3/26/04

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

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)? NO
If yes, explain.

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? YES
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:
- 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~~ NO
  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? YES
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)

- 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 #:
- 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

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

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 [redacted] more precisely.

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

/S/

Valerie Jimenez
Regulatory Project Manager, HFD-510

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/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

3/25/04

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.

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

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/s/

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

3/25/04

NDA FILEABILITY CHECKLIST

NDA Number: 21-654 Applicant: Ross Products/Abbott Stamp Date: 1/12/04
Drug Name: Omacor (omega-3-acid ethyl esters) Capsules, 1 gram

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	x		
2	Is the section indexed and paginated adequately?	x		
3	On its face, is the section legible?	x		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	x		
5	Is a statement provided that all facilities are ready for GMP inspection?	x		Acceptable EER received.
6	Has an environmental assessment report or categorical exclusion been provided?	x		Exclusion is requested.
7	Does the section contain controls for the drug substance?	x		
8	Does the section contain controls for the drug product?	x		Final dissolution testing is not included.
9	Has stability data and analysis been provided to support the requested expiration date?	x		Only — data is given on — production batches but the firm is requesting — expiry. Supportive stability data out to — years is available.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		
11	Have draft container labels been provided?	x		
12	Has the draft package insert been provided?	x		
13	Has an investigational formulations section been provided?	x		
14	Is there a Methods Validation package?	x		Dissolution development report is included.
15	Is a separate microbiological section included?			This is not needed because the dosage form is a capsule.

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Review Chemist: M. Haber Date: March 11, 2004
Team Leader: M. Gautam-Basak Date: March 18, 2004
cc:

HFD-510/Division File

NDA Number: 21-654 **Applicant: Ross Products** **Stamp Date: 1/12/04**

Have all DMF References been Identified?

DMF Number	Holder	Description	LOA Included	Status
		Type II, drug product	Yes	**Pending**
		Type III,	Yes	**Pending**
DMF			Yes	Adequate, Reviewed by Dr. D. Klein
DMF			Yes	Adequate, Reviewed by Dr. D. Klein
DMF			Yes	Adequate, Reviewed by Dr. D. Klein
DMF			Yes	Adequate, Reviewed by Dr. D. Lin
DMF			es	Adequate, Reviewed by Dr. D. Christodoulou

APPEARS THIS WAY
ON ORIGINAL

Drug Substance

The active pharmaceutical ingredient is omega-3-acid ethyl esters. It is a purified, [redacted] mixture of the desired fatty acid ethyl esters containing 0.4% of α-tocopherol [redacted]
The fatty acids are isolated from the body oil of fatty fish species such as *Engraulidae*, *Carangidae*, *Clupeidae*, *Osmeridae*, *Salmonidae* and *Scombridae*.

Site of manufacturing is Pronova Biocare a.s, Sandefjord, Norway.

The drug substance (K85EE) contains about [redacted] eicosapentaenoic acid (EPA, C20:5 n-3) and [redacted] docosahexaenoic acid (DHA, C22:6 n-3). The total amount of omega-3-acid ethyl esters (C18:3 n-3, C18:4 n-3, C20:4 n-3, C21:5 n-3, and C22:5 n-3) is not less than [redacted]

Release tests include [redacted]

PRONOVA BIOCARE

Specification

Product: K85EE	Specification no.:	Previous specification no.:	
This edition approved: 220803	Previous edition approved: 160503	First edition approved: 050900	Shelf life/retest period:
Prepared by:	Verified by:	Authorized by:	

Test	Min. value	Max. value	Unit	Method

PRONOVA BIOCARE

Specification

Product: K85EE	Specification no.:	Previous specification no.:	
This edition approved: 220803	Previous edition approved: 160503	First edition approved: 050900	Shelf life/retest period:
Prepared by:	Verified by:	Authorized by:	

Test	Min. value	Max. value	Unit	Method

Drug substance stability is adequate. Data is provided for — lots for — and — lot for — The retest period for the drug substance in — at temperatures not to exceed 25°C.

Drug Product

The Omacor drug product is a soft gelatin capsule containing one gram of drug substance. Type II DMF # [redacted] contains drug product manufacturing information. No manufacturing information is given in the NDA. DMF [redacted] was reviewed by Dr. F. Zielinski on 11/16/00 for NDA 21-274 and found adequate.

The components and composition of the capsules are:

Component	mg/capsule
Active Ingredient	
Omega-3-acid ethyl esters	
Inactive Ingredients	
α-Tocopherol	4
Partially hydrogenated vegetable oils including soybean oil	
Capsule Shell	
Gelatin NF	
Glycerin, Natural USP	
, EP	
Print	

Site of manufacturing and packaging is Cardinal Health, St. Petersburg, FL 33716

APPEARS THIS WAY
ON ORIGINAL

Redacted 1

page(s) of trade secret and/or confidential commercial information (b4)

One packaging configuration: [redacted] bottle with induction seal
Commercial 120 capsules/bottle
Physician's sample 28 capsules/bottle

Primary Stability Data:
Three commercial scale batches packaged in [redacted] bottles:

25°C/60% RH	[redacted]
30°C/60% RH	[redacted]
40°C/75% RH	[redacted]

The sponsor has proposed an expiration-dating period of [redacted] at 25°C.

EA: The firm has requested a categorical exclusion.

Draft Initial Filing Comments (for 74-day Letter):

1. Provide an estimate of the amounts of all impurities with identification as far as is 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. Provide representative certificates of analysis for starting materials, including the crude fish oils. Define '[redacted]' more precisely.

3. Provide a brief description of the production of fish oil from whole fish.

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/s/

Martin Haber
3/24/04 02:52:28 PM
CHEMIST

Mamta Gautam-Basak
3/25/04 08:01:49 AM
CHEMIST
Concur

3/25/04

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:

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,

/S/

{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

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:

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, 1 gm.

We also refer to the labeling teleconference between representatives of your firm and the FDA on October 12, 2004. The purpose of the meeting was to discuss the administrative unbundling of your application and Division proposed labeling.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

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

Enclosure

NDA 21-654

MEMORANDUM OF TELECON

DATE: October 12, 2004

APPLICATION NUMBER: NDA 21-654, Omacor (omega-3-acid ethyl esters) Capsules, 1g

BETWEEN:

Name: Jeffrey Salon, MD, Medical Affairs
Alan Ryan, PhD, Project Manager
Kevin Mahan, PhD, Section Head, Device and Pharmaceutical R & D
Charles Paule, Ph.D., Section Manager, Biostatistics
Pamela Anderson, RD, Ph.D., Director, Regulatory Affairs
Elizabeth Zola, Pharm D., Associate Director Regulatory Affairs
Sondra Miller, Director, Innovation and New Ventures

Phone: 877-648-8345
Representing: Ross Products

AND

Name: Mary Parks, M.D., Deputy Director and Medical Team Leader
Karen Davis Bruno, Ph.D., Pharmacology/Toxicology Team Leader
Indra Antonipillai, Ph.D., Pharmacology/Toxicology Reviewer
Wei Qiu, Ph.D., Biopharmaceutics Reviewer
Lee Ping Pian, Ph.D., Statistics Reviewer
Valerie Jimenez, Regulatory Project Manager

Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Administrative unbundling of the application and labeling

BACKGROUND: This application (NDA 21-654) was submitted to the Agency on January 9, 2004, for [redacted]
Upon review of the application, it was determined that it was necessary for the application to be administratively unbundled because different actions will be taken on some indications. Therefore, the original submission of NDA 21-654 is indicated for treatment of [redacted] On October 12, 2004, the Agency held a teleconference with the participants of Ross Products to discuss proposed labeling. The Agency began by informing the sponsor of the administrative unbundling of their application.

DISCUSSION:

- The sponsor inquired why the Agency decided to unbundle the application [redacted]
- The Agency responded that [redacted]
  The Agency further stated that the application was unbundled to [redacted]
- The sponsor asked if there was any insight on the [redacted]

- The Agency stated that [ ] could not be discussed prior to the letter being issued. The [ ] was again emphasized.
- The sponsor then asked if [ ]
- The Agency responded that the are being reviewed as one application that had been assigned a new NDA number. Each NDA application would receive an action letter on the assigned goal date of November 12, 2004.
- The sponsor inquired about the proposed labeling [ ]. The statistician noted that this involved [ ]
- The Agency explained that the proposed labeling was an attempt to clearly present efficacy data [ ] but acknowledged that [ ] However, the Agency noted [ ]

[ ]

- The sponsor requested another labeling meeting to allow time for addressing the labeling.
- The Agency encouraged submission of the sponsor's response to the proposed labeling in addition to reminding the sponsor that focus should be [ ] that is to be discussed at the next labeling meeting.

/S/

Valerie Jimenez
Regulatory Project Manager

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/s/

Valerie Jimenez
10/25/04 02:54:40 PM

2/9/04

NDA 21-654/Filing

Review completed 2/4/04
Signed off in DFS on 2/9/04

45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

NDA 21-654: This NDA is a 505(b)(1) application.
Submission date: 1/9/04
Sponsor: Ross Products Division, Abbott Laboratories, Columbus, Ohio.
Drug: Omacor (K85) soft gelatin capsules.
Introduction: Omacor is a purified [ ] mixture of FA ethyl esters containing 0.4% of α-tocopherol in a mixture of partially hydrogenated vegetable oils including soybean oil [ ] It is isolated from fish oil. The drug product is a one gram capsule consisting of at least 900 mg of omega-3-ethyl esters. One gram of the drug contains mostly a mixture of two unsaturated fatty acids, eicosapentanoic acid ethyl ester (EPA, 465 mg, — and docosahexaenoic acid ethyl ester (DHA, 375 mg, — & vitamin E (4 mg ——— The drug has additional fatty acid ethyl esters [ ] Thus, the total amount of omega-3-acid ethyl esters is approximately — It also contains glycerol, gelatin and purified water. Its indication here is to reduce triglyceride (TG) levels. The recommended doses of omacor are 4 g/day.

Omacor lowers triglyceride (TG) by increasing mitochondrial and proximal beta oxidation of FA. [

]

Omacor has been approved in several European countries including (Norway since 1995, France, Austria since 2002, Germany since 2003, etc) for both treatment of hypertriglyceridmia (at doses of 2-4 g/day) and for post-myocardial infarction (at doses of 1 g/day).

ITEM: NDA	**YES**	**NO**	**COMMENT**
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	Yes		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	Yes		

3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	Yes		No new pharm/tox data have been provided. Sponsor has presented all the data that was previously submitted to
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA (genotox, reprotox, adequate duration of chronic tox, carcinogenicity)	Yes		Have electronic files of the carcinogenicity studies been submitted for statistical review? The carcinogenicity and other preclinical studies have previously been reviewed on this drug Most of the non-clinical studies were conducted under IND 45,998 (in our Division), or under previously submitted However, carcinogenicity rat & mouse tumor incidence data diskettes were not provided for the statistical review in the format currently required This reviewer discussed it with Dr. T. Sahlroot, (a team leader statistician) and a statistician Cynthia Liu to see if the sponsor has now provided this data diskettes in a correct electronic format, and was told that they have complied.

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (i.e., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	Yes		The non-clinical studies were completed under IND 45,998

6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (i.e., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	Yes		Sponsor has provided CMC information, and DMF for omacor ([ ] . One gram capsule of the drug product consists of EPA ethyl ester (465 mg), DHA ethyl ester (375mg), & vitamin E (4 mg as antioxidant). It also contains glycerol, gelatin and purified water. The drug substance is derived from fish oil [ ] the purified TG esters of omega-3-acids. The remaining components of the drug substance are ethyl esters of alpha-linoleic acid, [ ] This drug is approved in several European countries including (Norway, France, Austria, Germany, etc) for both treatment of hypertriglyceridmia (at doses of 2-4 g/day) and for post-myocardial infarction (at doses of 1 g/day).
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	Yes		The route of administration is oral in toxicity studies — IND 45,998), which is the intended route in humans.
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	Yes		Yes, the draft labeling submitted in general is in accordance with 21 CFR label, and data express human dose multiples in mg/m2.

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	Yes		
10) Reasons for refusal to file: Not applicable			

Reviewing Pharmacologist: Indra Antonipillai, HFD-510

Supervisory Pharmacologist: Karen Davis-Bruno

File name: 21654-filing

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

/s/

Indra Antonipillai
2/9/04 01:43:11 PM
PHARMACOLOGIST
From the pharm/tox point of view this application is filable
This application is filable

Karen Davis-Bruno
2/9/04 02:06:21 PM
PHARMACOLOGIST
concur with filability

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-654**	**Brand Name**	**Omacor®**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Omega-3-acid ethyl esters**
Medical Division	**510**	**Drug Class**	**Lipid lowering**
OCPB Reviewer	**Wei Qiu, Ph.D.**	**Indication(s)**	**As an adjunct to diet to reduce triglyceride levels**
OCPB Team Leader	**Hae-Young Ahn**	**Dosage Form**	**capsules**
Related IND(s)		**Dosing Regimen**	**1 g**
Date of Submission	**Jan 9, 2004**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**Sept 24, 2004**	**Sponsor**	**Ross Products Division, Abbott Laboratories**
PDUFA Due Date	**Nov. 12, 2004**	**Priority Classification**	**standard**
Division Due Date	**Oct. 1, 2004**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	x	2		**One in healthy subject and one is patients with hyperlipidemia**
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
Mutual:				
In-vitro:	x			Not included.
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
hyperlipidemia	x	10		**Baseline and endpoint serum concentrations only**
hypertension	x			**literature**
IgA nephropathy	x			**literature**
Meta Analysis:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	x			Literature
Phase 3 clinical trial:				

Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	3		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**15**		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	x	
Comments sent to firm ?		1. The sponsor should submit all the validation for GC and HPLC methods for analysis of EPA and DHA. 2. The sponsor should submit datasets for studies CK85-001, CK85-002, CK85-007, and K85-91003/K85-92006. 3. The sponsor should submit dataset used for population pharmacokinetics and pharmacodynamics analysis. 4. The sponsor should submit complete study report for population pharmacokinetics and pharmacodynamics and study report for pooled analysis of dose proportionality. 5. The sponsor should submit in vitro drug-drug interaction data and report.
QBR questions (key issues to be considered)	**1. Relative bioavailability 2. Dose proportionality 3. Bioavailability in patients with hyperlipidemia, hypertension and IgA nephropathy 4. Population PK and PD analysis**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

On Jan 9, 2004, Ross Products Division, Abbott Laboratories Inc. submitted an original NDA Omacor® (Omega-3-acid ethyl esters) capsule 1 g as an adjunct to diet to reduce triglyceride levels. Each capsule contains one gram of omega-3-acid ethyl ester drug substance consisting of at least 900 mg of omega-3-ethyl esters. These are predominately comprised of approximately 840 mg of the ethyl esters of eicosapentaenoic acid (EPA), approximately 465 mg and docosahexaenoic acid (DHA), approximately 375 mg.

There were 4 PK studies conducted in support of this application. In 11 efficacy trials, serum lipid concentrations were determined at baseline and endpoints.

1. CK85-001: Ethylester K85: a 14 day multiple dose rising tolerance study
2. CK85-002: Absorption of different forms of omega-3 fatty acids in man-comparison between an ethylester (K85) and a triglyceride (TG30)

3. CK85-007: Comparative effects of prolonged intake of highly purified fish oil as ethyl-ester or triglyceride on lipids, hemostasis, and platelet function in normalipemic men
4. K85-91003/K85-92006: Bioavailability of omega-3 fatty acids, a double blind comparison of three different concentrates

Results of these studies are summarized as followings:

1. CK85-001: After 2 week treatment, in subjects receiving K85 4, 8, and 14 g daily, the increases in mean percentages of EPA in total serum phospholipids were 4.8, 7.9, and 9.2 times, respectively, over baseline. The increases in incorporation of DHA were less marked and not dose dependent, ranging from 1.8 to 1.9 times over baseline for each group.
2. CK85-002: For active-EPA 12 and 24 g daily, the increases in mean percentages of EPA in total serum phospholipids were 4.7 and 5.4 times, respectively, over baseline. Incorporation of DHA for these groups was 1.3 to 1.4 times over baseline.
3. CK85-007: In subjects receiving 4 g of K85 or an equivalent amount of EPA/DHA as a triglyceride compound (Active-EPA) for 7 weeks, there was similar increases in percentages of EPA (~3 times) and DHA (~1.5 times) in serum phospholipids. The investigators concluded that omega-3 fatty acids were equally well absorbed as either ethyl esters or triglycerides.
4. K85-91003/K85-92006: Subjects received 5.1 g of omega-3 fatty acids per day for 2 weeks. The first group received a 62.5% ethyl ester concentrate, the second group received an 80% ethyl ester concentrate, and the third group received an 84% ethyl ester concentrate (K85). There was a clear tendency towards a higher increase in the group receiving the most concentrated formulations of omega-3 fatty acids (mean relative increases from baseline: 62.5% ethyl ester group=308%; 80% ethyl ester group =345%; and 84% ethyl ester [K85] group=417%). The mean absolute increase in serum phospholipid EPA content in the group receiving K85 was higher than the increases observed in the groups receiving 62.5% and 80% ethyl ester groups.

The sponsor indicated that they conducted a pooled analysis for dose proportionality over the range of 2, 4, 6 and 8 g per day using data from studies CK85-012, CK85-013, K85-92004, CK85-014, CK85-017, CK85-019, CK85-022, CK85-023, K85-95014, K85-95011, K85-95012. In the pooled analysis, changes from baseline in EPA uptake were dose proportional for K85 2, 4, and 8 g daily. The change from baseline for K85 6 g daily was equivalent to that at 4 g daily. For DHA, the change from baseline in uptake was highest at K85 4 g daily. Subjects receiving K85 8 g daily showed similar DHA levels to those receiving K85 4 g daily.

In the following efficacy trails, serum concentrations of EPA and DHA were determined at baseline and endpoint to evaluate treatment compliance: CK85-013, CK85-014, CK85-017, CK85-019, CK85-022, CK85-023, K85-92004, K85-94010, and K85-94009. According to the sponsor, a population pharmacokinetics and pharmacodynamics analysis was conducted. It was concluded that treatment effects on mean percent change from baseline to the end of the study in EPA/DHA incorporation in the K85 treated subjects were independent ($p<=0.001$) of gender, age (>=49 years vs. <49 years), diabetic status, and hypertensive status. The percent change from baseline in EPA uptake was less pronounced in the US and Norway subject populations compared to subjects from Sweden, England, and Holland. For DHA, the percent increase in uptake in US subjects was 2 to 4 times larger than for subjects from any European country examined.

The following literatures were included in this NDA:

1. CK85-006: Absorption of the n-3 eicosapentaenoic and docosahexaenoic acids as ethyl esters and triglycerides by humans
   This is an open-label, placebo-controlled, crossover design with a 1- to 2-week washout period between each dose. It was performed in 5 healthy volunteers, 2 females and 3 males. All participants received 4 different "fatty meals" in a fasting state in the morning consisting of different fatty acid preparations: (1) 40 g EPAX-5000TG (triglyceride ester of omega-3 fatty acid; (2) 28 g K85; (3) 28 g K85 + 12 g olive oil; (4) 40 g olive oil (placebo meal). The investigated concluded that both formulations of omega-3 (ethyl ester and triglyceride) were equally well absorbed into different lipid classes in serum. Concomitant ingestion of other unsaturated fatty acid compounds (eg., olive oil) did not affect the absorption of omega-3 fatty acids from K85.

2. CK85-027: Bioavailability of Omega-3 fatty acids: ethylester preparations are as suitable as triglyceride preparations
   In subjects receiving equivalent total amount of omega-3 fatty acids, triglycerides containing 32% omega-3 fatty acids (6 g daily), ethyl esters containing 54% omega-3 fatty acids (3 g daily), or ethyl esters containing 84% (K85) omega-3 fatty acids (2 g daily). After 7 to 14 days, EPA levels has risen 5 to 6 times over baseline in all 3 treatment groups. Increases of 2 times over baseline in DHA levels were observed for the triglyceride and the 84% ethyl ester groups, and an increase of 1.7 times over baseline in DHA levels was observed for the 54% ethyl ester group.

3. CK85-003: Effect of eicosapentaenoic and docosahexaenoic acids on blood pressure in hypertension

Administration of K85 2, 4, or 8 g daily for 8 weeks resulted in significantly increased incorporation of EPA and DHA in serum phospholipids compared to placebo. Incorporation of EPA into serum phospholipids was higher in the 8 g group than in the 2 g group, but the extent of incorporation of EPA was similar between the 8 g and 4 g groups. The DHA increases were less marked and not dose dependent. This article concluded that dietary enrichment with 6 g per day of 85% eicosapentaenoic and docosahexaenoic acids can lower blood pressure in subjects with hypertension.

4. K85-95015: A randomized trial of high-dose compared with low-dose omega-3 fatty acids in severe IgA nephrophthy After 6 months of K85 4 g daily treatment, incorporation of EPA into serum phospholipids increased 3.9 times over baseline. Incorporation of DHA was 1.7 times over baseline at 6 months. At K85 8 g daily for 6 months, incorporation of EPA into serum phospholipids increased 5.5 times over baseline. Incorporation of DHA was 2.2 times over baseline at 6 months.

5. K85-99023: Early modifications of fatty acid composition in plasma phospholipids, platelets and mononucleates of healthy volunteers after low doses of n-3 polyunsaturated fatty acids

11/19/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 45, 988

Pronova Biocare, A. S.
Attention: Robert J. Matis
Associate Director, Regulatory Affairs
Ross Products Division, Abbott Laboratories
D-104070, RP3-2
625 Cleveland Avenue
Cleveland, OH 43215-1724

Dear Mr. Matis:

Please refer to the teleconference between representatives of your firm and FDA on October 20, 2003. The purpose of the meeting was to discuss IND 45,988, and plans to submit a New Drug Application (NDA 21-654) for Omacor (omega-3-acid ethyl esters) Capsules.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

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

Sincerely,

{See appended electronic signature page}

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: October 20, 2003

TIME: 12:05 PM – 12:45 PM

LOCATION: Conference Room 14B-45/ Teleconference (Dial-in)

SPONSOR: Pronova Biocare, A. S.

TYPE OF MEETING: Type B Guidance Meeting

DRUG: Omacor (omega-3-acid ethyl esters) Capsules

APPLICATION: IND 45, 998

MEETING CHAIR: Mary Parks, M.D., Deputy Director, Division of Metabolic and Endocrine Drug Products (DMEDP)

MEETING RECORDER: Enid Galliers, Chief, Project Management Staff, DMEDP

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1. Mary Parks, M.D.	Deputy Division Director and Medical Team Leader	DMEDP, HFD-510
2. Sheldon Markofsky, Ph. D.	Acting Chemistry Team Leader	DNDC II, ONDC, HFD-820
3. Mamta Gautam-Basak Ph.D.	Chemistry Team Leader	DNDC II, ONDC, HFD-820
4. Martin Haber, Ph. D.	Chemistry Reviewer	DNDC II, ONDC, HFD-820
5. Karen Davis-Bruno, Ph.D.	Supervisory Pharmacologist	DMEDP, HFD-510
6. J. Todd Sahlroot, Ph.D.	Biometrics Team Leader	DB II, OPaSS, HFD-715
7. Enid Galliers	Chief, Project Management Staff	DMEDP, HFD-510

EXTERNAL ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name Agent for Pronova Biocare
1. Alan Ryan, Sr.	Sr. Research Scientist, Pharmaceutical R & D	Ross Products Division, Abbott Laboratories
2. Jeffrey E. Salon, M.D.	Medical Director, Medical Nutrition R & D	Ross Products Division, Abbott Laboratories
3. Kevin B. Mahan	Section Manager, Device and Pharmaceutical R & D	Ross Products Division, Abbott Laboratories
4. A. Dee Kanonchoff	Research Scientist	Ross Products Division, Abbott Laboratories
5. Charles L. Paule	Section Manager, Biostatistics	Ross Products Division, Abbott Laboratories
6. Robert J. Matis	Associate Director, Regulatory Affairs	Ross Products Division, Abbott Laboratories

BACKGROUND:

On October 20, 2003, the sponsor requested a guidance teleconference to discuss questions regarding the filing of a New Drug Application for Omacor Capsules. Previously the Agency held a pre-NDA meeting with the sponsor on October 31, 2001.

MEETING OBJECTIVES:

To obtain input from the Agency regarding the sponsor's proposed NDA submission and to resolve certain chemistry, manufacturing, and controls issues.

DISCUSSION:

1.a. As a paper submission is our preferred structure (and it was the initial understanding that this would be a paper filing), will the Agency accept a submission comprised of 180 paper volumes and an e-file as described in the briefing document?

FDA Response:

- *During this teleconference the sponsor clarified that there will be 251 volumes submitted as archival copies. The sponsor assured the Division that the efficacy data had been compiled as requested by the FDA statistician at the last pre-NDA meeting (October 31, 2001). The eight key studies are randomized, double-blind, placebo-controlled lipid-altering studies for which raw data are available. Safety data are also available from these trials. Additional data are available from uncontrolled or open-*

label studies. The raw data for all 22 studies will be submitted in electronic format. The Division asked that sponsor to provide in the Integrated Summary of Efficacy (ISE) the effects of drug treatments on TGs, VLDL-C, non-HDL-C, LDL-C, and HDL-C. ApoB lipoprotein changes were also requested if available from these studies, and the firm agreed to provide those data wherever available. The Division noted that the proposed indication [ ] *and inquired whether combination studies had been conducted. The sponsor responded that the NDA would include one open-label, combination study involving Omacor with* [ ]

- *For the ISE and the Integrated Summary of Safety (ISS), the Agency stated that a pooled analysis of the eight pivotal studies would be acceptable. The applicant should list the studies and use a simple, robust model for the statistical analysis of ISE data.*

- *For the Chemistry section of the application, the firm was asked to list the source country and BSE certification for the soft gel capsules.*

- *The background package states that the capsules contain partially hydrogenated vegetable oils. The NDA should provide the composition of partially hydrogenated vegetable oils, specifically, a description of the trans fatty acid content.*

- *Also, a list of updated manufacturing/testing sites and any DMF references should be provided.*

- *All electronic datasets must comply with the FDA/CDER guidance regarding electronic NDA submissions so they can be archived. (Post-meeting note: Any data previously supplied on CD to an IND were not archived, and they need to be submitted in the appropriate electronic format as part of the archival copy of the NDA.)*

- *Information on patient drop-outs should be included in the electronic dataset.*

1.b What are the Division requirements for the Review Copies?

FDA Response:

- *Desk copies should only be discipline-specific. In addition, all reviewers should receive a desk copy of the initial volume containing the cover letter, table of contents, and proposed labeling. The sponsor stated that most of the volumes contained reference articles. The Agency requested that desk copies of the reference articles NOT be made available as desk copies. However, the sponsor should provide a summary of where these references are located in the archival jackets and provide the reference information wherever relevant to a study protocol or clinical study report.*

- *For the biometrics review, the sponsor was asked to assemble paper final reports and protocols only for the eight pivotal studies and ISE.*

- *A paper copy of the NDA submission is acceptable for review.*

- *Post-meeting note: FDA will also need the electronic carcinogenicity data previously submitted to FDA on CD for a Biometrics review and for archival purposes of the NDA. The (archival and review) copy of the submission should include the carcinogenicity study reports.*

2. Providing all stability data satisfy established stability specification, does the Agency agree that the combination of historical stability information and the ongoing stability program using all stability batches as described are:

a. ...sufficient to demonstrate stability of the Omacor® Capsules at room temperature (25° C)?

FDA response:

- *This is a review issue, but available stability data [redacted] can be submitted as supporting data. The appearance specification should be revised to include the [redacted] Regarding primary stability data (to support the NDA), ICH conditions should be used.*

2.b. . . . will be adequate to support a [redacted] expiry dating for Omacor® Capsules?

FDA response:

- *This is a review issue but, in general, expiry should be supported by real-time stability data.*

3.a. Does the Agency agree, in consideration of the physical properties of the API, that the traditional requirement for a dissolution test for an oral dosage form is not appropriate for this product and should be waived?

FDA Response:

- *Although an emergency prevented the biopharmaceutics team leader from attending the meeting, the Agency commented that the dissolution requirement cannot be waived. FDA suggested that the sponsor needed to demonstrate that it had conducted dissolution testing with a variety of [redacted] and provide the results. If possible, some more specific comments on this issue would be provided as a post-meeting note to these minutes. Otherwise, the FDA could arrange a teleconference with the sponsor to elaborate on this issue.*

- *Post-meeting note (Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader, DPE II, OCPB [HFD-870]): The Agency allows sponsors to use [ ] However, it is the Agency's policy that [ ] should be used as minimally as possible. In addition, the sponsor proposed UV absorbance at —. The Agency recognizes that UV at — is unspecific, and it recommends that a more specific detection method be used in a dissolution test.*

Additional FDA comments and requests :

- *For the studies and tests reported in the NDA, the sponsor should indicate whether the market formulation or another formulation was used.*

- *The sponsor was reminded that the proprietary name, Omacor®, was not acceptable to the Agency under the NDA [ ] While there are no objections from DMEDP to their resubmitting this name under this NDA, another review will need to be conducted by the Office of Drug Safety's Division of Medication Errors and Technical Support (DMETS) to determine if Omacor® is acceptable. The sponsor was advised to consider "back-up" trade names should DMETS make an unfavorable recommendation that is upheld by the review division.*

Clinical

- *The sponsor was asked if there were drug interaction studies between Omacor and warfarin. The sponsor stated that no specific studies were conducted; however, there is a substantial number of patients in the clinical trials who took Omacor concomitantly with warfarin or aspirin. The sponsor was asked to summarize the number of patients using Omacor with warfarin from this clinical trial database.*

Chemistry, Manufacturing, and Controls

- *No annual reports have been submitted since 2000. Please submit a complete update of the CMC section as an amendment to the IND.*

- *The composition of the drug product and updated proposed regulatory specifications (list of tests, acceptance criteria and analytical procedures or test methods) for drug substance and drug product should be submitted as soon as possible to the IND.*

Biopharmaceutics

- *The sponsor replied to questions regarding testing of the product in various special populations that Omacor had been studied in patients with IgA nephropathy and with hypertension, but not hepatic impairment. The sponsor has not seen any differences*

based on age or gender or among patients with hypertension or various dyslipidemias and normal volunteers.

POST-MEETING NOTE - ADDITIONAL INFORMATION FROM ROSS PRODUCTS DIVISION:

- Ross Products Division is the agent for Pronova Biocare, which is the sponsor of the IND for Omacor. However, Ross Products will be the applicant for the NDA, and the firm plans to submit the NDA by December 15, 2003.

- Ross inquired on November 19, 2003, whether submission — would affect the filing of the NDA. Ms. Galliers commented that there usually are requirements for specific studies [redacted]

  FDA recommended [redacted] if the firm wanted to adhere to the mid-December submission timeline.

Minutes Prepared by /s/ 11/19/03
Enid Galliers
CPMS, HFD-510

Chair Concurrence: /s/ 11/19/03
Mary H. Parks, M.D.
Deputy Director, HFD-510

MEETING MINUTES

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

/s/

Enid Galliers
11/19/03 04:13:38 PM

12/21/01

Meeting Date: October 31, 2001	Time: 03:00 PM Location: PKLN 3rd flr "Potomac"
IND 45,998	Omacor (Omega-3 [n-3] polyunsaturated fatty ester) Capsules
Type of Meeting:	Pre-NDA
External Participant:	Ross Products Division, agent for Pronova Biocare
Meeting Chair:	David G. Orloff, M.D., Division Director
External Participant Lead:	Jeffrey E. Salon, MD, Associate Medical Director Pharmaceuticals
Meeting Recorder:	William C. Koch, R.Ph., Regulatory Project Manager

FDA Attendees and titles:

David G. Orloff, M.D., Division Director
Mary H. Parks, M.D., Deputy Division Director
Shiao-Wei Shen, M.D., Clinical Reviewer
Karen Davis-Bruno, Ph.D., Supervisory Pharmacologist
Sheldon Markofsky, Ph.D., Acting Chemistry Team Leader
Todd Sahlroot, Ph.D., Team Leader, Biometrics 2
Enid Galliers, Chief, Project Management Staff
William C. Koch, R.Ph., Regulatory Project Manager

External participant Attendees and titles:

[ ], MD, [ ]
Jeffrey E. Salon, MD, Associate Medical Director Pharmaceuticals, Ross
[ ] MD, Medical Consultant, Ross
Charles L. Paule, Manager Biostatistics, Clinical Operations, Ross
Patricia L. Welch, Associate Director, Drug Regulatory Affairs, Ross

Meeting Objectives:

This meeting was requested by the agent on September 12, 2001, to discuss the sponsor's analysis and formatting of clinical data to be submitted in the original NDA submission.

Discussion Points: (General Discussion)

The Division asked what the proposed mechanism of lipid lowering effect is and what the significance of the observed increases in LDL-C is.

Several mechanisms for increased LDL levels have been proposed including the shift to increasing LDL production from VDL-C as triglyceride (TG) production is decreased hepatically. The sponsor recommends that the evaluation of increased LDL-C level focus not only on the percent increase, but the absolute change.

The Division advised the sponsor to reference any previously approved NDA's which market the same drug substance or drug product in their proposed Omacor NDA.

The Division requested that relevant chemistry, manufacturing and control (CMC) data from the [redacted] NDA be included in the proposed new NDA and that any CMC changes from the [redacted] NDA should be highlighted in the proposed new NDA.

The Division requested that tumorigenicity data from both rodent studies be submitted in the proposed Omacor NDA in the correct electronic format.

The Division pointed out that at this time, there are no clinical studies that demonstrate the reduction of cardiovascular mortality and morbidity associated with the independent lowering of TG levels.

The Division also pointed out that the lowering of triglyceride levels, by itself, has not been established as an acceptable effectiveness endpoint. It has been allowed in labeling for some lipid-altering drugs with demonstrated clinical effectiveness from clinical outcome trials or for drugs with significant LDL-lowering efficacy, an established surrogate measure of cardiovascular (CV) benefit. The labeling in all of these approvals required disclaimers that state that the clinical benefits of independently lowering TG (or raising HDL-C) levels are not known at this time.

The Division stated that the pharmacologic effect of omega-3 fatty acids is TG-lowering, however, studies also demonstrate an LDL-raising effect. Furthermore, Omacor has not been demonstrated in clinical outcome trials to reduce cardiovascular (CV) mortality and morbidity as a result of TG-lowering.

TG-lowering data alone would not be sufficient for a marketing approval of Omacor and other data should be obtained to support the clinical effectiveness of TG-lowering by omega-3 fatty acids.

The Division stated that [redacted]

Since Omacor is a dietary supplement and derived from a food, the Division stated that it is willing to consider the submission of published literature that might link the lipid-altering effects of omega-3 fatty acids with a clinical benefit.

The supportive data obtained from literature must be from adequate and well-controlled studies which consistently show a significant lowering of CV risk associated with the lipid changes obtained from omega-3 fatty acid treatment.

The sponsor should attempt to provide the agency with raw data from these referenced clinical studies, but these data are not necessarily required for the filing of the application.

Although published literature may support the approval of Omacor as a TG-lowering agent, [redacted]
targeted population.

The Division reminded the sponsor that If the supportive clinical studies used an omega-3 fatty acid formulation different from Omacor, a pharmacokinetic study may be required to bridge the two products.

In addition, the Division stated that the LDL-raising phenomenon observed with Omacor needs to be characterized in both percentage changes and absolute changes.

Discussion Points: (Questions submitted by industry)

Ross plans to use the following approach in analyzing and formatting the clinical information developed with this product. Is this acceptable to the Division?

1 In the individual studies, the primary outcome was reduction of serum triglycerides (TG). The baseline value was defined as a mean of two or three TG measurements, usually one week apart. The end-of-study value was the mean of two TG measurements that may have been obtained up to four weeks apart.

In the individual studies, Ross intends to use the protocol-defined mean end-of-study value in the primary analyses of HTG.

In the ISE, Ross plans to use the final single TG value for the analyses because the time interval between the final two values was variable and often too great to be clinically relevant.

The secondary analyses for the individual studies will use the last single TG value whereas the ISE will use the mean of the final two values.

The Division stated the integrated summary of efficacy (ISE) should emphasize the results of the individual studies with respect to consistency of outcomes, special populations, etc.

The sponsor's proposed pooled analysis is considered exploratory. For this analysis the sponsor should explore questions related to the appropriate use of the drug.

The sponsor replied that the study population would be re-categorized by clinical class, and the data would be analyzed and presented in a way to best support the proposed indications in the final labeling.

2 All efficacy analyses will be based on hyperlipidemia type (Type IIb, Type IV/V).

3 For all analyses, subjects will be assigned to Fredrickson and Lees' hyperlipidemia groups using the following classification:

Type IIb: TG > 177mg/dL, LDL = 175 mg/dL
Type IV/V: TG > 177 mg/dL, LDL < 175 mg/dL

An LDL-C level of 175 mg/dL was chosen as the midpoint of the NCEP ATP III "high" category.

ATP III Classification of LDL-C (mg/dL)

LDL-C level (mg/dL)	Classification
< 100	Optimal
100 – 129	Near optimal/above optimal
130 – 159	Borderline high
160 – 189	High
190	Very high

The lower limit for TG is equivalent to the 2 mmol/L limit used in the studies conducted in Europe.

The Division requested that the sponsor complete a separate analysis for Fredrickson Type V hypercholesterolemia.

The Division further requested that the sponsor perform absolute LDL-C levels at study endpoint.

4 All subjects will be included in the ISS; analyses of adverse events by hyperlipidemia type will be supportive.

The Division agrees with this approach.

5 Many of the original study reports used a nonparametric approach for the primary analyses. Ross proposes a nonparametric approach as the primary analysis for the individual reports and a parametric approach as the primary analysis for the ISE and the ISS. We believe the parametric approach is better suited for the integrated analyses. Parametric results will be provided as supportive documentation in the individual reports and nonparametric results will be provided as supportive documentation in the ISE/ISS.

The Division stated that the appropriate analysis for the pooled data, either parametric or non-parametric, will depend on what the data will support.

6 Ross proposes to use the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 2.0 as a standard of comparison for laboratory parameters in all studies.

The Division agrees with the use of the NCI Common Toxicity Criteria, however, this type of analysis can hide outliers. The Division stated that the actual lab values would be needed for the review of safety.

7 In all clinical studies, subjects underwent a dietary run-in period to determine eligibility before randomization and treatment. Data collected during this period are available only for subjects who were subsequently enrolled in the study. Consequently, Ross intends to present only treatment-emergent adverse events.

The Division agrees with this approach.

8 Initial review of the data does not indicate any safety concerns. Thus, Ross intends to use by-subject listings, as generated for individual study reports, as case report form tabulations.

The sponsor added that the line listings would be submitted as opposed to case report forms themselves.

The Division agrees with this proposal.

9 For all studies included in the ISE, Ross will provide complete study reports that are compliant with the ICH E3 guideline. For all other studies, Ross will provide abbreviated study reports.

The Division agrees with this proposal.

10 Ross will provide documentation of the analysis data sets, i.e., the derived variables, using PROC CONTENTS. SAS data sets will be provided in the SAS XPORT transport format, if requested.

The Division agrees with the format of the datasets as presented in the pre-meeting information. (refer to ATTACHMENT)

11 Ross plans to request a waiver for pediatric studies. No controlled clinical studies in pediatric populations have been conducted nor are any studies planned. In type IIb patients use of K85 would be limited to a small subset of patients who do not respond to the combination of diet and pharmacological agent. Pediatric patients with type IV/V are rarely identified.

The Division inquired about the possibility of studying [ ]

The sponsor responded that this population usually does not have elevated TG's.

The Division agrees to [ ] of pediatric studies at this time

12 Pronova proposed the trade name Omacor™ [ ] This name was rejected [ ] because of potential confusion with Inocor® and Amicar®. What is the current agency time frame for clearing an acceptable trade name?

The Division responded that the proposed trade name could be approved 60 days prior to an approval date.

Decisions (agreements) reached:

The use of the NCI Common Toxicity Criteria is agreed to.

The presentation of only treatment-emergent adverse events in the ISS is agreed to.

The submission of by-subject listings, as generated for individual

study reports, as case report form tabulations is agreed to.

The submission of complete study reports that are compliant with the ICH E3 guideline in the proposed NDA is agreed to.

The format of the datasets as presented in the pre-meeting information is agreed to.

Unresolved or issues requiring further discussion:

- None

Action Items:

The sponsor will re-categorize by clinical class the study population, and the data will be analyzed and presented in a way to best support the proposed indications in the final labeling

The Division requests that tumorigenicity data from both rodent studies is submitted in an appropriate electronic format in the NDA.

Post-meeting Activity:

The Division requests that all CMC deficiencies communicated by the Agency from the previous Omacor NDA be responded to in the proposed new NDA.

/S/

{See appended electronic signature page}

Prepared by: _____, Meeting Recorder

William C. Koch, R.Ph. date

Regulatory Project Manager

/S/

{See appended electronic signature page}

Concurrence: _____, Meeting Chair

David G. Orloff, M.D. date

Director

ATTACHMENT

PRE-NDA MEETING HANDOUT
SUBMISSION OF EFFICACY DATASETS

Please follow the guidance for the submission of electronic data. This guidance may be found at www.fda.gov/cder/guidance. Choose Electronic Submissions and then choose #3. In the guidance document, go to K. Item 11: Case Report Tabulations (CRT's).

This handout provides further detail regarding the submission of efficacy data.

Submit the following efficacy datasets to the FDA electronic data room (EDR):

1. Primary efficacy dataset
2. Secondary efficacy dataset

These datasets should contain the following variables:

1. unique patient ID
2. center number
3. race
4. age
5. gender
6. treatment group
7. week or month (i.e. visit decoded) where zero denotes the time of randomization
   - this variable is present when the data was collected at several visits; it will be missing when there Is only one record per patient
8. other important demographic/prognostic variables
9. last week completed for the patient
10. completer? (1=yes patient completed whole study, 0=patient discontinued early)
11. LOCF indicator variable (1=record contains the last efficacy value on study; 0=not the last value
12. raw and derived data for the efficacy variables
    - derived data (e.g. change from baseline or percent change from baseline data)
    - baseline should be included with each record as well as for the time 0 record
    - the value at that visit

Provide in hardcopy to the statistical reviewer a printout of the PROC CONTENTS and a printout of about 50 observations for each efficacy dataset.

The following is a general example of how the primary efficacy data may be recorded for two patients; patient 21 completed the study and patient 33 did not complete.

Pt	Ctr	Race	Gender	Trt	Week	Last week	compl	Locf	Base Eff	Eff	CH Eff
21	2	1	1	1	-2	6	1	0	BX	X	x-bx
21	2	1	1	1	0	6	1	0	BX	BX	0
21	2	1	1	1	2	6	1	0	BX	X	x-bx
21	2	1	1	1	4	6	1	0	BX	X	x-bx
21	2	1	1	1	6	6	1	1	BX	X	x-bx
33	3	1	2	0	-2	2	0	0	BX	X	x-bx
33	3	1	2	0	0	2	0	0	BX	BX	0
33	3	1	2	0	2	2	0	1	BX	X	x-bx

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

/s/

David Orloff
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