

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-853

21-654s016

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 21-853***

SUPPL #

HFD # 510

Trade Name Omacor

Generic Name omega-3-acid ethyl esters

Applicant Name Reliant Pharmaceuticals

Approval Date, If Known 6/12/07

***This NDA was administratively split off from NDA 21-654, submitted 1/9/04, when it became apparent that one of the indications being sought would not be approved. NDA 21-654 was AP on 11/10/04, and NDA 21-853 was AE. NDA 21-853 provided for an additional indication, but it was not granted. However, information for concomitant use with statin drugs was added to the CLINICAL TRIALS section of the package insert.

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 NO

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

505(b)(1)

c) 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 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.

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:

d) Did the applicant request exclusivity?

YES NO

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

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

YES NO

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

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

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

NDA# NDA 21-654 Omacor

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:

OM6-A Randomized, Double-Blind, Placebo-controlled Study to Assess the Efficacy and Safety of Combined Omacor and Simvastatin Therapy in Hypertriglyceridemic Subjects.

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 #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

OM6-A Randomized, Double-Blind, Placebo-controlled Study to Assess the Efficacy and Safety of Combined Omacor and Simvastatin Therapy in Hypertriglyceridemic Subjects.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 45,998 YES NO
! Explain:

Investigation #2
IND # YES NO
! Explain:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**Appears This Way
On Original**

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this page is the manifestation of the electronic signature.**

/s/

Eric Colman
7/9/2007 10:00:16 AM
Eric Colman for Mary Parks



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-853

Reliant Pharmaceuticals, Inc.
Attention: Mary Chen
Senior Manager, Regulatory Affairs
110 Allen Road
Liberty Corner, NJ 07938

Dear Ms. Chen:

We acknowledge receipt on December 12, 2006 of your December 11, 2006 resubmission to your new drug application for Omacor (omega-3-acid ethyl esters) Capsules.

We consider this a complete, class 2 response to our November 4, 2004 action letter. Therefore, the user fee goal date is June 12, 2007.

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

Sincerely,

{See appended electronic signature page}

Kati Johnson
Project Manager
Division of Metabolism & 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
1/23/2007 07:40:53 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-654
NDA 21-853

Reliant Pharmaceuticals, Inc.
Attention: Keith S. Rottenberg, Ph.D.
Sr. Vice President, Research & Development
110 Allen Road
Liberty Corner, NJ 07938

Dear Dr. Rottenberg:

We acknowledge receipt on November 23, 2004, of your November 22, 2004, correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug applications (NDA):

Name of Drug Product: Omacor (omega-3-acid ethyl esters) Capsules, 1g

NDA Number: 21-654/21-853

Name of New Applicant: Reliant Pharmaceuticals, Inc.

Name of Previous Applicant: Ross Products Division, Abbott Laboratories

Your correspondence provided the information necessary to effect this change, and we have revised our records to indicate Reliant Pharmaceuticals, Inc. as the sponsor of record for these applications.

All changes in the NDAs from those described by the original owner, such as manufacturing facilities and controls, must be reported to us prior to implementation. Refer to the *Guidance for Industry: Changes to an Approved NDA or ANDA* for information on reporting requirements. We request that you notify your suppliers and contractors who have DMFs referenced by your applications of the change in ownership so that they can submit a new letter of authorization (LOA) to their Drug Master File(s).

We remind you that you must comply with the requirements for an approved NDA (NDA 21-654) set forth under 21 CFR 314.80 and 314.81. In addition, you are responsible for any correspondence outstanding as of the effective date of the transfer.

NDA 21-654
NDA 21-853
Page 2

Address all communications concerning this NDA should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Fishers Document Room, 8B-45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question me call at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

Valerie Jimenez
Regulatory Project Manager
Division of Metabolic and Endocrine Drug
Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Ross Products Division, Abbott Laboratories
Attention: Elizabeth M. Zola, Pharm.D.
Associate Director, Regulatory Affairs
625 Cleveland Avenue
Columbus, OH 43215-1754

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/s/

Valerie Jimenez
1/5/05 01:47:53 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-654

Ross Products Division, Abbott Laboratories
Attention: Elizabeth M. Zola, Pharm D
Associate Director, Regulatory Affairs
625 Cleveland Avenue
Columbus, OH 43215-1754

Dear Ms. Zola:

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

Name of Drug Product: Omacor (omega-3-acid ethyl esters) Capsules

Review Priority Classification: Standard (S)

Date of Application: January 9, 2004

Date of Receipt: January 12, 2004

Our Reference Number: NDA 21-654

The application was sufficiently complete to permit a substantive review, therefore, the application was filed on March 12, 2004, in accordance with 21 CFR 314.101(a). The user fee goal date will be November 12, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We reference the deferral granted on October 31, 2001, for the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

NDA 21-654

Page 2

U.S. Postal Service/ Courier/Overnight Mail:

Center for Drug Evaluation and Research

Division of Metabolic and Endocrine Drug Products, HFD-510

Attention: Fishers Document Room, 8B-45

5600 Fishers Lane

Rockville, Maryland 20857

If you have any questions, call me at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

Valerie Jimenez

Regulatory Project Manager

Division of Metabolic and Endocrine Drug
Products

Office of Drug Evaluation II

Center for Drug Evaluation and Research

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/s/

Valerie Jimenez
3/25/04 08:29:10 AM

ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 21-853	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Omacor Established Name: omega-3-acid ethy esters) Dosage Form: Capsules		Applicant: Reliant Pharmaceuticals
RPM: Kati Johnson		Division: 510 Phone # 301-796-1234
<p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected</p> <p>Date:</p>
❖ User Fee Goal Date 6/12/07		
❖ Action Goal Date (if different)		
❖ Actions		
• Proposed action		X AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (<i>specify type and date for each action taken</i>)		None AE 11/10/04
❖ Advertising (<i>approvals only</i>) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (<i>indicate dates of reviews</i>)		X Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): Type 6	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation	
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	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
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other: Other comments: This NDA was administratively split from NDA 21-654	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<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 	<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"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

❖ Exclusivity	
<ul style="list-style-type: none"> • NDAs: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) <p>Firm did not receive a new indication so summary not filled out</p>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> • Is approval of this application blocked by any type of exclusivity? • NDAs/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> • NDAs: 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> • NDAs: 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> • NDAs: 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> 	<p>X <input type="checkbox"/> No <input type="checkbox"/> Yes</p> <p>X No <input type="checkbox"/> Yes If yes, NDA/BLA # and date exclusivity expires:</p> <p>X No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:</p> <p>X No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:</p> <p>X No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:</p>
❖ Patent Information (NDAs and NDA supplements 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. 	<p>x Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.</p>
<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. • [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). 	<p>21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified</p> <p>21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)</p> <p><input type="checkbox"/> No paragraph III certification Date patent will expire</p>
<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> • [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. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner’s receipt of the applicant’s</p>	<p><input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified</p> <p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>

<p>notice of certification?</p> <p>(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)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(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)?</p> <p><i>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).</i></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</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)).</p> <p><i>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.</i></p> <p>(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)?</p> <p><i>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).</i></p> <p><i>If "No," continue with question (5).</i></p> <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</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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<p>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 Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
Summary Reviews	
<p>❖ Summary Reviews (e.g., Office Director, Division Director) (<i>indicate date for each review</i>)</p>	<p>6/15/07 concurrence with primary review</p>
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (<i>indicate date</i>)</p>	
Labeling	
<p>❖ Package Insert</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>❖ Patient Package Insert</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>❖ Medication Guide.</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
<p>❖ Labels (full color carton and immediate-container labels)</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	
<p>❖ Labeling reviews and minutes of any labeling meetings (<i>indicate dates of reviews and meetings</i>)</p>	<p><input type="checkbox"/> DMETS <input type="checkbox"/> DSRCS <input type="checkbox"/> DDMAC <input type="checkbox"/> SEALD <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs</p>

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>) Firm did not receive the requested indication	<input type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	
❖ Pediatric Page (all actions) Firm did not receive the requested indication	<input type="checkbox"/> Included
❖ 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
❖ Postmarketing Commitment Studies	X <input type="checkbox"/> None
<ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) Incoming submission documenting commitment 	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	X
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) Pre-NDA/BLA meeting (<i>indicate date</i>) EOP2 meeting (<i>indicate date</i>) Other (e.g., EOP2a, CMC pilot programs) 	<input type="checkbox"/> No mtg
	<input type="checkbox"/> No mtg
❖ Advisory Committee Meeting	X No AC meeting
<ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	
❖ <u>Federal Register</u> Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	N/A
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	X None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications) N/A	
<ul style="list-style-type: none"> <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>) <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>) 	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	X Not a parenteral product
❖ Facilities Review/Inspection N/A	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	(N/A)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	<input type="checkbox"/> None requested
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	6/15/07
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	Page 13 of 6/15/07 review
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	X None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	X Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	N/A
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	X Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	X None requested
• Clinical Studies	
• Bioequivalence Studies	
• Clin Pharm Studies	
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 5/11/07
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 6/4/07

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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/s/

Kati Johnson
6/26/2007 09:25:59 AM

ADRA Review #1 of Action Package for NDAs 21-645 and 21-853, Omacor (omega-3-acid-ethyl esters) Capsules, 1 g

Reviewer: Lee Ripper, HFD-102

Date pkg received: October 25, 2004. Reviewed 10/27-29/04

Date original NDA received: January 12, 2004

UF GOAL DATE: November 10, 2004

Action type: 1 indication AP - as an adjunct to diet to reduce very high (equal to or greater than 500 mg/dL) \uparrow TG levels in adults.;

1 indication NA - unbundled into NDA 21- 853 \uparrow

b(4)

RPM: Valerie Jimenez

Drug Classification: 1S

505(b)(1) application

Patent Info: AC, form 3542a submitted

Debarment Certification: AC

Safety Update: Dated 5/24/04, see MOR, page 46

Clinical Inspection Summary: N/A, no inspections requested

ODS/DMETS Review of Trade Name: DMETS does not recommend use of name "Omacor" 4/27/04, 11/8/04. 11/10/04: *Office Director's memo overrules DMETS recommendation.*

DSRCS Review of PPI/MedGuide: No PPI/MedGuide

DDMAC Review: 5/21/04, finds name "Omacor" acceptable from promotional viewpoint.

EA: Categorical exclusion granted, CMC review, page 50

EER: AC 3/2/04

Financial Disclosure: See #1 below.

Filing Checklists CMC, BP, PT, RPM

CMC section to Eric Duffy, 10/29/04; CM 11/10/04

P/T section to Ken Hastings, 10/29/04; CM 11/2/04

1. Financial disclosure information was only submitted for the principal investigator for each study. 5 studies had only 1 site, but 3 studies had multiple sites (7, 5, and 2). Usually we expect there to be at least one investigator at each site who is responsible for evaluating patients. Applicant should be asked to provide FD information (outcome payments, proprietary interests, equity interest, not SPOOS) for investigators at other sites or provide explanation that principal investigator was responsible for patients at all sites. 10/27: *I spoke with Beth Zola at Ross. She will contact Pronova Biocare re: the additional required info.* 10/29: *Form 3454 submitted for principal investigators at all sites. Acceptable*
2. What is the status of Biopharm's recommendation for a \uparrow

\uparrow Per

b(4)

Dr. Meyer, the issue with 3A4 induction and statins turned out to be not too striking or important; any residual concerns can be handled by the statin studies done for type IIa and IV.

3. There is nothing in the action package about DSI inspections. *10/29: Mary Parks states that no DSI inspections were conducted.*
4. PI is still under negotiation.
5. Applicant needs to submit full-color mocked-up carton and immediate container labels. RPM states that Ross has been asked to submit them. *11/1 and 8 submission of color mock-ups.*

Lee Ripper
ADRA, ODE II

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/s/

Leah Ripper
11/10/04 02:25:57 PM
CSO

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 20, 2004

TO: NDA 21-654 Omacor (omega-3-acid ethyl esters) Capsules, 1 gm
NDA 21-853 Omacor (omega-3-acid ethyl esters) Capsules, 1 gm

FROM: Valerie Jimenez, HFD-510
Division of Metabolic and Endocrine Drug Products

SUBJECT: **Application Unbundled**
NDA 21-654, Omacor (omega-3-acid ethyl esters) Capsules, 1 gm

Omacor was submitted on January 9, 2004, and is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with Fredrickson and Lees' type V hyperlipidemia. This application is a new molecular entity. Upon review of the application, the decision was made to administratively unbundle (split) the application and review the indications separately. NDA 21-853 is the new application number that was assigned to the indications of [] and has a chemical classification of type 6-new indication. The original application, NDA 21-654, indicated for Fredrickson and Lees' type V hyperlipidemia has a chemical classification of type 1-new molecular entity. On October 12, 2004, the firm was notified of the Agency's decision.

b(4)

**Appears This Way
On Original**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-654

INFORMATION REQUEST LETTER

Ross Products Division, Abbott Laboratories
Attention: Elizabeth M. Zola, Pharm D
Associate Director, Regulatory Affairs
625 Cleveland Avenue
Columbus, OH 43215-1754

Dear Ms. Zola:

Please refer to your January 9, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Omacor (omega-3-acid ethyl esters) Capsules.

We also refer to your submissions dated January 20, May 10, July 1, and July 20, 2004.

We are reviewing the Biopharmaceutical and Chemistry, Manufacturing and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. Provide [] for the drug substance and reference standards. Provide [] on the eicosapentaenoic acid ethyl ester (EPA-EE) and docosahexaenoic acid ethyl ester (DHA-EE) standards. In addition, provide physical property data such as density, refractive index, etc. b(4)
2. Provide the in-process test methods (not intermediate specifications) carried out in order to show that the production of the drug substance is proceeding as expected.
3. Regarding the drug substance specifications, [] b(4)
4. Provide solubility profiles of Omacor as well as dissolution profiles for capsules from 3 batches (12 unit/batch) under the current proposed condition and two other conditions such as various concentrations of [] different apparatus or agitation. b(4)
5. Provide the manufacturers, DMF references, and letters of authorization for the drug product container/closure system.

If you have any questions, call Valerie Jimenez, Regulatory Project Manager, at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

David Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Mary Parks
8/17/04 11:02:34 AM
for Dr. Orloff

NDA 21-654

Executive CAC

Date of Meeting: August 10, 2004

Committee: David Jacobson-Kram, HFD-024, Chair
Joseph Contrera, Ph.D., HFD-901, Member
Abby Jacobs, Ph.D., HFD-024, Member
Chuck Resnick, Ph.D., HFD-110, Alternate Member
Indra Antonipillai, Ph.D., HFD-510, Presenting Reviewer

Author of Draft: Indra Antonipillai

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA #: 21-654

Drug Name: Omacor (Ethylester K85) soft gelatin capsules

Sponsor: Ross products Division, Abbott laboratories, Columbus, Ohio.

Background:

Omacor is isolated from fish oil. It is composed primarily of the unsaturated omega-3 fatty acid esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Its mechanism of action is unknown but the poly-unsaturated omega-3 fatty acids depress other lipids (essentially triglycerides) by inhibiting hepatic triglycerides and possibly apoprotein synthesis. They replace arachidonic acid (AA) in phospholipids with EPA and DHA. Omacor is indicated alone, or in combination with HMG-CoA reductase inhibitors in hypertriglyceridemic patients. Omacor does not have mutagenic/genotoxic potential.

Mouse carcinogenicity study

In a 2-year carcinogenicity study in mice ~~---~~ :CD-1(CR)BR, 51/sex/dose), doses of 100, 600, 2000 mg/kg/day were administered orally by gavage (in corn oil) for 80 weeks in males and for 88 weeks in females. The actual doses achieved in the carcinogenicity study were 90, 540, 1860 mg/kg/day.

b(4)

The sponsor did not submit the dose selection/study design for ECAC review prior to conducting the carcinogenicity study. The highest dose selection (2000 mg/kg/day) for the mouse carcinogenicity study was based on a 13-week dose range study in mice where 4000 mg/kg/day produced no overt toxicity except increases in liver weights in the high dose group (4-7%) and skin dermatitis (in 2/2 males). However, a high dose of only 2000 mg/kg/day was chosen for the 2-year mouse assay, which was well below a MTD. The duration of the study was also shorter than the standard 2-year duration because of the sponsor's decision to terminate the study at 50% survival. However mortality in mice was not affected in the actual study. Therefore the study could have been continued for the full time period.

In the present carcinogenicity study, no AUC exposures to EPA and DHA were provided, but plasma levels of EPA increased with the dose (males 0.4-1.4, 2.6, 10.3, 29.2 mg/L at 0, 115, 530, 1860 mg/kg/day respectively, females 3-3.4, 2.3, 12.1, 41.3 mg/L respectively), while DHA values did not change (males 130-150, 166, 176, 179 mg/L; females 121, 126, 135, 141 mg/L respectively). This suggests that systemic levels of DHA in plasma from diet had not been exceeded.

Omacor had no effect on mortality or body weights in mice. No significant non-neoplastic lesions were observed in mice. Uterine smooth muscle tumors (benign uterine leiomyoma and malignant uterine leiomyosarcoma) were increased in the high dose group (combined tumors in drug

treated mice were 9/51 vs 8/102 in controls, $p=0.019$), but these were not considered statistically significant for a common neoplasm.

In conclusion, the mouse carcinogenicity assay produced negative results. The study suffers from a number of deficiencies: the high dose used was below MTD, the assay was not carried out to the optimal 2-year duration (mice were sacrificed in weeks 80-88), the diet may have contained EPA, DHA and linolenic acid (a source of EPA, DHA), and the volume of vehicle (corn oil) varied with dose.

Rat carcinogenicity study

A 2-year carcinogenicity study in rats (CD (SD)BR, 50/sex/dose) was conducted, where doses of 100, 600, 2000 mg/kg/day were administered orally (by gavage) for 101 weeks in males and 89 weeks in females using a corn oil vehicle. AUC values were not provided, but plasma levels of EPA (available only in males) increased only at the high dose (3.5, 2.9, 3.5, 10 mg/L at 0, 90, 540, 1800 mg/kg/day respectively). In contrast, DHA levels were unchanged at all doses (21, 29, 32, 29 mg/L respectively),

b(4)

As stated earlier, the sponsor did not submit the dose selection/study design for ECAC review prior to conducting the rat carcinogenicity study. The highest dose selected (2000 mg/kg/day) for rat CAC study was based on a 13-week dose range study, in which 4000 mg/kg/day produced clinical signs (severe desquamation, tail necrosis), gross foot/leg lesions (in 29/40 rats vs 0/40 controls), and humane sacrifice of 20/20 male rats due to the severe desquamation and tail necrosis indicating that 4000 mg/kg/day exceeds MTD. Therefore, a high dose of 2000 mg/kg/day as selected was appropriate. The duration of the study was shorter than the standard 2-year duration, again because of the sponsor's decision to terminate the study at 50% survival. The controls, low dose and mid dose survival rates were below 50% by the middle of week 80, which is why sponsor terminated the study in week 89 in females. However mortality in rats across the groups was not affected in this study and the study could have been continued for the full two-year period.

Omacor did not affect the mortality, or the body weights, and did not produce significant neoplastic or non-neoplastic lesions in this 2-year bioassay in rats.

In summary, although the duration of the study was shorter (89-101 weeks) than the standard 2-year optimal duration, the dose selection was adequate, and the drug at these doses (100, 600, 2000 mg/kg/day) did not produce significant toxicity/mortality or carcinogenicity in rats.

Executive CAC Recommendations and Conclusions:

Mouse

The Committee concurred that the mouse study did not meet the generally acceptable standards for adequate assessment of carcinogenicity. No drug-related tumors were observed in the mouse assay. The study suffers from a number of deficiencies: the high dose used was below MTD, the assay was not carried out to the optimal 2-year time duration (mice were sacrificed in weeks 80-88), the diet may have contained EPA, DHA and linolenic acid (a source of EPA, DHA), and the volume of vehicle (corn oil) was varied with dose. Despite these deficiencies the committee felt that the study need not be repeated.

NDA 21-654

Rat:

The committee noted that the doses used were adequate in rats, although there were a number of deficiencies: the study duration was less than the standard two year duration, the diet may have contained EPA, DHA and linolenic acid (a source of EPA, DHA), and the volume of vehicle (corn oil) was varied with dose.

The rat study was negative for carcinogenicity.

In conclusion, although the study duration was less than optimal, the dose selection was adequate and ECAC accepts the study. The rat study was negative for carcinogenicity.

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

cc:/

/Division File, HFD-510, NDA 21-654
/Team leader, HFD-510 Davis Bruno
/Reviewer, HFD-510 Antonipillai
/CSO, HFD-510, Jimenez
/HFD-024, ASeifried

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/s/

David Jacobson-Kram
8/13/04 10:55:35 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-654

Ross Products Division, Abbott Laboratories
Attention: Elizabeth M. Zola, Pharm D
Associate Director, Regulatory Affairs
625 Cleveland Avenue
Columbus, OH 43215-1754

Dear Dr. Zola:

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

We also refer to your proprietary trade name review.

We have reviewed the referenced material and have the following comments and recommendations.

Trade Name

We find the proprietary name, Omacor, acceptable from a promotional perspective.

Container Label

1. You must print the established name in letters that are at least half as large as the proprietary name to be in accordance with 21 CFR 201.10(g)(2).
2. The product strength should appear immediately following or below the established name and be more prominent on the label.
3. Relocate the net quantity (ex. "120 Capsules") away from the product strength.
4. The packages should include Child Resistant Closures (CSC).

If you have any questions, call Valerie Jimenez, Regulatory Project Manager, at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff

6/4/04 04:47:35 PM

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-654

Trade Name: Omacor
Generic Name: omega-3-acid ethyl ester
Strengths: 1 g Capsules

Applicant: Ross Products Division of Abbott Laboratories

Date of Application: January 9, 2004
Date of Receipt: January 12, 2004
Date clock started after UN: N/A
Date of Filing Meeting: February 9, 2004
Filing Date: March 9, 2004
Action Goal Date (optional): N/A

User Fee Goal Date: November 12, 2004

Indication(s) requested: As adjunct to diet to reduce triglyceride levels in adult patients with Fredrickson and Lees' type IIb hyperlipidemia.

Type of Original NDA: (b)(1) X (b)(2) _____
OR

Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S X P _____
Resubmission after withdrawal? NO Resubmission after refuse to file? NO
Chemical Classification: (1,2,3 etc.) 1
Other (orphan, OTC, etc.) N/A

User Fee Status: Paid X Exempt (orphan, government) _____
Waived (e.g., small business, public health) _____

Form 3397 (User Fee Cover Sheet) submitted: YES
User Fee ID # 4539
Clinical data? YES X NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication?

NO

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

NO

- Is the application affected by the Application Integrity Policy (AIP)?
If yes, explain. NO
- If yes, has OC/DMPQ been notified of the submission? N/A
- Does the submission contain an accurate comprehensive index? YES
 - Was form 356h included with an authorized signature?
If foreign applicant, both the applicant and the U.S. agent must sign. YES
 - Submission complete as required under 21 CFR 314.50?
If no, explain: YES
 - If an electronic NDA, does it follow the Guidance? YES
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?
- Additional comments:
- If in Common Technical Document format, does it follow the guidance? N/A
 - Is it an electronic CTD? YES
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?
Clin Stat/Data Sets Labeling
Pharm/Tox Tumor Data Sets
Additional comments:
 - Patent information submitted on form FDA 3542a? YES
 - Exclusivity requested? NO
Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.
 - Correctly worded Debarment Certification included with authorized signature? YES
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,
“*[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.*” Applicant may not use wording such as “To the best of my knowledge”

- Financial Disclosure forms included with authorized signature?
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.) YES
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. YES
- List referenced IND numbers: IND 45,998
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 10/31/01 YES
If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A
- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
If no, did applicant submit a complete environmental assessment? N/A

- If EA submitted, consulted to Nancy Sager (HFD-357)? YES
- Establishment Evaluation Request (EER) submitted to DMPQ? YES
 - If a parenteral product, consulted to Microbiology Team (HFD-805)? N/A

If 505(b)(2) application, complete the following section: N/A

- Name of listed drug(s) and NDA/ANDA #: N/A
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) N/A
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9). N/A
- Is the rate at which the product’s active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). N/A
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

IF FILED, and if the applicant made a “Paragraph IV” certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

___ 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications

that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
 - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?
N/A
 - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
N/A
 - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A
 - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?
N/A
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):
 - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).
N/A
 - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.
N/A
 - EITHER
The number of the applicant's IND under which the studies essential to approval were conducted.
IND # _____ N/A
OR
A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?
N/A
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?
N/A

Appears This Way
On Original

Appears This Way
On Original

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 9, 2004

BACKGROUND:

This NDA was submitted as a 505(b)(1) application. It is classified as a new molecular entity and is indicated as adjunct to diet to reduce triglyceride (TG) levels in adult patients with Fredrickson and Lees' type _____ and V Hyperlipidemia.

b(4)

ATTENDEES:

ASSIGNED REVIEWERS:

Discipline

Reviewer

Medical:	Mary Parks, M. D.
Secondary Medical:	Ruth Penn, M. D.
Statistical:	Todd Sahlroot, Ph. D.
Secondary Statistical	Lee Ping Lian, Ph. D.
Pharmacology:	Karen Davis Bruno, Ph. D.
Secondary Pharmacology:	Indra Antonipillai, Ph. D.
Chemistry:	Mamta Gautam Basak, Ph. D.
Environmental Assessment (if needed):	
Biopharmaceutical:	Hae Young Ahn, Ph. D.
Secondary Biopharmaceutical	Wei Qui, Ph. D.
DSI:	
Regulatory Project Management:	Valerie Jimenez
Other Consults:	Cynthia Liu, Ph. D.

Per reviewers, are all parts in English or English translation? YES
 If no, explain:

CLINICAL FILE X REFUSE TO FILE _____

- Clinical site inspection needed: YES NO
- Advisory Committee Meeting needed? NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A

CLINICAL MICROBIOLOGY NA X FILE _____ REFUSE TO FILE _____

STATISTICS FILE X REFUSE TO FILE _____

BIOPHARMACEUTICS FILE X REFUSE TO FILE _____

- Biopharm. inspection needed: NO

PHARMACOLOGY NA _____ FILE X REFUSE TO FILE _____

- GLP inspection needed: NO

CHEMISTRY FILE X REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES
- Microbiology N/A

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

X The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ No filing issues have been identified.

X Filing issues to be communicated by Day 74. List:

1. An estimate of the amounts of all impurities with identification as far as possible. Provide the GC chromatograms with tabulated area percent for each peak for representative batches of drug substance and product and for reference standards.
2. Representative certificates of analysis for starting materials, including the crude fish oils. Define C more precisely. **b(4)**
3. A brief description of the production of fish oil from whole fish.
4. All the validation for GC and HPLC methods for analysis of EPA and DHA.
5. Datasets for studies CK85-001, CK85-002, CK85-007, and K85-91003/K85-92006.
6. Dataset used for population pharmacokinetics and pharmacodynamics analysis and complete study report for population pharmacokinetics and pharmacodynamics.
7. Study reports for pooled analysis of dose proportionality.
8. In vitro drug-drug interaction data and report.

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

DUE DATES:

Reviews in DFS= September 17, 2004
Final Draft to TL= September 24, 2004
Date to Division Director= October 1, 2004
Date to ODE II= October 22, 2004

Valerie Jimenez
Regulatory Project Manager, HFD-510

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

/s/

Valerie Jimenez
3/26/04 07:50:08 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-654

Ross Products Division, Abbott Laboratories
Attention: Elizabeth M. Zola, Pharm D
Associate Director, Regulatory Affairs
625 Cleveland Avenue
Columbus, OH 43215-1754

Dear Ms. Zola:

Please refer to your January 9, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Omacor (omega-3-acid ethyl esters) Capsules.

We also refer to your submission dated January 20, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on March 12, 2004, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues and request that you submit the following information:

1. An estimate of the amounts of all impurities with identification as far as possible. Provide the GC chromatograms with tabulated area percent for each peak for representative batches of drug substance and product and for reference standards.
2. Representative certificates of analysis for starting materials, including the crude fish oils. Define [] ' more precisely. **b(4)**
3. A brief description of the production of fish oil from whole fish.
4. All the validation for GC and HPLC methods for analysis of EPA and DHA.
5. Datasets for studies CK85-001, CK85-002, CK85-007, and K85-91003/K85-92006.
6. Dataset used for population pharmacokinetics and pharmacodynamics analysis and complete study report for population pharmacokinetics and pharmacodynamics.
7. Study reports for pooled analysis of dose proportionality.

8. In vitro drug-drug interaction data and report.

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 additional 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.

If you have any questions, call Valerie Jimenez, Regulatory Project Manager, at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug
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/

Valerie Jimenez
3/25/04 03:21:22 PM
Signing for Enid Galliers, Chief, Project Management Staff