sufficient to support the NDA filing?

FDA Response: The nonclinical development strategy appears reasonable. Final reports of the required studies are needed with initial NDA submission.

Meeting Discussion: The sponsor cited the guidance for PDUFA V, saying that submitting the final report of a draft audited preclinical report (e.g. carcinogenicity) was an example of an application component that would qualify as a delayed submission. The FDA reiterated the need for a final report, stating that this provision requires prior agreement between the sponsor and Division and the need for submission of complete submission for NDA filing in accordance with PDUFA V. After some further discussion, the sponsor agreed to submit the final carcinogenicity study reports in the initial NDA submission.

Post-Meeting Comment: The negotiated submission of information following the initial NDA submission (delayed submissions under “The Program”) under PDUFA V only pertains to moieties designated as a New Molecular Entity (NME). We have no documentation that your product has been designated as such. In the absence of that designation, the NDA is expected to be complete upon submission and will be reviewed under the traditional timelines (6- month clock for priority applications; 10-month clock for standard applications).

Question #2

To assess the carcinogenicity profile of EPANOVA, the Sponsor has conducted a 26-week carcinogenicity study in Tg-rasH2 mice and a 104-week carcinogenicity study in rats which is ongoing. The NDA will include the final study report for the 26-week Tg-rasH2 mice study. The Sponsor plans to submit (b) (4)

FDA Response: No, we do not agree. (b) (4)

to support the NDA filing for EPANOVA, all final study reports of the non-clinical studies including the 104-week carcinogenicity in rats (on going) and SAS datasets must be submitted with the NDA submission.

Meeting Discussion: See response to Question #1.

Clinical

Question #1

Background

Clinical efficacy and safety of EPANOVA will be demonstrated in the multicenter, randomized, placebo (olive oil) controlled trial OM-EPA-003 (EVOLVE). Supportive safety and efficacy will be provided by data from the OM-EPA-004 (ESPRIT) trial. Long term safety of EPANOVA will be supported by data from the EPIC trials. The remaining clinical requirements for the NDA will be provided by the PK studies (OM-EPA-001, SPC-275-4, EPIC-3), drug interaction studies with warfarin (OM-EPA-006) and simvastatin (OM-EPA-007), and an evaluation of potential QTc prolongation in the EVOLVE study.

Does the Agency agree that the proposed content of the clinical package is adequate for filing the NDA?

FDA Response:

Clinical

We agree that the proposed content of the clinical package is adequate for submission of the NDA.

Clinical Pharmacology

If the formulation used in your pivotal Phase 3 study is different from the to-be-marketed formulation, a bridging study will be necessary to establish bioequivalence between these formulations before submission of the NDA; otherwise the proposed content appears reasonable for filing. You should also include the following information in the NDA submission:

- **Information on the difference of omefas pharmacokinetics between severe hypertriglyceridemia patients and healthy volunteers since you studied healthy volunteers in the Phase 1 studies**
- **Information on the difference of omefas pharmacokinetics between severe hypertriglyceridemia patients and Crohn's disease patients since you plan on using Study TP0309 (EPIC-3) to support your future NDA.**
- **The protein binding, enzymes, and transporters that are responsible for the distribution and disposition of omefas.**

Meeting Discussion: Prior to the meeting, the sponsor provided 2 slides (attached) to respond to the clinical pharmacology requests. The sponsor will provide information on the differences of omefas pharmacokinetics between severe hypertriglyceridemia patients, Crohn's Disease patients, high triglyceride patients and healthy volunteers within the clinical pharmacology summary of the future NDA. The sponsor will also provide the general clinical pharmacokinetic information of omefas from the published literature in the future NDA.

These proposed approaches were found acceptable by the agency. The sponsor confirmed that the formulation used in the clinical studies is the same as the to-be-marketed formulation. The

sponsor also confirmed that they studied the to-be-marketed formulation in the food effect study (OM-EPA-001).

Question #2

Background

As agreed at the end-of-phase 2 meeting in June 2010 and in the Agency letter dated May 31, 2011, the safety of EPANOVA for the severe hypertriglyceridemia indication will be supported with data from phase 2 and 3 clinical trials in patients with Crohn's disease conducted by the previous Sponsor. The overall total number of subjects exposed to EPANOVA (including clinical pharmacology trials, hypertriglyceridemia clinical trials, and Crohn's disease clinical trials) is 1312.

The estimated exposure in subject-years for EPANOVA is 112.6 in clinical trials conducted in subjects with hypertriglyceridemia and 378.3 for subjects with Crohn's disease. There were approximately 193 subjects with over 1 year EPANOVA exposure in the Crohn's disease studies.

Does the Agency agree that the studies provide an adequate safety database of reasonable size and duration?

FDA Response: Yes, we agree that the studies provide adequate safety database of reasonable size and duration.

Meeting Discussion: None.

Question #3

Background

The Sponsor plans to present the safety data from the clinical trials using the following integrated analysis sets - Pool A: EVOLVE and ESPRIT (olive oil (placebo) = 314, EPANOVA = 731), Pool B: EPIC 1/2/3 (placebo = 372, EPANOVA = 432) and EPIC-1E, Pool C: Long Term EPANOVA (≥ 1 year) Exposure (from EPIC 1/2/3 and 1E) (EPANOVA = 193).

Does the Agency agree with the proposed integration for the ISS?

FDA Response: Yes, the three proposed pools (A, B, and C) are reasonable for the ISS. In addition, please breakdown Pool A by each study (EVOLVE and ESPRIT) for further analysis.

Meeting Discussion: The sponsor confirmed that Pool A will be broken down by each study (EVOLVE and ESPRIT).

Question #4

It is anticipated that Section 2.7.4 Summary of Clinical Safety would be sufficiently detailed to serve as the narrative portion of ISS while still concise enough to meet the suggested size

limitations for Module 2. As such it is proposed that the narrative portion of the ISS be located in Section 2.7.4 and the appendices of tables, figures, and datasets located in Section 5.3.5.3.

Does the Agency agree with the proposed location of the ISS?

FDA Response: Yes.

Meeting Discussion: None

Question #5

The primary evidence of efficacy for EPANOVA to support the treatment of adult patients with severe hypertriglyceridemia (≥ 500 mg/dL) is established on the basis of the OM-EPA-003 (EVOLVE). Therefore, the Sponsor does not plan to provide an Integrated Summary of Efficacy in Section 5.3.5.3 Reports of Analyses of Data from More than One Study, but will reference Section 5.3.5.3 to the clinical study report for EVOLVE. A second supportive controlled trial has been conducted evaluating EPANOVA as adjunct to statin therapy and diet in high-risk patients with persistent high TG levels (≥ 200 and < 500 mg/dL) despite being on a statin (Protocol OM-EPA-004 ESPRIT). No other efficacy studies have been conducted. The results of these studies cannot be pooled for any subgroup analysis as the patient populations and study endpoints are different. The sponsor plans to present these studies individually in the clinical summary (Section 2.7.4) and compare the studies based on their pre-specified endpoints and the data elements common to both studies.

Does the Agency agree with the approach and that the requirements for an ISE have been met?

FDA Response:

Clinical: Yes

Statistical: Even if the studies cannot be pooled, provide a comprehensive presentation by charting the similarities and dissimilarities of the studies. In 5.3.5.3, you may refer to the Section where you present these comparisons.

Meeting Discussion: None.

Question #6

The Sponsor plans to include case report forms for deaths, other serious adverse events and withdrawals for adverse events from the EVOLVE and ESPRIT clinical trials. Case report forms from the EPIC trials and other trials conducted by the previous Sponsor will not be included.

Does the Agency agree with this approach?

FDA Response: Please confirm you are willing to provide the CRFs from the EPIC trials if requested.

Meeting Discussion: The sponsor confirmed their willingness to provide CRFs from the EPIC trials, if requested.

Regulatory

Question #1

Omthera intends to submit a New Drug Application pursuant to Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act in 1Q/2Q 2013. The archival copy of the NDA will be submitted entirely in electronic format in accordance with the *Guidance for Industry: Providing Regulatory Submissions in Electronic Format—Human Pharmaceutical Product Applications and Related Submissions using the eCTD Specifications (June 2008)*.

Does the Agency have any specific requests regarding the electronic submission or any paper review copies?

FDA Response: Please see the attached document entitled “Pre-NDA General Advice for Planned Marketing Applications” for a list of requests regarding electronic submissions. In addition, we request that laboratory data be presented in conventional units.

We request that you scan any paper review copies in a text readable format and include in the electronic submission.

Lastly, we request that you use the attached DSI site selection tool from the Office of Scientific Investigations and include in the electronic submission.

Meeting Discussion: None.

Question #2

Financial certification for investigators for the EPANOVA trials conducted by Omthera will be provided in the NDA. The Sponsor does not plan to include financial certification or disclosure information for investigators for the clinical trials conducted by the previous Sponsor.

Does the Agency consider this acceptable?

FDA Response: According to 21 CFR part 54, applicants who submit a marketing application for a drug are required to include certain information concerning the compensation to, and financial interests and arrangements of, any clinical investigator conducting clinical studies covered by the regulation. This regulation applies to clinical studies that the applicant relies on to establish that the product is effective, and any study in which a single investigator makes a significant contribution to the demonstration of safety. If these situations are not applicable to the trials conducted by the previous sponsor, then we find your proposal acceptable.

Meeting Discussion: None.

Question #3

Omthera had previously stated at the end-of-phase 2 meeting that the Sponsor would be requesting a deferral for pediatric studies. The Sponsor is now requesting a full pediatric waiver in severe hypertriglyceridemia as severe hypertriglyceridemia is highly uncommon in the pediatric population and completion of the necessary studies in the pediatric population is highly impracticable. The request for a full waiver from pediatric studies will be included in the NDA.

Background

Hypertriglyceridemia is widely believed to be rare in children; however epidemiologic data have been limited. A recent study (Christian et al) of data from National Health and Nutrition Examination Survey (NHANES) (ages 12–19 years) and a large managed-care claims database (ages 5–19 years) confirmed that severe hypertriglyceridemia (≥ 500 mg/dL) in childhood is rare. NHANES found only 3 children with TG ≥ 500 for a weighted percentage of 0.2%. The managed-care database of nearly 3 million children found 257 children with severe hypertriglyceridemia among the 65,258 with fasting laboratory data. Guidelines from the American Academy of Pediatrics Committee on Nutrition recommend pharmacologic therapy only in children 10 and above, and rarely as low as 8 in cases of familial hypertriglyceridemia. The small numbers of patients, particularly in young children, and children's responsiveness to diet, severely limit the feasibility of conducting clinical trials in children with triglycerides ≥ 500 mg/dL.

Does the Agency agree with this approach?

FDA Response: Please include your justification for the full pediatric waiver in severe hypertriglyceridemia with your NDA submission.

Meeting Discussion: None.

Question #4

The Sponsor believes that labeling and routine reporting requirements are sufficient to mitigate risks and preserve benefits of the use of EPANOVA. Therefore, the Sponsor does not plan to submit a Risk Evaluation and Management Strategy (REMS) with the NDA.

Does the Agency agree?

FDA Response: At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and if it is necessary, what the required elements will be. We will determine the need for a REMS during the review of your application.

Meeting Discussion: None.

Question #5

As per the recommendations of the Agency at the end-of-phase 2 meeting in June 2010 regarding submission of the NDA in the 505(b)(1) category, the Sponsor has performed the following non-clinical studies as per CFR 314.50(d)(2)(ii) for a complete nonclinical development package: chronic toxicology (2 species), genotoxicity (*in vitro* and *in vivo*), reproductive and developmental toxicology (rat and rabbit), and carcinogenicity (rat and mouse). The Sponsor plans to provide supportive information from literature for nonclinical pharmacology and pharmacokinetic data. The Sponsor considers the literature to be supportive information but not required for a complete nonclinical package. Based on the nonclinical studies performed with EPANOVA, the Sponsor plans to submit the NDA as a 505(b)(1) application.

Does the Agency agree with this approach?

FDA Response: Reliance on any information, required for approval, for which you either do not own or have right of reference to, will require submission of a 505(b)(2) application.

Meeting Discussion: The firm reiterated their position that their application will be submitted as a 505(b)(1) application. Any literature that is reference they consider general medical knowledge as fatty acids are endogenous compounds. The data reference will relate to the general absorption, distribution, metabolism and excretion of long-chain fatty acids. The sponsor stated that none of the referenced information will be included in any labeling.

The firm's current timeline for submission of the NDA is May 2013.

Additional Clinical Pharmacology comment:

You have not included Study OM-EPA-002 in the list of studies you plan to submit in the NDA. Please confirm your plan for submitting the report for Study OM-EPA-002 in the application. We also remind you of the comment in the End-of-Phase 2 meeting minutes concerning this 16-week dose-response (red blood cell membrane omega-3 fatty acids) study: You should explore the following correlations:

- 1) between pharmacokinetics of omega-3 fatty acids and pharmacodynamics (red blood cells membrane omega-3 fatty acids) and**
- 2) between pharmacodynamics and lipid parameters (e.g., triglyceride and LDL-C).**

Meeting Discussion: The background package included a list of studies that they intend to include for supporting the future NDA. The firm stated that Study OM-EPA-002 was never conducted; however, information from other studies [OM-EPA-006 (ECLIPSE 2), OM-EPA-003 (EVOLVE), and OM-EPA-004 (ESPRIT)] to be included in the application will provide the requested information. This approach appeared to be reasonable by the agency.

3 ISSUES REQUIRING FURTHER DISCUSSION

None

4 ACTION ITEMS

None

5 ATTACHMENTS AND HANDOUTS

Pre-NDA Meeting Discussion Materials

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/s/

KATI JOHNSON
12/18/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107616

MEETING MINUTES

Omthera Pharmaceuticals, Inc.
Attention: Joan Drucker, MD
c/o Radiant Development
515 North State Street, Suite 2700
Chicago, IL 60654

Dear Dr. Drucker:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Epanova (omefas) Capsules.

We also refer to the End-of-Phase 2 meeting between representatives of your firm and the FDA on June 2, 2010. The purpose of the meeting was to discuss your proposed development plan.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-1234.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2

Meeting Date and Time: June 2, 2010, 2 pm – 3 pm
Meeting Location: Food and Drug Administration, White Oak Campus
Building 22, Conference Room 1311
10903 New Hampshire Avenue
Silver Spring, MD 20993

Application Number: IND 107616
Product Name: Epanova[®] (omefas) Capsules
Indication: Hypertriglyceridemia
Sponsor/Applicant Name: Omthera Pharmaceuticals, Inc.

Meeting Chair: Eric Colman, MD
Meeting Recorder: Kati Johnson

FDA ATTENDEES:

Division of Metabolism & Endocrinology Products
Eric Colman, MD-Deputy Director, Lipid Team Leader
Iffat Chowdhury, MD-Clinical Reviewer
Karen Davis Bruno, PhD-PharmTox Supervisor
Parvaneh Espandiari, PhD-PharmTox Reviewer
Kati Johnson-Project Manager

Office of Translational Sciences, Office of Clinical Pharmacology
Sally Choe, PhD-Team Leader
Sang Chung, PhD-Clinical Pharmacology Reviewer

Office of Translational Sciences, Office of Biostatistics
Todd Sahlroot, PhD-Deputy Director, Division of Biometrics II
Japobatra Choudhury, PhD-Statistical Reviewer

Office of New Drug Quality Assessment
Su Tran, PhD-CMC Lead
Martin Haber, PhD-Chemistry Reviewer

SPONSOR ATTENDEES:

Omthera Pharmaceuticals, Inc.
George Horner- Chairman of the Board
Gerald Wisler-President and CEO
Michael Davidson, MD-Chief Medical Officer

(b) (4) -CMC Regulatory Advisor Consultant
(b) (4), CMC Regulatory Advisor Consultant
(b) (4) Clinical Regulatory Advisor Consultant
Joan Drucker, MD-Clinical Regulatory Advisor Radiant Development, Radiant
Research Inc.
(b) (4) Clinical Operations Advisor (b) (4)

1.0 BACKGROUND

The sponsor submitted the IND on March 25, 2010, which included a request for an End-of-Phase 2 meeting to discuss their plans to develop Epanova[®] (omefas) Capsules, as an adjunct to diet, for the treatment of severe hypertriglyceridemia (≥ 500 mg/dL). According to the sponsor, Epanova is a mixture of (b) (4)% DHA and (b) (4)% EPA in their free fatty acid forms, and has the potential advantage of greater bioavailability than existing omega-3-fatty acid alternatives. Currently, the only FDA approved fish oil product is LOVAZA, which consists of approximately 46% EPA and 37% DHA, along with other fish oil components.

Epanova[®] was previously investigated for the treatment of Crohn's Disease under IND (b) (4) in the Division of Gastrointestinal Products.

According to the background package, the sponsor is proposing to conduct the following safety and efficacy studies:

OM-EPA-003- (description begins on page 13 of these minutes)

OM-EPA-004- (description begins on page 18 of these minutes)

The firm is undecided at this time whether they will be submitting a 505(b)(1) or 505(b)(2) NDA.

2. DISCUSSION

NOTE: the firm's background material and questions are in regular text. FDA preliminary comments, conveyed to the firm prior to the meeting, are in **bolded** text. Any meeting discussion is in **bolded underlined** text.

GENERAL DEVELOPMENT QUESTIONS

The proposed NDA for Epanova[®] for the indication for treatment of very high triglycerides (TG > 500 mg/dL) will include protocols OM-EPA-003 (pivotal) and supportive protocols OM-EPA-004 (triglyceride and non-HDL-C reduction in patients on statins with persistent hypertriglyceridemia, i.e. TG > 200 mg/dL), OM-EPA-001 (improved bioavailability with and without high fat meals compared to Lovaza) and OM-EPA-002 (improved incorporation of EPA in the RBC, a biomarker associated with clinical benefits).

Q1. Background:

The triglyceride (TG) lowering properties and other clinical benefits of EPA and DHA are well known. The Food and Drug Administration (FDA) undertook an initiative in 1997 to review the body of evidence bearing on the safety of EPA and DHA, administered or consumed, since EPA

and DHA are food components of fish oil products. In view of considerable information from various published sources, the FDA affirmed that aggregate amounts of EPA+DHA at 3 g/day or less would be considered Generally Recognized as Safe (GRAS: Menhaden Oil. US Fed Reg 1997; 62[108]:30751-30757).

It is our understanding that the FDA has the ability to approve drugs based on a robust single trial. Phase 3 protocol designs similar to OM-EPA-003 were approved by the Agency for other omega-3 products. For example, a Phase 3 study of the ethyl ester of eicosapentaenoic acid (AMR101), 240 patients with very high fasting triglyceride levels ≥ 500 and ≤ 2000 mg/dL are randomized 1:1:1 to either placebo, 2 or 4 gm active daily for 12 weeks was reported to have received a SPA in May 2009. The design of OM-EPA-004 is very similar to the Phase 3 trial for AMR101, with more patients (225 vs. 160) receiving active therapy. The design of OM-EPA-003 is also significantly larger than the Lovaza (omega-3 acid ethylesters) Phase 3 trial, both in numbers (300 versus 84) and doses (2, 3, 4 g/day versus 4 g/day), and very similar to the Phase 3 protocol approved by the FDA for Amarin's AMR101 (ethyl-EPA) including the duration of 12 weeks. The Lovaza Phase 3 study duration was 16 weeks. The AMR101 trial is listed on Clinicaltrials.gov.

Regarding dosing in the OM-EPA-003 study, because omefas in Epanova capsules is a mixture omega-3 fatty acids that contains 75% EPA+DHA, as well as other Omega 3 and Omega 6 fatty acids, the proposed maximum dose of 4 gm in the OM-EPA-003 trial would provide 3 gm of EPA+DHA and be in compliance with the GRAS: Menhaden Oil ruling.

Question 1: Is the single Phase 3 hypertriglyceridemia protocol (OM-EPA-003) sufficient for regulatory approval of the indication for severe hypertriglyceridemia?

FDA Preliminary Response: In part, the sufficiency of a single clinical trial for the indication “as an adjunct to diet to reduce triglycerides in adult patients with very high (≥ 500 mg/dL) triglyceride levels” depends on whether you plan to claim or imply “superiority” of your product to Lovaza. We will expand on our response to this question at the meeting.

Meeting Discussion: The firm stated that it is not their intent to claim superiority to Lovaza® with regard to reduction in TG. They plan to stress the improved bioavailability and lack of food effect and the dosing flexibility of Epanova®. They also stated that they (b) (4)

The Division reiterated that implied superiority claims for TG lowering would necessitate more than one head-to-head clinical trial.

1a. Would the safety exposure from OM-EPA-003 and OM-EPA-004, in conjunction with the safety data from over 400 patients who received 4 grams daily for 52+ weeks of therapy in studies of patients with Crohn's Disease, be sufficient for registration?

Background: Exposure to Epanova in the previous Crohn’s Disease patients is summarized in [Table 3-1](#). Overall, the EPIC studies included 393 patients, with exposure ranging from 1 to 743 days, including the extension study (EPIC-1E). Greater than 90% were Caucasians, ~50% male or female, mean age ranged from 36 to 41 years (range:18 to 82 yrs).

Table 3-1. Exposure to Epanova in Clinical Studies

| | EPIC-1 | | EPIC-2 | | EPIC-3 | EPIC-1E |
|--|---------------|---------------|---------------|---------------|--------------|---------------|
| | Epanova | Placebo | Epanova | Placebo | Epanova | Epanova |
| Duration of exposure¹ (days) | | | | | | |
| N | 183 | 181 | 183 | 183 | 25 | 77 |
| Mean ± SD | 265.6 ± 139.2 | 250.6 ± 142.6 | 246.2 ± 156.1 | 248.4 ± 160.6 | 326.7 ± 93.7 | 443.9 ± 195.9 |
| Range | 1-432 | 2-409 | 2-431 | 12-446 | 17-410 | 1-743 |
| Number of capsules² | | | | | | |
| N | 177 | 173 | 175 | 177 | 25 | 77 |
| Mean ± SD | 968.4 ± 550.0 | 903.8 ± 541.6 | 897.6 ± 611.6 | 900.6 ± 617.9 | 1239 ± 382.4 | 1581 ± 744.4 |
| Range | 1-1702 | 9-1753 | 2-1761 | 17-1775 | 43-1583 | 47-2864 |
| Patient-Years³ | | | | | | |
| | 134.6 | -- | 123.4 | -- | 22.4 | 93.6 |

Note: SD=Standard deviation; Epanova escalated from 1 to 2 gm/daily for Weeks 1 and 2, respectively, then 4 gm/daily thereafter.

¹ Calculated if date of last dose was available

² Calculated if numbers of capsules dispensed and returned were available for all visits

³ Calculated as number of patients x mean duration (years)

Healthy patients, enrolled in SPC 275-4, were exposed to Epanova in 4 doses: Epanova soft gel capsule 2 g/day, 4 g/day or 8 g/day; and Epanova hard gel capsule 4.5 g/day. Each dose was taken by 12 healthy patients for a period of 43 days or 1.4 patient-years per dose. Total exposure to Epanova by healthy individuals with all doses combined was 5.6 patient-years.

The 003 protocol includes doses of 2 g/day, 3g/day or 4 g/day for 12 weeks, 75 patients per dose, for a total of 225 patients. The 004 protocol, a combination of Epanova and a statin, includes doses of 2 g/day, 3 g/day and 4 g/day, each with a statin, for 6 weeks, 150 patients at each dose, for a total of 450 patients. These patients could continue in a proposed extension study for up to 6 months, before enrolling in the possible CV outcomes trial.

The ICH recommends that 100 patients be exposed for a minimum of 1 year in safety studies (<http://www.ich.org/LOB/media/MEDIA435.pdf>). The Sponsor assumes its studies will fulfill this requirement.

FDA Preliminary Response: Possibly; the applicability of the safety data from the EPIC trials to IND 107,616 will depend upon the details of the safety assessments conducted under IND (b) (4). The answer to this question will also depend on whether you submit data from OM-EPA-004 with the NDA.

Meeting Discussion: The sponsor clarified that the study report for OM-EPA-004 would be included in the initial NDA submission. Given this information, the number of patients in the EPIC studies becomes less important. In response to a question, the sponsor agreed to provide a comprehensive list of the safety assessments that were monitored during the EPIC trials.

1b. Are the planned studies evaluating dosages of 2, 3, and 4 grams daily of Epanova acceptable to establish one or more dosages in the product label?

Background: The basis for establishing a dose range for the indication stems from the anticipated superior bioavailability of Epanova over other omega-3 formulations and lack of food effect. The food-effect constraint with ethyl ester formulations was recently emphasized in the EMEA assessment of Amarin's AMR101 for treatment of Huntington's Disease, dated March 04, 2010.

See page 13, section III.2 Clinical Aspects:

“Ethyl-eicosapent acts as a pro-drug for eicosapentaenoic acid (EPA), since no ethyl ester has been detected [in plasma]. EPA ethyl ester is poorly absorbed as compared with the triglyceride form from single doses with no food or low-fat food, but the absorption is significantly increased when co-ingested with fat (either as high-fat meal or as olive oil) from single doses, or with a regular meal from multiple doses as compared with the triglyceride form. Therefore, EPA is incompletely absorbed from oral administration, but absorption is largely improved when co-administered with fat. Thus it is recommended that the drug is taken with or after food.”

FDA Preliminary Response: Protocol OM-EPA-003 is the only study proposed in the Briefing Document that would support the ≥ 500 mg/dL hypertriglyceridemia indication. In order to make informed drug development decisions on trial design and regimen selection, the Division encourages the sponsor to use all prior knowledge, including dose-response models, for their drug product. Furthermore, the potential approval of one or more dosages will depend on the efficacy and safety results from the clinical trial(s).

Meeting Discussion: In response to a question, the firm stated their intent to submit the protocol for OM-EPA-003 for review under the Special Protocol Assessment procedure.

1c. The expected triglyceride-lowering efficacy for Epanova is at least 20% for any dose, which we believe is a clinically important difference. Does FDA agree? If not, what is the minimum percent TG-lowering required for registration?

Background: As shown in the following figures, Epanova at 4 g/day for 30 or more weeks resulted in a decrease in serum triglycerides of at least 20%, relative to baseline levels that were >150 mg/dL, whereas placebo showed reductions <10%, or a slight increase, in Crohn's disease patients (*Figure 3-1*). In healthy subjects with normal TG levels, reductions from baseline of approximately 20-25% were seen after 6 weeks of treatment with 4 g of Epanova (*Figure 3-2*). In a recent metanalysis of 47 clinical trials in hyperlipidemic patients, the dose dependent reduction of triglycerides correlated with both EPA+DHA intake and the initial TG level. (*Int J Cardiol.* 2009 Jul 24;136(1):4-16. Epub 2008 Sep 6). Therefore in severe hypertriglyceridemic patients, the triglyceride reduction is expected to be greater than 20% (i.e. > 100 mg/dl decrease in triglycerides).

Figure 3-1 Treatment Effect of Epanova® (4 g/day) on Serum Triglycerides in EPIC-1 and EPIC-2

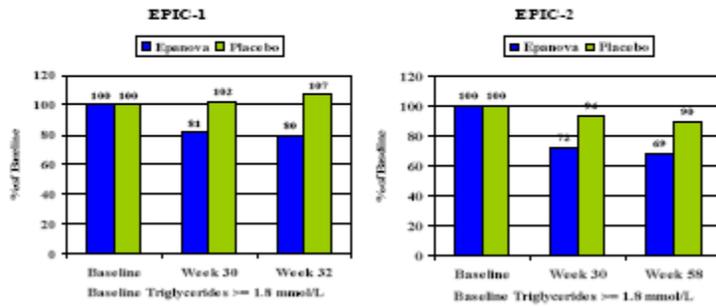
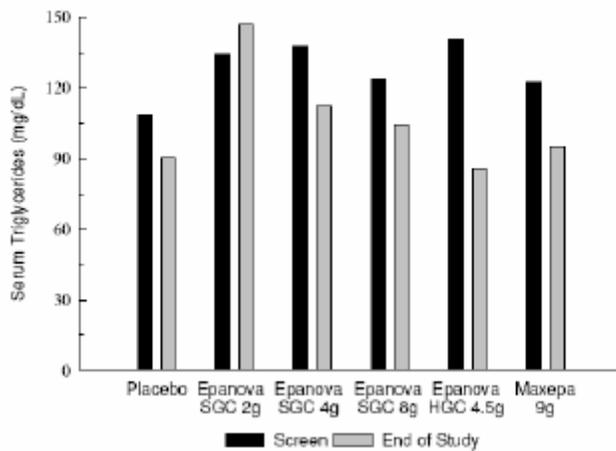
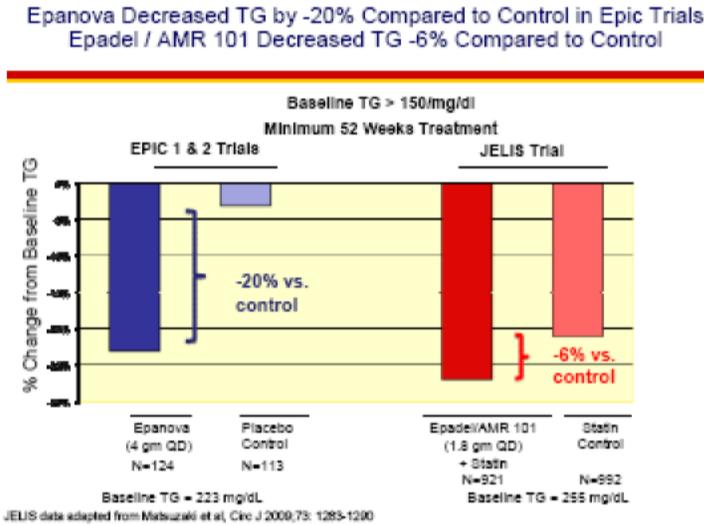


Figure 3-2 Treatment Effect of Placebo, Epanova SGC, Epanova HGC, and MaxEPA on Serum Triglycerides in SPC 275-4 (Healthy Volunteers) (Screen= Day 1; End of Study= Day 43)



A comparison of the EPIC trials (Epanova in Crohn's disease patients) to the JELIS trial (EPA-ethyl ester in combination with statin therapy in hypercholesterolemic patients), shows that Epanova, 4 g/day for at least 52 weeks, resulted in a 20% reduction in serum triglycerides relative to baseline, whereas the addition of Epadel/AMR101 (EPA-ethyl ester) to a statin regimen resulted in a 6% reduction from baseline (*Figure 3-3*).

Figure 3-3 Comparison of TG lowering in the EPIC and JELIS trials



FDA Preliminary Response: We request that you submit your justification that a 20% decrease in TG is a “clinically-important difference”.

Meeting Discussion: The firm does not have a justification that a 20% decrease in TG is “clinically important”. According to the firm, Lovaza® lowered TG approximately 30%.

Study OM-EPA-003 is powered to show a 20% difference at the lowest dose (2 mg/day). The Division surmised that there may not be a market for the lowest dose given that patients with TG > 500 mg/dL are likely to require multiple potent drugs. The statisticians added that if there is the expected variability in the TG results, statistical significance (p=.05) could be obtained with only a 14% reduction in TG.

1d. [Redacted] (b) (4)

Background: It is common to include supporting Phase 3 studies in the “Clinical Trials” section of the label. For example, [Redacted] (b) (4)

FDA Preliminary Response: An NDA submission that includes a clinical trial with [Redacted] (b) (4)

Meeting discussion: None

Question 2: Omthera initially submitted a 505(b)(1) application on March 25, 2010. We plan to rely on information in the public domain about omega-3 products and omega-3 formulations. Based upon the wealth of information about omega-3 products, including all the preclinical and clinical data, we are requesting to confirm that you agree that this information can be used to complement our package and that this application is a 505(b)(1). In this regard, we request that the available preclinical and clinical data does not have to be repeated and that no additional information, other than that currently planned, is required for a 505(b)(1) application. If the Agency does not consider this applicable for a 505(b)(1), is the information in the existing and planned package adequate for a 505(b)(2) application?

Background:

Although in IND No. 107,616 we had designated we were filing Epanova under 505(b)(1), we understand from FDA input that the 505(b)(2) designation is felt to be more appropriate. The initial rationale for the 505(b)(1) was based on the fact that the Sponsor has conducted extensive original preclinical and clinical work that has been completed, or is planned, and that the information in the public domain being referenced on DHA and EPA, which occur naturally in the body, are considered GRAS and are available in various forms without a prescription. It would be helpful for the Division to clarify that it still considers any reference to the available public information to require a 505(b)(2) designation.

As noted above, preclinical and clinical studies have been conducted with Epanova and are provided below. With the exception of nonclinical carcinogenicity, genotoxicity/mutagenicity and reproductive/developmental toxicity studies, a complete preclinical package has been submitted with IND No. 107,616 in support of Epanova. Included preclinical studies are:

1. Omefas® (Epanova®): Cytochrome P450 Inhibition Study (Screening in Human Liver Microsomes) (Study No. 03101701).
2. Omefas® (Epanova®): Inhibition of Cytochrome P450 Isoenzymes 2B6, 2C8, and 2C9 (Study No. 300101).
3. Investigation of the Influence of Omefas® on the “*in vitro*” Permeation of Methotrexate Across Caco-2 Cell Monolayer (Study No. STP 033/00).
4. 4-week Subacute Toxicity Study of Omefas® (Active Principle of Epanova®) by Oral Administration to Rats. (b)(4) Report No. 22004. Final Report. April 21, 2008.
5. 2-Week Dose-Range-Finding Study for a 4-Week Subacute Toxicity Study of Omefas® (Active Principle of Epanova®) by Repeated Oral Administration to CD® Rats. (b)(4) Report No. 20129/06. Final Report. March 7, 2007.
6. 4-week Subacute Toxicity Study of Epanova® Coated Capsules by Oral Administration to Dogs. (b)(4) Report No. 22005. Final Report. April 28, 2008.
7. Dose-Range-Finding Study for a 4-week Subacute Toxicity Study of Epanova® Coated Capsules by Repeated Oral Administration to Beagle Dogs. (b)(4) Report No. 20130/06. Final Report. March 7, 2007.

Similarly, a large clinical database of over 1300 patients (over 400 from the Crohn’s development program and 900 from the hypertriglyceridemia program) will be available for review at the time of the initial NDA. Many of the specific clinical studies (e.g., QTc, additional

drug-interaction, etc.) that are normally to be included in an NDA are not considered necessary for Epanova since EPA and DHA occur naturally within the body.

FDA Preliminary Response: The preclinical data requirements will be addressed by the Pharmacology/toxicology Review Team. However, from the clinical standpoint, a GRAS designation would not preclude the necessity of a complete and adequate NDA.

The requirements for a 505(b)(1) application are addressed in 21 CFR § 314.50(d)(2)(ii) which refers to the submission of studies “assessing the drug’s acute, subacute, and chronic toxicity [including] carcinogenicity”. A 505(b)(2) application is required to submit the same information as a 505(b)(1), but can rely on the Reference Listed Drug for data for which there is no right of reference.

Question 3:

(b) (4)

Background:

(b) (4)

(b) (4)

FDA Preliminary Response: The pediatric waiver issue will be determined at a later date.

Meeting Discussion: The Division acknowledged the request for a (b) (4) waiver, of the requirement for pediatric studies under PREA (Pediatric Research and Equity Act). (b) (4)

4 PROTOCOL QUESTIONS

4.1 OM-EPA-003 (Epanova Dose-Finding in Hypertriglyceridemia)

Background (see Appendix A, Attachment 1, for the full protocol):

In patients with severe hypertriglyceridemia (≥ 500 mg/dL), the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults recommended that triglyceride (TG) reduction should be considered the primary target of treatment (Circulation. 2002; 106:3143-421 and update Circulation. 2004; 110:227-239). The NCEP panel recognized that statins are not powerful TG-lowering drugs, and therefore recommended the use of specific therapies to lower TG levels in patients with severe hypertriglyceridemia (fish oils to replace some long-chain triglycerides in diet, fibrates or nicotinic acid).

During the last 30 years, epidemiological studies reported a relationship between lower serum triglyceride concentrations and the consumption of omega-3 fatty acids-rich fish. Further, clinical studies have shown that consumption of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) reduce the risk of cardiovascular disease and lower elevated serum triglyceride concentrations. Marine-based omega-3 fatty acids (EPA and DHA) were shown to be more effective than the plant-based alpha-linoleic acid products, with the former lowering serum TG levels 25-30% after consuming 3-4 g/day EPA+DHA compared to controls. Therefore, marine omega-3 fatty acids represent a class of compounds with demonstrated efficacy in reducing elevated TG levels.

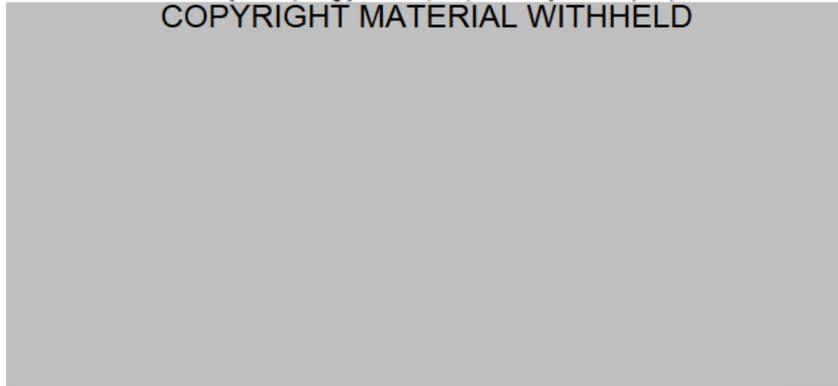
A fatty fish diet provides only modest doses of the polyunsaturated omega-3 fatty acids (EPA and DHA) needed to treat severe hypertriglyceridemia. Therefore, omega-3 concentrates are more suitable for this purpose. Unprocessed marine oil products contain only approximately 30% omega-3 fatty acids while the concentrates, after ethanol extraction and distillation, contain approximately 80% omega-3 in the form of ethyl esters.

Recently, a concentrate of omega-3-acid ethyl esters (Lovaza®) was approved by the Food and Drug Administration (FDA) as an adjunct to diet for the reduction of very high (≥ 500 mg/dL) triglyceride levels in adult patients. This product provides $\frac{(b)}{(4)}\%$ content of EPA+ DHA ethyl esters. Epanova® has $\frac{(b)}{(4)}\%$ ethyl esters into omega-3 free fatty acids (FFAs) with a final concentration of 75% EPA + DHA (omefas). Therefore, intestinal absorption of the omega-3 FFAs in Epanova will not require the hydrolysis break down with pancreatic lipase as is required for the ethyl ester form in the small intestine (see *Figure 4-1*). It is also important to note that the molecular weight of the free fatty acid EPA and DHA in Epanova is less than the molecular weight of ethyl ester EPA and DHA in Lovaza. Accounting for this difference, 465 mg of ethyl-EPA is equivalent to 426 mg of EPA in the free fatty acid form and 375 mg of ethyl-DHA is equivalent to 346 mg of DHA in the free fatty acid form. Therefore, the $\frac{(b)}{(4)}\%$ EPA + DHA in Lovaza is comparable to the 75% EPA + DHA in Epanova.

Figure 4-1 Digestion and Absorption of EPA and DHA as Ethyl Esters or Free Fatty Acids
(not reproduced here)

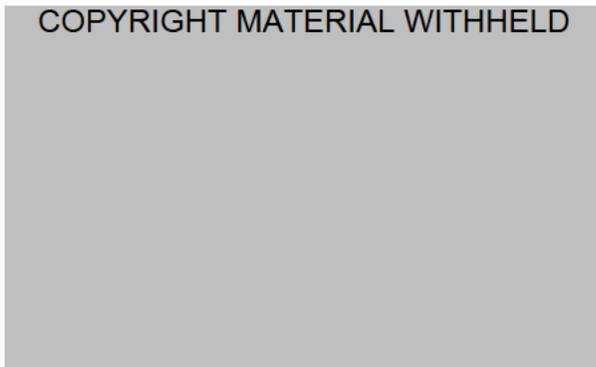
Previous studies have demonstrated that the triglyceride form of marine omega-3 fatty acids, EPA and DHA are more resistant to pancreatic lipase hydrolysis compared to other polyunsaturated fatty acids. Furthermore, ethyl ester omega-3 fatty acids are up to 50 times more resistant than the natural triglyceride form to pancreatic lipase hydrolysis. Several studies have compared human intestinal absorption of fish oil fatty acids in the form of triglyceride, ethyl ester and FFA and found that FFAs have up to 5 times more bioavailability as determined by the plasma area under the curve (AUC) than the ethyl ester form. (see [Figure 4-2](#) and [Figure 4-3](#))

Figure 4-2 Plasma Concentrations of EPA after Digestion and Absorption of Omega-3 Free Fatty Acids, Triglycerides (TGs) and Ethyl Esters (EEs)



Source: Lawson and Hughes, 1988

Figure 4-3 Mean Plasma Levels of EPA/AA after a Single Administration of 0 g placebo, 1.680 g Triglycerides (TG), 1.345 g Free Acids and 1.860 g Ethyl Esters (EE)



Source: Beckmann et al. *Journal of Lipidology* 1999;4(4):400-4

Pancreatic lipases are secreted into the intestines in response to fat intake. Patients with hypertriglyceridemia are advised to restrict fat intake and therefore pancreatic lipase secretion may be impaired with severe hypertriglyceridemia, which could lead to pancreatic insufficiency and fat malabsorption. Absorption of the FFA form of omega-3 EPA and DHA would not be compromised by a fat intake restriction and would offer a therapeutic advantage over the ethyl ester to the patient with severe hypertriglyceridemia.

Epanova as an FFA formulation has 100% bioavailability, which, unlike ethyl esters, has little or no dependence on meal fat content. In a Phase 2b, open-label, clinical study of Epanova in which patients were taking 4 g per day for 52 weeks without regard to meal timing, trough plasma levels of EPA had reached a steady-state level by Week 16 at which EPA levels increased 351% from baseline. This is in contrast to a Lovaza study in which 16 weeks of 4 g per day dosing increased trough EPA levels only 163% from baseline (Harris; J Cardiovasc Risk. 1997; 4:385-91). In the Epanova study, red blood cell membrane EPA also stabilized at Week 16.

Epanova capsules are coated with a polyacrylate material that (b) (4)

Mild GI effects were reported in the Epanova clinical trials, but there was no relationship between the dose of Epanova administered and the severity or incidence of GI adverse events, and moreover, the frequency of GI effects in placebo and Epanova groups were comparable. This lack of a dose-response relationship between the severity and incidence of GI effects following exposure to Epanova is also consistent with the published literature reports of adverse events following EPA and DHA exposure.

While changes in bleeding time, low-density lipoprotein cholesterol (LDL-C), and glucose have been previously presented as possible negative effects of EPA and DHA exposure, data from clinical trials using Epanova at doses of 4 g/day have not reported such effects.

Rationale:

Previous studies have demonstrated that ethyl ester omega-3 fatty acids are poorly absorbed compared to free fatty acid (FFA) formulations. The difference in bioavailability is partially offset if the ethyl ester form is consumed with a high fat meal. However, Lovaza 4 grams per day, is presently indicated for the treatment of severe hypertriglyceridemia and is administered regardless of meal timing. Epanova as an FFA formulation should have improved bioavailability compared to Lovaza regardless of meal timing. Furthermore, Epanova may have an apparent bioavailability advantage over Lovaza with regard to diet because the NCEP ATP III guidelines recommend that patients with severe TG elevations adhere to the lower fat TLC diet.

Dosing with Epanova, 2 to 4 g per day, is based on the assumption that 4 g per day is the maximum therapeutic dose and is in agreement with the FDA ruling that EPA and DHA aggregate amounts are regarded as safe (GRAS status) at a maximum EPA + DHA total of 3 g per day. Epanova contains approximately 75% EPA+DHA FFA, giving 3 g per day with 100% bioavailability at the maximum 4 g dose. Lovaza, approved at 4 g per day, has approximately (b) (4)% EPA+DHA ethyl esters, which is equal to approximately (b) (4)% FFA; however, the amount available for absorption, because of the required pancreatic digestion, is assumed to be considerably less than (b) (4) g per day. The Lovaza prescribing information for the indication of severe hypertriglyceridemia (≥ 500 mg/dL) recommends a daily dose of 4 grams per day (either 2 grams twice per day or 4 grams once per day). The primary concept of this protocol

is that the comparatively greater bioavailability of EPA+DHA free fatty acids of Epanova over Lovaza ethyl esters could result in an acceptable efficacy at a lower dose per day (perhaps 2 or 3 g per day).

The current protocol (OM-EPA-003) will investigate the efficacy of Epanova required for regulatory approval of its indication as an adjunct to diet in severe hypertriglyceridemia. The study is a prospective, double-blind, randomized, parallel 4-arm design including 300 patients for 12 weeks of treatment and 8 clinic visits (one screening, three lead-in/baseline, and four treatment). Patients currently on lipid modifying prescriptions or supplements will undergo an initial four-week lead-in period during which they will discontinue use of any non-study-related lipid-lowering agents, and follow the NCEP Therapeutics Lifestyles Changes (TLC) diet. After the washout/diet lead-in phase, patients who meet the entry criteria will be randomized 1:1:1:1 to receive either placebo (olive oil, 4g/day), Epanova 2 g/day (plus 2g/day placebo), Epanova 3g/day (plus 1g/day placebo) or Epanova 4g/day, and continue the TLC diet. Patients will consume their 4 capsules every day without regard to meal timing over a 12-week treatment period.

Primary Objectives:

The primary objectives of this study are to evaluate the efficacy and safety of Epanova in patients with severe hypertriglyceridemia defined as serum TG values ≥ 500 and < 2000 mg/dL (≥ 5.65 mmol/L and < 22.60 mmol/L). The primary efficacy analyses will evaluate the effects of each dose of Epanova, relative to placebo, on fasting serum TG levels after 12 weeks of treatment. The primary safety and tolerability evaluation will be the review of adverse events at each dose, compared to placebo.

Secondary Objectives:

- to assess the effects of each dose of Epanova on fasting levels of non-high density lipoprotein cholesterol (non-HDL-C), high density lipoprotein cholesterol (HDL-C), LDL-C, and apolipoprotein B (apo B).
- to evaluate the effects of each dose of Epanova on other safety parameters including blood pressure, routine chemistry and hematology tests, urinalyses, and electrocardiograms.
- to assess the effects of each dose of Epanova on other lipid and lipoprotein parameters including total cholesterol (TC), TC : HDL-C ratio, very low density lipoprotein (VLDL) cholesterol, apolipoprotein A-I (apo A-I), apolipoprotein C-III (apo C-III), and remnant lipoprotein cholesterol (RLP-C).

Tertiary Objectives:

- to measure the effects of each dose of Epanova on serum EPA, DHA, and arachidonic acid (AA).
- to evaluate the effect of each dose of Epanova on lipid subfractions.
- to evaluate the effect of each dose of Epanova on lipoprotein-associated phospholipase A2 (Lp-PLA2) and high sensitivity C-reactive protein (hs-CRP).

Overall Study Design and Sample Size:

This is a prospective, double-blind, randomized, parallel 4-arm study with 300 patients for 12 weeks of treatment (see [Figure 4-4](#): Flow Diagram) and 8 clinic visits (one screening, two diet

lead-in, one randomization and four treatment; see Table 6.1: Schedule of Procedures). Patients will undergo an initial four-week lead-in period, stopping use of prohibited medications, and following the NCEP TLC diet. After the diet lead-in phase, patients who meet the entry criteria will be randomized 1:1:1:1 to receive either placebo (olive oil) 4 g/day, Epanova 2 g/day plus placebo 2 g/day, Epanova 3 g/day plus placebo 1 g/day, or Epanova 4 g/day every day for 12 weeks. Patients will consume the dose of 4 capsules daily, without regard to meals, for 12 weeks. At scheduled visits, the daily dose will not be taken until after fasting blood draws are collected. Any patient who terminates the study early will undergo procedures scheduled for the Week 12 visit. The study duration for each patient (including screening and diet lead-in) will be approximately 16 weeks.

A patient sample size of N=75 per arm is expected to provide at least 90% power to detect a decrease of 20% or more in TG levels compared to placebo, assuming a common standard deviation (SD) in percent changes of 35% and a two-sided alpha = 0.05 adjusted for multiple dose testing versus placebo. A total study population of 300 patients will be enrolled. The sample size does not account for attrition or noncompliance of patients.

Dosing with Epanova, 2 to 4 g per day, is based on the assumption that 4 g per day is the maximum therapeutic dose and is in agreement with the FDA ruling that EPA and DHA aggregate amounts are regarded as safe (GRAS status) at a maximum EPA + DHA total of 3 g per day.

Question 4: The sample size of 300 patients (225 exposed to Epanova, 75 to placebo) is expected to provide at least 90% power to detect a decrease of 20% or more in TG levels for any dose compared to placebo. Is this sample size estimate sufficient to show efficacy for the indication: “as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with very high (≥ 500 mg/dL) TG levels”?

FDA Preliminary Response: Justify why your sample size does not account for attrition.

Meeting Discussion: According to the firm, attrition was factored into the sample size.

4a. Is the sample size of 225 patients exposed to Epanova sufficient for safety, when combined with exposure data from OM-EPA-004 and previous studies in patients with Crohn’s disease?

FDA Preliminary Response: See response to 1a.

Meeting Discussion: see Meeting Discussion for Question 1a.

4b. Is the study duration of 12 weeks sufficient?

FDA Preliminary Response: Most likely, but we defer a final response until after we have had a chance to see what safety assessments were made during the EPIC studies.

Meeting Discussion: The firm requested clarification of the preliminary response. The Division stated that the preference with all TG lowering drugs is for longer term (greater than 12 weeks) of controlled data, rather than open-label data.

If the safety assessments were appropriate in the EPIC studies, then the safety data from those studies may be acceptable for the current IND. The data from the EPIC trials become less important if completed data from OM-EPA-004 are submitted with the NDA.

The firm reiterated their commitment to submit the safety assessments for the EPIC trials.

4c. Are the patient population and inclusion/exclusion criteria appropriate (i.e., men or women, ≥ 18 yrs; serum TG values at screening in the range ≥ 500 mg/dL and < 2000 mg/dL and body mass index ≥ 20 kg/m²)?

FDA Preliminary Response: Most likely yes, but a final response will be provided with the Special Protocol Assessment.

Meeting Discussion: None

4d. Is the endpoint (triglyceride reduction) appropriate?

FDA Preliminary Response: Yes

Meeting Discussion: None

4.2 [Redacted] (b) (4)
[Redacted] (b) (4) [Redacted] (b) (4)

[Redacted] (b) (4)

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FDA Preliminary Response: We would be amenable to a teleconference following receipt of a protocol synopsis.

4.3 OM-EPA-001 and -002 (Epanova-Lovaza Bioavailability)

Question 6: We believe that the bioavailability studies OM-EPA-001 and -002 provide important information to the prescribing physician and propose  (b) (4)

 Does the Agency agree?



FDA Preliminary Response:

No. We recommend presenting the comparative bioavailability and food effect information in the Pharmacokinetics section (12.3) and the pharmacodynamic information in the Pharmacodynamics section (12.2).

Additional Comments:

- 1. Protocol OM-EPA-001: single dose comparative pharmacokinetic study and food effect study:
You should consider a baseline adjustment for the EPA and DHA pharmacokinetics if pre-dose plasma concentrations of EPA and DHA are not negligible, and report both unadjusted and adjusted pharmacokinetic parameters.**
- 2. Protocol OM-EPA-002: 16 weeks dose-response (red blood cell membrane omega-3 fatty acids) study:
You should explore the following correlations: 1) between pharmacokinetics of omega-3 fatty acids and pharmacodynamics (red blood cells membrane omega-3 fatty acids) and 2) between pharmacodynamics and lipid parameters (e.g., triglyceride and LDL-C).**

Meeting Discussion: The sponsor said that the study was not powered for lipids. The agency said that this request pertains to the dose response question.

- 3. You should evaluate the drug interaction potential between Epanova and statins. To address the interaction potential, you can consider population pharmacokinetic analyses using sparse plasma sampling from Study OM-EPA-004 or conduct a dedicated in vivo drug interaction study.**
- 4. You should characterize a dosage form equivalence (e.g., equivalence between two capsules of 2 g and one capsule of 4 g) if components and composition are not proportional among formulations.**

Meeting Discussion: The product only comes in a 1 gram capsule, so the above comment on dosage form equivalence does not apply.

5 PRECLINICAL QUESTIONS

Question 7:

(b) (4)

(b) (4)

FDA Preliminary Response:

We do not agree. It is unclear whether Omthera plans to submit a 505(b)1 or a 505(b)2 NDA application for Epanova. A stand alone 505(b)1 application will require a complete nonclinical development package e.g. chronic toxicology (2 species), gentox (in vitro and in vivo), reprotox (rat, rabbit) and carcinogenicity (rat, mouse). A 505(b)2 application will require identification of a relevant reference listed product on which we can rely on the Agency's previous finding of safety and efficacy. Omthera will need to provide nonclinical toxicology data as well as requisite chemistry information that demonstrate sufficient similarity between Epanova and the reference listed drug to permit reliance, where scientifically justified, on certain existing information for a NDA. Additional nonclinical studies will be needed to support the safety of Epanova irregardless of the regulatory pathway chosen for NDA submission of your product.

Meeting Discussion:

The firm is currently undecided as to the type of application it will be submitting. If they choose to submit a 505(b)(1) application, they will have to conduct all preclinical studies (including carcinogenicity). Given the agency's response to Question 9 that the amount of exclusivity is only determined following approval, it is difficult to obtain sufficient capital to develop the compound in the absence of knowledge as to whether 3 years or 5 years of marketing exclusivity would be granted. A 505(b)(2) application relying on either the currently approved Lovaza or literature references for studies conducted using one or more components of Lovaza is problematic given that the "active component" of Lovaza has not been defined by the agency.

The firm again requested whether or not this product would be considered a new chemical entity (NCE) (and entitled to 5 years of exclusivity). The division suggested that they compile a package which makes their case for NCE designation, and we would attempt to work with the appropriate people within the agency to obtain a response to their question. The sponsor stated that this information was contained in the background package, so the division will initiate the internal discussion to attempt to resolve this issue.

The agency clarified that a 505(b)(1) NDA can be submitted for a compound that is not a NCE.

Epanova contains free fatty acid forms of DHA and EPA in different percentages compared to Lovaza. Should you decide to submit a 505(b)(2) NDA, 3-month comparative tox study with the listed drug e.g. Lovaza in an appropriate species, with complete CMC information will likely be needed. Referenced toxicity studies in literature using DHA and EPA identified in the briefing package are unlikely to be sufficient to support the NDA.

6 CHEMISTRY, MANUFACTURING AND CONTROL (CMC) QUESTIONS

Question 8: In view of the additional information provided by Omthera on manufacturing controls, does the Agency now agree with the previous conclusions on the designation of the (b) (4) as the starting material for omefas (i.e., the point at which pharmaceutical cGMP will be introduced) for drug substance manufacture of commercial supplies and/or that the GMP controls applied prior to the production of the (b) (4) are appropriate?

Background

At a meeting with the Division of Gastroenterology Products in December 2005, it was agreed with Tillotts Pharma AG that the starting material for the application of pharmaceutical GMPs would be the (b) (4) (see Appendix B). The question and response were as follows;

Q 4 Does the Agency agree with our designation of the starting material for drug substance manufacture?

Agency response:

(b) (4) *may be considered as starting materials for the manufacture of the drug substance provided that you have appropriate specifications for these materials, that you provide a complete description of the procedures used to produce (b) (4) and that you make a to notify the Agency of any changes to these procedures.*

The development of this product has been transferred to Omthera Pharmaceuticals Inc. (Omthera) and in December 2009, Omthera requested that the Agency confirm the acceptability of the definition of the starting material for the start of pharmaceutical GMPs.

The Division of Metabolism and Endocrinology Products (The Division) replied on February 2, 2010 (see Appendix B, Attachment 2) as follows:

Agency response

No, we do not agree with your proposal to designate (b) (4) as starting material of your drug manufacturing process. The starting material of your drug substance will be the crude fish oil. As per ICHQ7A,

(b) (4)
The drug/pharmaceutical GMPs will apply to the entire manufacturing process of the drug substance starting with the crude fish oil. In addition the following information on your biological starting material should be included in your submissions: species

identification, countries of origin, and a list of known diseases, pathogens and contaminants associated with fish. In FDA's experience, it is unrealistic to expect that a sponsor would be fully informed of changes in the non-drug GMP manufacture of the starting material by the non-drug GMP manufacturer, and that a specification alone cannot assure acceptable quality of a material.

In the following, Omthera has attempted to address each of the issues raised by the Division and to provide additional detail and clarity on the proposals relating to the GMPs to be used in manufacture of the drug substance.

Controls for Manufacturing the Starting Material

In the information supplied with the request of December 2009 (FDA response February 2, 2010; see Appendix B, Attachment 2), Omthera used the terminology "food GMP". This was an error relating to the earlier discussions with the Agency in December 14, 2005 (see Appendix B, Attachment 1) and should have referred to dietary supplement GMPs (21 CFR Part 111) as opposed to food GMP (generally understood as 21 CFR Part 110). We apologize for this error.

In order to plan and establish a strategy for commercial manufacture Omthera needs to confirm the Agency position regarding application of GMPs. As we reported previously, much of the Ocean Nutrition Canada (ONC) process for manufacture of fish-oil-derived commodity products used in dietary supplements such as omega-3 fatty acid esters, including some supplied for sale in the USA, is similar to the process for omefas up to the stage of conversion to free fatty acids. Readers will note later in this background that ONC is licensed by Health Canada to manufacture the two (b) (4). In the following, we are providing additional information that we trust will allow the Division to reconsider the request made in our December 2009 letter that the (b) (4) are acceptable as the defined starting material for the start of pharmaceutical cGMP as defined in ICH Q7A.

Omthera recognizes that tight controls should be applied following ONC's receipt of the (b) (4) fish oil, which is collected and initially processed in (b) (4). The crude fish oil (b) (4) will be received and tested for conformance to a specification to be developed as further data become available (the current specification for crude fish oil is provided in (Table 6-2), and thereafter, the processes (Figure 6-2) will proceed at ONC in accordance with dietary supplement GMP and the Fish and Fishery Products (Seafood) HACCP requirements, with hydrolysis, distillation, (b) (4) and bulk packaging being performed under pharmaceutical cGMP at BioVectra (Figure 6-3). The increasing standards of GMP, as defined in ICH Q7A, to be applied to steps of the API process are illustrated schematically in Table 6-1(not reproduced here) as they relate to the manufacture of omefas.

Additional information regarding, the dietary supplement GMPs, Seafood HACCP and ONC's quality system is provided below.

Following the Division's response of February 2, 2010, Omthera has reviewed the available guidance, in particular that provided in ICH Q7A, and compared its requirements to those in FDA's dietary supplement GMPs. Details of this comparison are provided in Appendix B, Attachment 3. We also reviewed the requirements of FDA's Seafood HACCP regulation (21 CFR 123). As a consequence of these reviews and the additional information provided, Omthera believes that the dietary supplement GMPs, taken together with the HACCP rules, provide sufficient and substantially the same level of control that ICH Q7A provides for manufacturing APIs for clinical supplies and for the early steps in a commercial API process.

The comparison of the dietary supplement GMPs and ICH Q7A show some differences. In some respects, particularly regarding the requirements for specifications and the level of detail set forth in some Subparts, the rules applicable to supplement manufacture appear more rigorous. In other respects, particularly with regard to process validation, the drug rules appear more rigorous.

The text of the dietary supplement GMPs requires manufacturers to demonstrate they can consistently meet specifications. While this language is similar to the definition of validation, there is no mention of the words "valid" or "validation" other than with reference to analytical methods. The critical steps in a manufacturing process that require validation are generally later in an API process than the steps performed by ONC. The Introduction of ICH Q7A, among other things, states, "the stringency of GMP in API manufacturing should increase as the process proceeds". The dietary supplement regulation does not require internal audits. While ICH Q7A includes an internal audit element, there is no such requirement in the cGMP regulations for finished pharmaceuticals. Despite there being no specific requirement for internal audits, beginning in April 2004 ONC arranged for third party audits against the ICH Q7A guideline.

Other requirements of the regulations applicable to dietary supplements, which on first reading appear less rigorous than ICH Q7A elements, include those for change control and product quality review. Regarding change control, it should be noted that the preamble to the regulation states that all written procedures must be approved or rejected by Quality Control. FDA has historically pointed to preambles as a source of policy guidance. The cGMP regulations for finished pharmaceuticals (21 CFR Part 211), which were a progenitor of ICH Q7A, likewise appear less rigorous than ICH Q7A regarding change control; however, guidance documents such as those for manufacturing APIs and reporting changes in CMC data have stressed the importance of change control in a manner similar to that in the dietary supplement GMP preamble. Regarding product quality review, we believe the Seafood HACCP requirement for performing an annual reassessment of a HACCP plan serves the same purpose.

FDA has taken the position that dietary supplements containing fish oil must comply with both the Seafood HACCP and Dietary Supplement GMP regulations. As a manufacturer of dietary supplements and a supplier of fish oil and fish oil products to the dietary supplement industry, ONC has been required to conduct a Hazard Analysis and establish Critical Control Points for such products for many years. According to FDA guidance, "at a minimum a HACCP plan must be reassessed annually to determine whether the hazard analysis is still appropriate and whether

the plan effectively controls the identified hazard(s). The processor must consider how or if any changes in the firm's operations could affect the adequacy of the hazard analysis or the HACCP plan. (For example, changes in the kinds of raw materials used in the product, the suppliers of the raw materials, the product formulation, the equipment or operations used to process the product, the way in which the product will be used by the consumer, or the types of consumers likely to use the product could have major impact.) If the reassessment indicates a deficiency in the plan, the plan must be immediately revised." ("HACCP Regulation for Fish and Fishery Products: Questions and Answers" Section VI. Verification §123.8 (21 CFR), FDA 1999.
<http://www.fda.gov/Food/FoodSafety/HazardAnalysisCriticalControlPointsHACCP/SeafoodHACCP/ucm194434.htm#III>)

We reviewed the Canadian requirements for verification and found they are quite similar. ONC has conducted such reviews and applies its HACCP experience to the omefas process.

The ONC Mulgrave facility's quality system is currently based on the Canadian HACCP requirements as enforced by the Canadian Food Inspection Agency and dietary supplement GMP standards of both FDA and Health Canada. Health Canada's Natural Health Products Directorate (NHPD) characterizes its GMPs as follows:

"Good Manufacturing Practices (GMPs) for natural health products (NHPs) must be employed to ensure product safety and quality. This requires that appropriate standards and practices regarding product manufacture, storage, handling and distribution of natural health products be met. The GMP for NHPs cover:

- specifications (product);
- premises;
- equipment;
- personnel;
- sanitation program;
- operations;
- quality assurance;
- stability;
- records;
- sterile products;
- lot or batch samples, and
- recall reporting.

The GMPs are designed to be outcome based, ensuring safe and high quality products, while giving manufacturers, packagers, labelers, importers and distributors of NHPs the flexibility to implement quality systems appropriate for their product lines and businesses."

On December 20, 2008 NHPD issued Site License #300145 (see Appendix B, Attachment 4) to ONC and March 20, 2009 issued a Natural Health Product GMP Certificate of Compliance, Certificate #0007761(see Appendix B, Attachment 5) to ONC's Mulgrave and Dartmouth, Nova Scotia manufacturing, packaging, labeling and importing sites. On May 25, 2009, NHPD issued Product Licenses to ONC for the manufacture of (b) (4) #80010388 (see Appendix B, Attachment 6) (b) (4)

In April 2004 and July 2007 ONC was audited for GMP compliance by the United States Pharmacopoeia under the USP Ingredient Verification Program. The USP audit handbook published in 2003, provided to ONC in advance of the audit, states that ICH Q7A is used as the audit standard. Although some minor observations were made, there were no major deviations reported. A routine audit under the USP program is scheduled for June 2010.

(b) (4) are made by ONC using the same processing steps that are used to produce the (b) (4) supplied as dietary supplements to the US market (*Figure 6-2*). The (b) (4) may be performed at either ONC or BioVectra and the specification for the (b) (4) is provided in *Table 6-2*. Omthera wishes to (b) (4) when moving to a commercial process with the understanding that the Agency will be notified of any change in (b) (4) for specific process steps. All subsequent steps (*Figure 6-3*) will be performed under pharmaceutical GMPs at BioVectra.

Biological starting material information

We note the Division's request that we include in our submission, information on our biological starting material including: species identification, countries of origin, and a list of known diseases, pathogens, and contaminants associated with the fish. The bulk of the fish oil used by ONC is (b) (4). The fish oils are (b) (4). The Food and Agricultural Organization (FAO) of the UN has reported that fish from the open seas have been found generally free of pollutants, including contamination by PCBs and dioxins, but heavy metals can be a problem in some parts of the world, particularly in larger, older fish. ("Fish contaminants," FAO Fisheries and Aquaculture Department, <http://www.fao.org/fishery/topic/14815/en>) A report by FDA said that those species which contain lower amounts of mercury include anchovy, sardine and the smaller mackerel species. ("Mercury levels in commercial fish and shellfish," FDA 2006, <http://www.fda.gov/Food/FoodSafety/ProductSpecificInformation/Seafood/FoodbornePathogensContaminants/Methylmercury/ucm115644.htm>).

These heavy metals are controlled by the specifications for the crude fish oil supplied to ONC (*Table 6-3-not duplicated here*).

It is recognized that fisheries change from year to year and the volume of certain species or the composition of the total catch may vary. Both ONC and the processors of crude fish oil in (b) (4) who supply ONC are required by regulations to have HACCP plans. Under those regulations, a harvester or supplier who expands or changes the area from which fish are obtained to include an area in which a contaminant or contaminants are known to exist, should reassess whether his HACCP plan should be changed to address any possible new hazard. ONC analyzes and monitors the contaminant profile of all purchased crude fish oils to assure the consistent high quality of this raw material source.

The fish oils used as starting materials are regularly used in food products and are fit for human consumption. The processes used to produce omefas are considered (b) (4) is highly unlikely. The crude fish oil process includes treatment with (b) (4) (u) (4) As the Division has cautioned, it is important that any process changes be notified to the sponsor and the Division to ensure any process changes will not have an adverse impact on the likelihood of (b) (4) surviving the process.

Process changes

Omthera commits to ensuring that its contractors and suppliers are in compliance with the appropriate GMPs. We noted the concern expressed by the Division regarding the notification of changes in the manufacturing processes. We particularly take note of the concern that a sponsor may not be fully informed of changes made by non-drug-GMP manufacturers. Accordingly, all our suppliers will be required by contract to have in place a change control procedure that specifies that all changes must be approved by the sponsor prior to implementation. In addition, an audit program to ensure compliance will be established.

Omthera will inform the Division of any changes to procedures used to manufacture omefas as noted in the minutes of the meeting with the Division of Gastroenterology Products in December 2005.

FDA Preliminary Response: We reviewed the additional information you provided, however, we reiterate our February 2, 2010 comments that the crude fish oil should be considered as the starting material.

Meeting discussion: The agency reiterated that the crude fish oil should be considered as the starting material and drug GMPs will apply (b) (4) from this material. This requirement is standard for a biologically derived product.

In support of a 505(b)(2) application, in addition to the nonclinical and/or clinical requirements, an adequate analytical comparison of your product and the referenced listed product will be required to permit reliance on FDA's previous findings of safety and/or efficacy. This comparison should include the drug composition, structural characterization, impurity profiles, and physical/chemical attributes.

Question 9: Does FDA agree that omefas is a New Chemical Entity (NCE) and eligible for new drug product exclusivity?

Background: In a previous meeting with FDA on December 14, 2005 (see Appendix B, Attachment 1), FDA stated that EPA and DHA were not the active ingredients in omefas, but rather the totality with the fatty acid components is the active drug substance. Specifically, the question asked was: "Does the Agency agree that EPA and DHA are the active ingredients and that other components constitute part of the composition of the mixture and are not considered impurities or active ingredients?" FDA's answer was "No. It is likely that

the minor fatty acid components will contribute to the total activity of the drug substance and consequently, in the absence of data to indicate otherwise, they are considered an integral part of the drug substance."

Omthera agrees with the agency's position that omefas should be considered the drug substance, and not the individual components.

FDA's regulations define new chemical entity as a "drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act" and active moiety means the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." (21 C.F.R. § 314.108(a))

Consistent with these definitions, Omthera believes that omefas is a NCE because:

- Omefas is a complex mixture. The additional free fatty acid components (not just EPA and DHA) contained in omefas are an integral part of the drug substance as previously communicated by FDA. This specific composition has not previously been approved by FDA and is controlled by the manufacturing process to meet specifications for composition.
- In addition, the composition of the mixture including the percentages of EPA and DHA in the mixture is distinct from Lovaza or AMR 101. It is well established that EPA and DHA have distinct physiological and pharmacological properties and thus a significant difference in ratio will likely translate into different pharmacological properties.
- Omefas is a composition consisting of free fatty acids and thus has covalent modification when compared to the previously approved drug, Lovaza, which is in the form of ethyl esters, principally EPA and DHA. [Figure 6-4](#) and [Figure 6-5](#) show the comparison of the omega-3 chemical structures for EPA and DHA and illustrate the differences.

Figure 6-4 Comparison of Omega-3 Chemical Structures - EPA

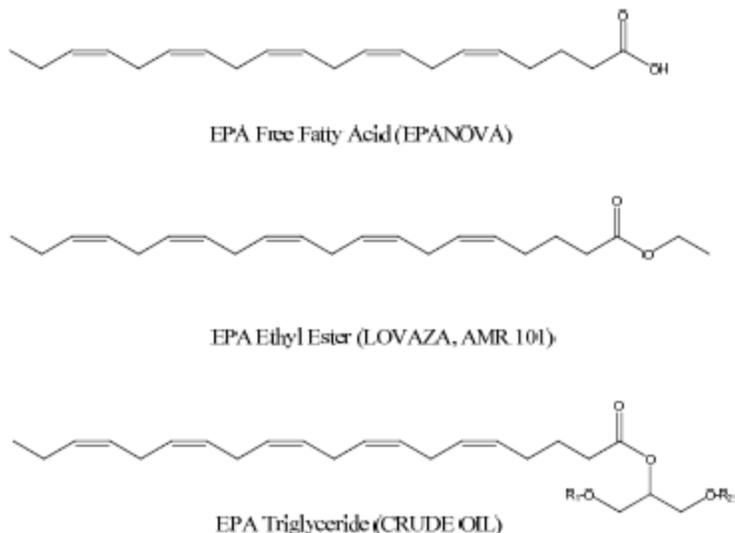
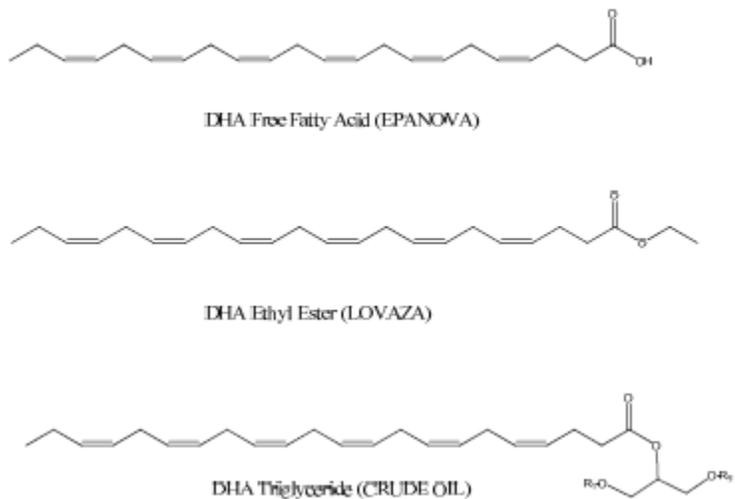


Figure 6-5 Comparison of Omega-3 Chemical Structures - DHA



Accordingly, Omthera is of the opinion that omefas should properly be recognized as a NCE, and eligible for new drug product exclusivity.

FDA Preliminary Response: Exclusivity is determined following NDA approval.

Meeting Discussion: see Question 7 discussion.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

- The firm will provide the safety assessments monitored during the EPIC trials (in Crohn's Disease patients) to allow the agency to determine whether the overall safety exposure (for a future NDA) is sufficient.
- Whether omefas is a New Chemical Entity entitling the sponsor to 5 years of marketing exclusivity following approval.

4.0 ACTION ITEMS

| Action Item/Description | Owner | Due Date |
|--|----------|--|
| List of specific safety assessments that were monitored during EPIC trials in Crohn's disease patients | Firm | This information was included in the firm's June 25, 2010 submission containing their version of the meeting minutes and are attached. |
| Document containing position on omefas being designated as NCE | Division | Not specified |

5.0 ATTACHMENTS AND HANDOUTS

- Safety Assessments from EPIC studies conducted in Crohn's disease patients.

1.11.2 Safety Information Amendment

At the End-of-Phase 2 meeting on June 2, 2010, FDA requested a list of the safety assessments performed in the previous clinical trials of Epanova for the indication of maintenance of remission in Crohn's disease. The following table comprises all of the safety assessments, sorted by protocol.

EPIC & SPC (Epanova) Safety Evaluations

| Assessments | SPC-275 Healthy N=48* 6 weeks | Epic-1 Crohn's N=187* 52 weeks | Epic-2 Crohn's N=189* 58 weeks | Epic-3 Crohn's N=25* 52 weeks | Epic-1E Crohn's N=82* 36 months |
|------------------------|--|--|--|---|---|
| Adverse events | all visits (Day 1, Day 43) | all visits (Wks 4, 8, 12, 16, 21, 26, 30, 35, 40, 44, 48, 52; post study wks 56, 64) | all clinic visits (Wks 2, 8, 16, 30, 44, 58, post study wks 62, 70)) | all visits (Wks 16, 30, 52; post study wk 64) | all visits (Mo 6, 12, 18, 24, 30, 36; post study wk 39) |
| Physical examinations | Brief Comprehensive | Wks -1, 4, 16, 30, 44 Wks 0, 52 | Wks 2, 8, 16, 30, 44 Wks 0, 58 | Wks -1, 16, 30 Wks 0, 52 | Months 6, 12, 18, 24, 30, 36 |
| Vital signs | (bp, hr, temp) (bp, hr, temp, wt) | Wks 0, 6 Wks 0, 6 | Wks -1, 0, 4, 16, 30, 44, 52 | Wks -8, 0, 2, 8, 16, 30, 44, 58 | Wks -1, 0, 16, 30, 52 |
| Hematology | | | | | |
| Leucocytes | Screening, EOT | Wks -1, 30, 52 | Wks -8, 0, 8, 16, 30, 44, 58 | Wks -1, 16, 30, 52, 64 | |
| Erythrocytes | “ | | | | |
| Hemoglobin | “ | Wks -1, 30, 52 | Wks -8, 0, 8, 16, 30, 44, 58 | Wks -1, 16, 30, 52, 64 | |
| Hematocrit | “ | Wks -1, 30, 52 | Wks -8, 0, 8, 16, 30, 44, 58 | Wks -1, 16, 30, 52, 64 | |
| Platelets | “ | Wks -1, 30, 52 | Wks -8, 0, , 8, 16, 30, 44, 58 | Wks -1, 16, 30, 52, 64 | |
| WBC Differential | “ | Wks -1, 30, 52 | Wks -8, 0, 8, 16, 30, 44, 58 | Wks -1, 30, 52 | |
| Serum Chemistry | | | | | |
| Total Protein | Screening, EOT | | | | |
| GOT | “ | Wks -1, 30, 52 | Wks -8, 0, 8, 16, 30, 44, 58 | Wks -1, 30, 52 | |
| GPT | “ | Wks -1, 30, 52 | Wks -8, 0, 8, 16, 30, 44, 58 | Wks -1, 30, 52 | |
| Uric acid | “ | | | | |

| Assessments | SPC-275 Healthy N=48* 6 weeks | Epic-1 Crohn's N=187* 52 weeks | Epic-2 Crohn's N=189* 58 weeks | Epic-3 Crohn's N=25* 52 weeks | Epic-1E Crohn's N=82* 36 months |
|--------------------------------------|--|---|---|--|--|
| BUN | “ | | | | |
| Creatinine | “ | Wks -1, 30, 52 | Wks -8, 0, 8, 16, 30, 44, 58 | Wks -1, 30, 52 | |
| CK | “ | | | | |
| Alkaline phosphatase | “ | Wks -1, 30, 52 | Wks -8, 0, 8, 16, 30, 44, 58 | Wks -1, 30, 52 | |
| Serum Glucose | “ | Wks -1, 30, 52 | | Wks -1, 30, 52 | |
| Potassium | “ | | | | |
| Sodium | “ | | | | |
| Total bilirubin | “ | | | | |
| Cholesterol | “ | Wks -1, 30, 52 | Wks 0, 30, 58 | | |
| Triglycerides | “ | Wks -1, 30, 52 | Wks 0, 30, 58 | | |
| HDL | “ | Wks -1, 30, 52 | Wks 0, 30, 58 | | |
| LDL | “ | Wks -1, 30, 52 | Wks 0, 30, 58 | | |
| VLDL | “ | Wks -1, 30, 52 | Wks 0, 30, 58 | | |
| Urinalysis | | Wks -1, 30, 52 | Wks 0, 30, 58 | Wks -1, 30, 52 | |
| Leucocytes | Screening, EOT | Wks -1, 30, 52 | Wks -1, 30, 58 | Wks -1, 30, 52 | |
| Nitrite/Nitrate | “ | Wks -1, 30, 52 | Wks -1, 30, 58 | Wks -1, 30, 52 | |
| pH | “ | Wks -1, 30, 52 | Wks -1, 30, 58 | Wks -1, 30, 52 | |
| Protein | “ | Wks -1, 30, 52 | Wks -1, 30, 58 | Wks -1, 30, 52 | |
| Glucose | “ | Wks -1, 30, 52 | Wks -1, 30, 58 | Wks -1, 30, 52 | |
| Ketone | “ | Wks -1, 30, 52 | Wks -1, 30, 58 | Wks -1, 30, 52 | |
| Urobilinogen | “ | Wks -1, 30, 52 | Wks -1, 30, 58 | | |
| Bilirubin | “ | Wks -1, 30, 52 | Wks -1, 30, 58 | | |
| Blood | “ | Wks -1, 30, 52 | Wks -1, 30, 58 | Wks -1, 30, 52 | |
| Hemoglobin | “ | | | | |
| Specific Gravity | | Wks -1, 30, 52 | Wks -1, 30, 58 | | |
| Laboratory evaluations (see Note) | | | | | Months 0, 12, 24, 36 |

*N= only subjects treated with Epanova

Note

Laboratory Evaluations: EPIC-1E – “Safety Laboratory” tests were required annually. No central laboratory was used, so only potentially clinically relevant laboratory abnormalities were reported.

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|------------------------------------|---|
| IND-107616 | ORIG-1 | OMTHERA PHARMACEUTICA LS INC | EPANOVA SOFT GELATIN CAPSULES, Omega-3 free fatty acids |
| IND-107616 | GI-1 | OMTHERA PHARMACEUTICA LS INC | EPANOVA SOFT GELATIN CAPSULES, Omega-3 free fatty acids |

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/s/

KATI JOHNSON
07/07/2010