CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-654

Administrative/Correspondence

EXCLUSIVITY SUMMARY for NDA # 21-654 SUPPL #
Trade Name Omacor Generic Name omega-3-acid ethyl esters

Applicant Name Ross Products Div., Abbott Laboratories HFD-510

Approval Date

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/ X / NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO / X /

      If yes, what type(SE1, SE2, etc.)?

   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 / X / NO /___/

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

      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 /_X_/

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 /_X_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

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

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /X__/

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

NDA #

NDA #

NDA #

2. Combination product.

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

YES /___/ NO /___/

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

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

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 9.

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 9:**

(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:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

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 /___/

Investigation #3 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:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(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 /___/

Investigation #3 YES /___/ NO /___/

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

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(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"):

Investigation #__, Study #

Investigation #__, Study #

Investigation #__, Study #

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 # _____ YES /___/	NO /___/ Explain:
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are

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

YES /___/ NO /___/

If yes, explain: _____

_____

_____

/S/

Valerie Jimenez
Regulatory Project Manager

Date November 10, 2004

/S/

Mary H. Parks, M. D.
Deputy Director
Division of Metabolic
and Endocrine Drug Products, HFD-510

Date November 10, 2004

cc:
Archival NDA
HFD- /Division File
HFD-510/Valerie Jimenez
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Mary Parks
11/12/04 02:13:08 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : 21-654 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

Stamp Date: January 12, 2004 **Action Date:** November 12, 2004

HFD 510 **Trade and generic names/dosage form:** Omacor (omega-3-acid ethyl esters) Capsules, 1 gm

Applicant: Ross Products **Therapeutic Class:** 1s

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: an adjunct to diet to reduce TG levels in adult patients

Is there a full waiver for this indication (check one)?

X **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- X **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete

and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Valerie Jimenez, HFD-510
Regulatory Project Manager

cc: NDA 21-654
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

f studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:_____**

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

ection D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**
Max_____	**kg_____**	**mo._____**	**yr._____**	**Tanner Stage_____**

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Valerie Jimenez, HFD-510
Regulatory Project Manager

cc: **NDA 21-654**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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/s/

Valerie Jimenez
10/25/04 12:10:38 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

OFFICE DIRECTOR'S DECISIONAL MEMORANDUM

Date:	Wednesday, November 10, 2004
NDA:	21-654;
Sponsor:	Ross Products/Abbott Laboratories
Trade (USAN) Name:	Omacor (omega-3-fatty acid ethyl esters) capsules
Author:	Robert J. Meyer, MD, Director, ODE II

Introduction

Hypertriglyceridemia is associated, variably, and depending upon severity and the nature of the lipoproteins in which triglycerides reside, with risk for pancreatitis and/or atherosclerotic vascular disease. The risk of pancreatitis appears to exist only in patients with extreme hypertriglyceridemia (i.e., plasma TG > 800-1000 mg/dL) as may be found in Fredrickson Types I (lipoprotein lipase deficiency) and V hyperlipidemia. In such patients, hyperchylomicronemia is a significant component of the TG elevation. Chylomicrons, intestinal-derived lipoproteins (containing apo B-48), are not believed to be directly atherogenic. This conclusion is based, in part, upon clinical observation in patients with hyperchylomicronemic syndromes and on animal models. The mechanism(s) by which they cause pancreatitis is not well understood, but in patients with intractable, marked hypertriglyceridemia, recurrent pancreatitis can occur and can lead to severe clinical sequelae, including chronic pancreatic exocrine and endocrine deficiency and death.

Hypertriglyceridemia due to elevations in hepatic-derived lipoproteins containing apo B-100 (VLDLs and their metabolic lineage) are potentially atherogenic. Indeed, these are the triglyceride-rich lipoproteins that characterize the atherogenic dyslipidemia of metabolic syndrome and diabetes. In the setting of insulin resistance and resultant increased flux of free fatty acids to the liver, hepatic synthesis of VLDL is increased and this, in conjunction with derangements in lipolysis of triglycerides in these particles for use as metabolic fuel (due to absolute and functional lipase deficiency), leads to hypertriglyceridemia, secondary hypoalphalipoproteinemia (low HDL), and the generation of small, dense LDL particles and VLDL remnants. The result is a potent atherogenic lipoprotein environment mediating the well known association between vascular disease and obesity, the metabolic syndrome, and diabetes.

This application proposes Omacor, 4 grams daily for the treatment of hypertriglyceridemia in patients [

]

[ ] The 4 grams may be taken all at once (4 capsules) or in divided doses. In considering this application, Dr. Parks has evaluated the lipoprotein changes demonstrated for Omacor therapy by subgroups of Fredrickson classification. This is clinically relevant both for reasons of pathophysiology and because of differences in associated clinical risks (i.e., pancreatitis vs. atherosclerosis). Her review finds that while Omacor is effective in reducing TG levels in all three subgroups, in patients with atherogenic dyslipidemias (types IIb and IV), TG lowering is associated with alterations in the lipoprotein profile that may well be pro-atherogenic, notably with rises in LDL-C. Insofar as patients in these subgroups are not at risk of pancreatitis due to elevated TG, there is concern of risk (of atherosclerosis) with Omacor used alone in the absence of clinical benefit. By contrast, the effect of Omacor to lower TG in Type V patients is likely to be clinically meaningful (i.e., likely reduction in risk of pancreatitis), though this has not been proven.

Due to the likelihood of approving one indication (use in patients with very high triglyceride levels as in Type V hyperlipidemia) .
application has been administratively split with the Type V remaining as NDA 21-654

Chemistry/ Microbiology
The source for the omega-3 ethyl esters in Omacor is natural fish oil. The oil is highly purified [ ] for the omega-3 ethyl esters eicosapetanoic acid (EPA) and docosahexanoic acid (DHA) , more than is the case in common fish oil omega-3 supplements. Each one gram capsule of the drug contains approximately 465 mg of EPA and 375 mg of DHA. Notably, there is a small amount of alpha-tocopherol in each capsule – about 4 mg. Despite the fish source, the final drug substance is remarkably well purified and relatively free of potentially associated toxic substances such as mercury and other heavy metals. The application has been found to be acceptable by the CMC team and the sites of manufacturing and testing have proven acceptable. From the CMC standpoint, this application is recommended for approval.

Pharmacology/Toxicology
The sponsor provided adequate data to support a 4 gm per day dosage of omega-3 ethyl esters chronically, although it should be noted that they do not have technically adequate carcinogenicity data. The sponsor conducted the normal batteries of mutagenicity testing (all resulting in negative tests) and they conducted both rat and mouse studies for carcinogenicity assessment, though both studies had some deficiencies. The mouse study was inadequate in design, duration and dosing, whereas the rat study was deficient mainly in duration. That said, both studies showed no signs of carcinogenicity and the ECAC determined that these studies were adequate to allow for approval, even if less than ideal. [ ] The target organs of toxicity included skin (rats/dogs), liver (rats), lungs (rats), adrenals (rats/dogs) , kidneys (dogs) and testis (dogs). The skin lesions were felt due to essential fatty acid deficiencies due to the diet high in the EPA/DHA, since palmitic and linoleic acid decreases when high doses of EPA and DHA are given. This was noted at high doses.

Other toxicities were noted at lower multiples of human exposure (2 fold or less), but since human experience is large with this drug (it has been approved in many European countries for years), it is felt that these findings may have limited relevance to humans. The reprotoxicity studies were largely unremarkable, except that the segment II study in rabbits showed some fetal loss at high doses. All other segment studies and other species studies for reprotox were negative. The application is considered approvable from the Pharmacology/Toxicology team, given appropriate modifications to the proposed label.

Biopharmaceutics

Omacor is well-absorbed orally, with the EPA and DHA being handled as other dietary fatty acids. While Omacor leads to higher levels of incorporation of EPA and DHA into serum phospholipids, the former was dose-dependant, but not apparently the latter. There was a dose-response relationship in effects on triglyceride levels (TG) however out to 8 mg daily (the highest dose assessed), with lowering of 22%, 27% and 37% respectively for 2, 4, and 8 mg of Omacor. While there appears to be minimal potential for important drug-drug interactions, there is literature that shows induction of CYP p450 in rats by EPA and DHA (including 3A4) and the biopharm team was concerned that this might decrease the effectiveness of 3A4 metabolized statins (such as simvastatin). They therefore recommended [ ] I do not accept that recommendation for the following reasons. First, there are no literature reports of important drug-drug interactions with fish oil supplementation, including in patients on cyclosporine – a drug very sensitive to 3A4 induction. Secondly, statins are dosed to effect and the labeling for Omacor will recommend following LDL-C, so even if this there were such an effect, clinically this would mean that patients would be appropriately titrated with their statin accordingly. Finally, if this induction potential is a clinically important issue, it would be best to do a clinical pharmacology study to evaluate it. [ ]

Clinical / Statistical

The pooled primary, pivotal clinical database comes from 8 studies. Original enrollment comprised 454 patients entered in these double-blind, randomized, controlled trials. The lipoprotein changes associated with Omacor and placebo are summarized in Table 1 of Dr. Parks' review, derived from data in tables 13 (TG), 17 (total-C), 19 (HDL-C), 20 (LDL-C), 24 (non HDL-C), and 25 (VLDL-C). Of note, while the median reductions in TG from baseline in patients treated with Omacor across the subgroups by Fredrickson class were all significantly different than placebo, only in the small number of patients with Type V were the changes in HDL-C, LDL-C, and non-HDL-C, taken together, suggestive of a lack of a potential deleterious effect of Omacor on atherogenesis. Indeed, non-HDL-C, taken as a measure of total cholesterol carried in potentially atherogenic lipoproteins (as opposed to in "good" HDL particles), only fell significantly relative to placebo in patients with type V. Notably, in patients with type IIb, where LDL-C elevation is a central component of the atherogenic profile, LDL-C remained largely unchanged, therefore showing no evidence of benefit for such patients, since in type IIb patients, atherogenesis is the clinical consequence that would lead to drug treatment. Additionally, in patients with type IV, mean LDL-C increased by over 30% relative to

placebo ($p<<<0.05$), and mean non-HDL-C remained essentially unchanged. [

]

Finally, patients with marked hypertriglyceridemia not due to lipoprotein lipase deficiency (type 1), had marked reductions (~40%) in TG, total cholesterol (~15%), elevations in HDL-C (~25%), in conjunction with a highly significant ~20% reduction in non-HDL-C, signifying the absence of any pro-atherogenic effect in patients treated to lower TG and the potential to reduce the risk of pancreatitis (though an actual showing of reduced risk for pancreatitis has not been accomplished). These finding in type V hyperlipidemia patients support benefit (lower TG and likely a lower risk of pancreatitis) that outweighs risk (no apparent increase in atherogenic lipids) for this population.

Data were submitted addressing the efficacy of Omacor in combination with statins, and one small category 2 study in patients with elevated TG and CHD was reviewed by Dr. Parks (summarized in table 26). While the data do support a superior effect of Omacor plus simvastatin on TG as compared to simvastatin alone, these data are inadequately robust and inadequately broad [ ] regarding combination therapy with simvastatin or with statins generally. Additionally, a comparison study to gemfibrozil in patients with marked elevated TG was conducted (table 27). Results show that gemfibrozil was markedly more effective in lowering TG and in increasing HDL-C than was Omacor.

The overall safety profile of Omacor was evaluated in several subject datasets, totaling over 600 patients. Exposures were relatively short (mean ~19 weeks) in the population included in the safety dataset, though it should be noted that omega-3-fatty acids are normal constituents of diet high in fish. Additionally, Omacor has received marketing approval in 14 countries around the world and the sponsor states that no spontaneous reports of adverse events or serious adverse events have been reported between 1994 and 2002.

There were no deaths or serious adverse events attributed to Omacor in this application. The overall rate of adverse events was low, with taste perversion (specifically "fishy taste") the only AE occurring in a significantly higher percentage of Omacor-treated patients than in those treated with placebo. The most common AEs reported in patients receiving Omacor were related to the digestive system. There was no effects of dyslipidemic subclass, age, or gender on the safety profile. There were no clinically relevant differences in laboratory analyses between Omacor and placebo patients.

Financial disclosure
The sponsor adequately addressed the issues of financial disclosure and there appears to be no financial arrangements that would lead FDA to suspect any bias or undue influence on results of the studies that form the basis for approval.

DMETS/nomenclature
While OMACOR was deemed acceptable by DDMAC, DMETS recommended against approval of the drug with this name due to its confusion with Amicar (epsilon amino caproic acid), a drug used for the treatment of bleeding in the setting of bleeding diatheses. While I am in agreement that the potential for confusion with Amicar exists, I don't think the likelihood of medical errors is high nor the consequences serious. Firstly, aminocaproic acid tends to be used primarily intravenously, even though available orally. Secondly, while fish oils have to potential to inhibit platelet function, this is not an acute or dramatic effect. Finally, the Omacor capsules are a distinctive soft-yellow oil filled capsule that is dissimilar in appearance to Amicar. Therefore, we will not take DMETS's recommendation on the name and will approve the drug with the name Omacor.

Labeling
The labeling has largely been successfully negotiated. A few key points worth noting as departures from the proposed labeling of the sponsor. [redacted]

Recommendation
Given the above discussed data and information, Dr. Parks and Dr. Orloff (who signed and concurred with Dr. Parks' primary review) recommend that only the indication to lower TG in patients [redacted] be approved at this time, and I concur.

1. Indication to lower plasma TG in patients with [redacted] hyperlipidemia: **Approval – NDA 21-654**

2. [redacted]

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/s/

Robert Meyer
11/10/04 12:16:31 PM
MEDICAL OFFICER

11/16/04

ADRA Review #1 of Action Package for NDAs 21-645 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) and high (200-499 mg/dL) TG levels in adults.;

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
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

Per Dr. Meyer, the issue with 3A4 induction and statins turned out to be not too striking

or important; t
1

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.*

/S/

Lee Ripper
ADRA, ODE II

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

/s/

Leah Ripper
11/10/04 02:16:48 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: November 10, 2004

To: Elizabeth Zola, Pharm.D.. Associate Director, Regulatory Affairs	**From:** Valerie Jimenez Regulatory Project Manager
Company: Ross Products	Division of Metabolic and Endocrine Drug Products
Fax number: (614) 624-3519	**Fax number:** (301) 443-9282
Phone number: (614) 624-3316	**Phone number:** (301) 827-9090

Subject: Omacor Action Letters

Total no. of pages including cover:

Comments:

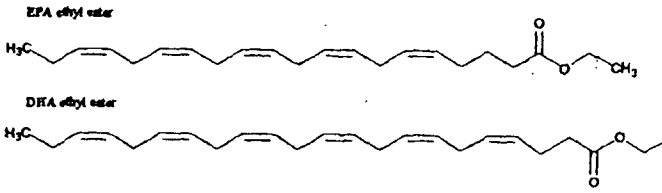
Document to be mailed: ☑ YES ☐ NO

11/1/04

OMACOR® consult:

Abbott/Ross, the applicant for NDA 21-654 (OMACOR®), requested that the FDA change the established name for the drug product from *omega-3-acid ethyl esters* (USAN, adopted in 2002) to [ ] and stated that [ ] is the INN for the drug substance in OMACOR®. In fact, [ ] is the INN for 5,8,11,14,17-eicosapentenoic acid, ethyl ester (all-*Z*, also known as EPA ethyl ester), one of the two major components of the drug substance and [ ] is the INN for 4,7,10,13,16,19-docosahexenoic acid ethyl ester (all-*Z*, also known as DHA ethyl ester), the other major component of the drug substance. *There is no INN corresponding to the drug substance*, which is a natural product derived from fish oil, and contains the two major compounds (EPA and DHA ethyl esters) along with several other minor compounds. The two major components of the mixture are the following (reproduced from the USP Dictionary of USAN and International Drug Names, 2003 edition):

Omega-3-acid Ethyl Esters [*2002*]. $C_{22}H_{34}O_2$ (EPA ethyl ester) . 330.51 (EPA ethyl ester); $C_{24}H_{36}O_2$ (DHA ethyl ester). 356.55 (DHA ethyl ester). [Omega-3 Marine Triglycerides is BAN; Doconexent (DHA ethyl ester) and Icosapent (EPA ethyl ester) are INN.] EPA ethyl ester: (1) 5,8,11,14,17-Eicosapentaenoic acid, ethyl ester, (all-Z)-; (2) Ethyl (5Z,8Z,11Z,14Z,17Z)-eicosa-5,8,11,14,17-pentaenoate. DHA ethyl ester: (1) 4,7,10,13,16,19-Docosahexaenoic acid, ethyl ester, (all-Z)-; (2) Ethyl (4Z,7Z,10Z,13Z,16Z,19Z)-docosa-4,7,10,13,16,19-hexaenoate. *CAS-86227-47-6* [EPA ethyl ester]; *CAS-81926-94-5* [DHA ethyl ester]. *Hypolipidemic*. Omacor (Pronova Biocare, Norway). ◇*K85*



Comments:

- Neither of the established names (USAN or that proposed by the applicant, derived from the INN's for the major components) were based on the system of pharmacology-based stems, but were based on the chemical structure of the compounds.
- The "INN" as proposed by the applicant, is actually a combination of the INN's for the two major components. There is no INN corresponding to the natural product mixture.
- The USAN could apply to any mixture of carboxylic acid ethyl esters with a double bond at the omega position of the side chain. The USAN does not even specify that the mixture contains two different molecules. *However, the USAN was designed to correspond to the mixture* (natural product containing EPA and DHA ethyl esters, among other compounds). The name omega-3-acid ethyl esters was chosen as being suitable for a complex mixture. Other proposed USAN's, incorporating more specific nomenclature [ ] were rejected for the mixture. The USAN Council

recommended adopting the terms icosapentate and doconexentate for the individual major components.

- Historically, the FDA has utilized the USAN as the established name for drug products, when there is an adopted USAN. The INN could be used IN CASES WHERE THERE IS NO ADOPTED USAN. Since the USP is the official compendium in the U.S.A., the USAN should be used, when available.
- Federal regulations *imply* that the USAN should be used, when available per 21 CFR 299.4(c) and (d), but do not state this definitively. The regulations state that the FDA recognizes the skill and experience of the USAN Council in deriving names of drugs (299.4(c)) and agrees with "Guiding Principles for Coining Adopted Names for Drugs", published in USAN and the USP Dictionary of Drug Names. Note: neither the INN nor the USAN follow the "Guiding Principles for Coining Adopted Names for Drugs", since neither is based on the system of pharmacology-based stems.

Evaluation: The USAN, 3-omega acid ethyl esters, is the most suitable name for the actual drug substance (mixture of a variety of acid esters from fish oil, with EPA and DHA ethyl esters as the major components). *The USAN should be used as the established name for the drug substance.* The applicant's proposed established name [ ] is not acceptable for the following reasons:

- [ ] is NOT a recommended INN (rINN) for the drug substance, but consists of the rINN's for the pure individual components, EPA and DHA ethyl esters. INN's are not typically adopted for mixtures. As of this time, there is no provisional INN (pINN) or rINN for the drug substance.
- The proposed established name [ ] implies that there are no other components to the drug substance, when, in fact, there are (%).

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

/s/

David Lewis
11/1/04 02:01:46 PM
CHEMIST
The USAN omega-3-acid ethyl esters should be used as the established name for the drug, not the name coined by the applicant and referred to as the INN [ ].
I removed the last two bullet points from the end of the review per your suggestion.

Guiragos Poochikian
11/1/04 02:05:54 PM
CHEMIST

99 pages redacted from this section of the approval package consisted of draft labeling

11/8/04

Office of Drug Safety

MEMO

To: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products, HFD-510

From: Charlie Hoppes, R.Ph., M.P.H.
Safety Evaluator, Division of Medication Errors and Technical Support, HFD-420

Through: Alina Mahmud, R.Ph.
Team Leader, Division of Medication Errors and Technical Support, HFD-420

Carol Holquist, R.Ph.
Director, Division of Medication Errors and Technical Support, HFD-420

CC: Valerie Jiminez
Project Manager, Division of Metabolic and Endocrine Drug Products, HFD-510

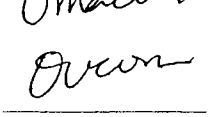
Date: October 28, 2004

Re: ODS Consult 04-0042-1; Omacor (Omega-3-Acid Ethyl Ester Capsules) 1 gram; NDA 21-654

This memorandum is in response to a October 13, 2004, request from the Division of Metabolic and Endocrine Drug Products for a re-review of the proprietary name, Omacor. In a review dated April 2, 2004, the Division of Medication Errors and Technical Support (DMETS) did not recommend use of the proposed proprietary name, Omacor. Labels and labeling were not available for review at that time. Draft container labels and package insert labeling have been submitted for review and comment at this time.

Since the completion of the first review, DMETS has identified two additional proprietary names, Oracort and Ovcon, as having the potential for confusion with Omacor. Oracort also has the potential to sound similar to Omacor. The name Oracort was not reviewed further due to numerous differentiating product characteristics such as the product strength, indication for use, frequency of administration, route of administration and dosage formulation.

Ovcon-35 and Ovcon-50 are proprietary names for the oral contraceptive products, Ethinyl Estradiol/Norethindrone Tablets, 0.035 mg/0.4 mg and 0.05 mg/0.4 mg, respectively. The name "Ovcon" may look similar to "Omacor" when scripted (see handwriting sample below).



Look-alike properties for the name pair may be attributed to the shared letters, "O", "c", and "o". The down and up-strokes in the "m" of Omacor may also look like the "v" in Ovcon. Finally, the "r" in Omacor may look like the "n" in Ovcon if its final stroke extends too far downward. Ovcon and Omacor are both available as a solid oral dosage form and, may both be given once daily, and share the route of administration (oral). The drug products differ with respect to strength (0.035 mg/0.4 mg and 0.05 mg/0.4 mg vs. 1 gram), dose (one tablet daily vs. 4 capsules daily), and indication (prevention of pregnancy vs. reduction of triglycerides). The names Ovcon and Omacor may also be differentiated orthographically with the addition of the numeric suffix to the Ovcon name. The blister card packaging of Ovcon is also quite distinctive and that product is accompanied by patient information. Overall, DMETS believes that the product differences between the two drugs minimize the potential for confusion and error between Ovcon and Omacor.

In the review of the container labels and package insert labeling of Omacor, DMETS has attempted to focus on safety issues relating to possible medication errors. The labeling forwarded with this consult is the same as the labeling reviewed in ODS Consult 04-0042, dated April 2, 2004. In addition to the comments provided in that review, DMETS has identified the following areas of possible improvement, which might minimize potential user error.

CONTAINER LABELS (120 capsule and 28 capsule physicians sample)

1. DMETS recommends omission of the statement, [ ], to increase the prominence of other labeling statements.

2. Revise the Usual Dosage statement to read, [ ] The third sentence may be shortened to read, [ ]

3. Revise the expression of strength to eliminate the duplicate, "Each capsule" statement.

In summary, DMETS continues to object to the use of the proprietary name Omacor based on its potential for confusion with Amicar. In addition, the Division of Drug Marketing, Advertising, and Communications (DDMAC) finds the proposed name, Orvaten, acceptable from a promotional perspective.

If you have any questions or need clarification, contact the Project Manager, Sammie Beam at 301-827-2102.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Charles Hoppes
11/8/04 03:20:46 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
11/8/04 05:01:58 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/8/04 05:10:29 PM
DRUG SAFETY OFFICE REVIEWER

Redacted 6

page(s) of trade secret

and/or confidential

commercial information

~~(b4)~~
(b5)

4/27/04

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 02/18/04	**DESIRED COMPLETION DATE:** 04/09/04 **PDUFA DATE:** 11/12/04	**ODS CONSULT #:** 04-0042

TO: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Valerie Jimenez
Project Manager
HFD-510

PRODUCT NAME: **Omacor** (Omega-3-Acid Ethyl Ester Capsules) 1 gram **NDA #:** 21-654	**NDA SPONSOR:** Ross Products Division, Abbott Laboratories

SAFETY EVALUATOR: Jinhee L. Jahng, Pharm.D.

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Omacor.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name, Omacor, acceptable from a promotional perspective.

/S/ /S/

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 2, 2004

NDA #: 21-254

NAME OF DRUG: Omacor (Omega-3-Acid Ethyl Ester Capsules)
1 gram

NDA HOLDER: Ross Products Division, Abbott Laboratories

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), for assessment of the proprietary name, "Omacor", regarding potential name confusion with other proprietary or established drug names. Container labels and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Omacor (Omega-3-acid ethyl ester capsules), a lipid-regulating agent, may reduce the synthesis of TG's in the liver because eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids. The mechanism of action of Omacor is not completely understood. Omacor is indicated in adjunct to diet to reduce the triglyceride (TG) levels in adult patients [ ] Omacor reduces TG levels when used as monotherapy [ ] The daily dose of Omacor is 4 grams per day. The daily dose may be taken as a single 4 gram dose or as two 2 gram doses. Omacor capsules will be supplied as 1 gram transparent soft-gelatin capsules in bottles of 120 count.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Omacor to a degree where potential confusion between

[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.

drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name, Omacor. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name, Omacor, acceptable from a promotional perspective.

2. The Expert Panel identified two proprietary names that were thought to have the potential for confusion with Omacor. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual dosage.

[4] WWW location http://www.uspto.gov/tmdb/index.html.
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name*	Dosage form(s), Established name	Usual adult dose	Other**
Omacor	Omega-3-Acid Ethyl Esters Capsules 1 gram	4 grams per day	
Inocor (not marketed)	Inamrinone Lactate Injection 5 mg/mL	For congestive heart failure: 0.75 milligram/kilogram intravenous bolus dose over 2 to 3 minutes, followed by a maintenance infusion of 5 to 10 micrograms/kilogram/minute. Doses up to 40 mcg/kg/min have been used for acute management of severe refractory congestive heart failure.	LA
Amicar	Aminocaproic Acid Injection 250 mg/mL Aminocaproic Acid Syrup 1.25 gram/5 mL Aminocaproic Acid Tablets 500 mg	16 to 20 mL (4 to 5 g) in 250 mL of diluent administered by infusion during the first hour of treatment, followed by a continuing infusion at a rate of 4 mL (1 g) per hour in 50 mL of diluent. 10 tablets (5 g) or 4 teaspoonfuls of syrup (5 g) administered during the first hour of treatment, followed by a continuing rate of 2 tablets (1 g) or 1 teaspoonful of syrup (1.25 g) per hour. Treatment would ordinarily be continued for about 8 hours or until the bleeding situation has been controlled.	SA/LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Omacor were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Omacor with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Omacor (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving

either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Omacor 2 caps BID #120	Omacor Take 2 capsules bid #120
Inpatient RX: Omacor 2 pb BID	

2. Results:

Most of the interpretations of the proposed name did not overlap, sound similar, or look similar to any currently marketed U.S. product. However, one of the misinterpreted names from the inpatient prescription study, Amacor, resembles the currently marketed U.S. product, Amicar. Many of the incorrect name interpretations were misspelled/phonetic variations of "Omacor". See Appendix A for the complete listing of interpretations from the verbal and written studies.

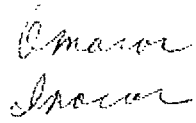
D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name, Omacor, the primary concerns related to look-alike and sound-alike confusion with Inocor and Amicar.

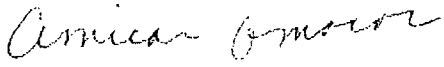
Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Omacor. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size.

1. Inocor has the potential to look like Omacor. Inocor is a prescription product which was discontinued in March 2000 and is no longer marketed in the United States. Inocor contains inamrinone, a phosphodiesterase inhibitor with positive inotropic and vasodilator activity. Inamrinone is used for the treatment of severe acute congestive heart failure refractory to other treatment modalities, including digitalis glycosides and vasodilators. Inocor and Omacor begin with letters which resemble each other when scripted ("Ino-" vs. "Oma-"), and they share the same suffix, "-cor" (see page 6). The products differ in strength (5 mg/mL vs. 1 gram), dosage form (injectable vs. capsule), route of administration (intravenous vs. oral), and dosing schedule. Although it was determined that the name Inocor is still available in the online version of MICROMEDEX, the name is not listed in the online Physicians Desk Reference, Drugstore.com, Destinationrx.com, 2003 Red Book, and Drug Facts and Comparisons. The generic product, inamrinone (a.k.a. amrinone) is available in the United States. Had the discontinuation date been more recent, the potential for generic substitution of Inocor might have raised some concerns. However, DMETS believes the potential for generic substitution is remote given its discontinuation

date. DMETS believes that the differences between the two drugs, coupled with the information that Inocor is no longer marketed in the United States, minimize the potential for confusion and error between Inocor and Omacor.



2. Amicar and Omacor were found to have look-alike and sound-alike similarities to one another. Amicar (aminocaproic acid) is a hemostatic agent that prevents the conversion of plasminogen to plasmin. Amicar is useful in enhancing hemostasis when fibrinolysis contributes to bleeding. Both Amicar and Omacor have three syllables and share similar sounds ("Am-" vs. "Om-" and "-car" vs. "-cor"). Additionally, they each have six letters and the prefixes, "Ami-" vs. "Oma-", as well as the suffixes, "-car" vs. "-cor", which resemble each other when scripted (see below). A loading dose of 4 to 5 grams of Amicar is administered followed by 1 gram doses every hour as needed for about 8 hours or until the bleeding situation is controlled. Amicar is available for oral or intravenous use. Similarly, Omacor has a daily dose of 4 grams which is administered orally. Confusion and error may occur if a verbal or written prescription order for "Amicar 4 grams" is misinterpreted for "Omacor 4 grams" or vice versa. Routes of administration are often omitted and the overlapping characteristics of Amicar and Omacar are significant. The opportunities for errors are likely in any situation where the prescriber communication is unclear or incomplete to the practitioners interpreting the medication order. Especially of concern is the fact that both products are available in only one strength, in which case a prescriber would not necessarily have to specify the product strength. A patient inadvertently receiving Amicar instead of Omacor may be subject to hypotension, heart failure, rhabdomyolysis, seizures, myopathy, renal failure, thrombosis formation, bleeding, and hepatic failure. On the contrary, inadvertent administration of Omacor instead of Amicar may subject the patient to an unresolved bleeding event and taste perversion. Any interruption in therapy is undesirable and should be prevented if possible. DMETS believes a likelihood for a dispensing error with Amicar and Omacor is likely.



Amicar Omacor

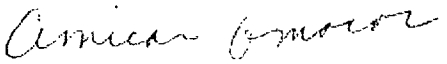
III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name, Omacor.

A. In reviewing the proprietary name, the primary concerns related to look-alike and sound-alike confusion with Amicar.

Amicar and Omacor were found to have look-alike and sound-alike similarities to one another. Amicar (aminocaproic acid) is a hemostatic agent that prevents the conversion of plasminogen to plasmin. Amicar is useful in enhancing hemostasis when fibrinolysis contributes to bleeding. Both Amicar and Omacor have three syllables and share similar sounds ("Am-" vs. "Om-" and "-car" vs. "-cor"). Additionally, they each have six

letters and the prefixes, "Ami-" vs. "Oma-", as well as the suffixes, "-car" vs. "-cor", which resemble each other when scripted (see below). A loading dose of 4 to 5 grams of Amicar is administered followed by 1 gram doses every hour as needed for about 8 hours or until the bleeding situation is controlled. Amicar is available for oral or intravenous use. Similarly, Omacor has a daily dose of 4 grams which is administered orally. Confusion and error may occur if a verbal or written prescription order for "Amicar 4 grams" is misinterpreted for "Omacor 4 grams" or vice versa. Routes of administration are often omitted and the overlapping characteristics of Amicar and Omacar are significant. The opportunities for errors are likely in any situation where the prescriber communication is unclear or incomplete to the practitioners interpreting the medication order. Especially of concern is the fact that both products are available in only one strength, in which case a prescriber would not necessarily have to specify the product strength. A patient inadvertently receiving Amicar instead of Omacor may be subject to hypotension, heart failure, rhabdomyolysis, seizures, myopathy, renal failure, thrombosis formation, bleeding, and hepatic failure. On the contrary, inadvertent administration of Omacor instead of Amicar may subject the patient to an unresolved bleeding event and taste perversion. Any interruption in therapy is undesirable and should be prevented if possible. DMETS believes a likelihood for a dispensing error with Amicar and Omacor is likely.



Amicar Omacor

B. In the review of the container labels and insert labeling of Omacor, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

1. CONTAINER LABEL

   a. We recommend that the established name be printed in letters that are at least half as large as the proprietary name to be in accordance with 21 CFR 201.10 (g)(2).

   b. The product strength should appear immediately following or below the established name and be more prominent on the label.

   c. Relocate the net quantity (ex. "120 Capsules") away from the product strength.

   d. We are unable to identify from the submitted materials that the container closure is child resistant. However, the packages should include Child Resistant Closures (CRC).

2. INSERT LABELING

   No comments.

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name, Omacor.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. DDMAC finds the proprietary name, Omacor, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

/S/

Jinhee L. Jahng, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

/S/

Alina R. Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Appendix A – DMETS Prescription Study Results

Inpatient	Voice	Outpatient
Omacor	Onacor	Omacor
Omacor	Onacor	Omaquar
Omacor	Onacor	Omaquar
Omacor	Omacor	Avocor
Omacor	Onacor	Omacor
Omacor	Onacor	Omacor
Omacor	Onacor	Omacor
Omacir	Oracor	Omocore
Omacar	Onacor	Emacor
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Amacor	Onacor	Omicor
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Omacor	Onacor	Omacor
Omacer	Onacor	Omacor
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Omacor	Omacor	Omacor
	Onacor	
	Oracor	

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/s/

Jinhee Jahng
4/21/04 11:29:04 AM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
4/21/04 11:36:45 AM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/23/04 07:52:18 AM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
4/27/04 07:52:21 AM
MEDICAL OFFICER

11/9/04

MEMORANDUM OF TELECON

DATE: October 25, 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
Robert A. Shalwitz, M.D., Medical Director, Pharmaceutical R&D
Egil Bodd, M.D., Ph.D., CEO and President Pronova Biocare
Elisabeth Hagen, Director, Medical and Regulatory Affairs, Pronova Biocare
Keith Rotenberg, Ph.D., Sr Vice President, R&D, Reliant Pharmaceuticals

Phone: 1-877-648-8345
Representing: Ross Products Division, Abbott Laboratories

AND

Name: Mary Parks, M.D., Deputy Director and Medical Team Leader
Karen Davis Bruno, Ph.D., Pharmacology/Toxicology Team Leader
J. Todd Sahlroot, Ph.D., Statistics Team Leader
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: Omacor Labeling-Package Insert

BACKGROUND: On October 22, 2004, the sponsor submitted their recommendations for the Omacor package insert (PI) for the October 25, 2004, labeling meeting.

DISCUSSION:

- The Division began by inquiring why the paragraph was added to the Clinical Pharmacology section of the package insert (PI). Additionally, it was noted that the paragraph was inaccurate and that other labels did not include [ ] as a target in therapy that conforms to the National Cholesterol Education Program (NCEP) guidelines and the is not recommended as a primary target.
- The sponsor insisted that the paragraph was a direct quote from the NCEP guidelines and the benefit reduces the risk of pancreatitis Further, the sponsor believes that the statement, taken from the NCEP Executive Summary, is accurate.
- The Division pointed out that the indication demonstrates a reduction of triglycerides (TG) in the prevention of pancreatitis . [ ] also that the laboratory cut-off was different. Furthermore, the submission displays a decrease in TG and noted greater effect in type V patients.

- The sponsor then stated that Omacor has [ ] profile and that there is a benefit as demonstrated by the literature and data submitted to the Food and Drug Administration (FDA).
- At this time the Division suggested re-visiting the Clinical Pharmacology PI section and proceeding on to the biopharmaceutics and pharmacology/toxicology comments.
- The Agency requested that the words, '[ ], be removed from the beginning of the second sentence of the Pharmacokinetic and Bioavailability Studies section of the **CLINICAL PHARMACOLGY** section of the proposed PI. Moreover, recommendation for the modification of the last sentence under **CLINICAL PHARMACOLOGY** section, Drug Interactions, Cytochrome P450-Dependent Monooxygenase Activities subsection, the word, — should be changed to "less likely". Finally, the final sentence under **PRECAUTIONS** section, Drug Interactions, Cytochrome P450-Dependent Monooxygenase Activities subsection, should be omitted.
- The Agency then requested that the statement "Standard lifetime carcinogenicity bioassays were not conducted in mice", at the end of the Carcinogenesis, Mutagenesis, Impairment of Fertility section, be moved to the end of paragraph 2 on page 8 instead of its current location at the end of the section. In the Pregnancy Category C section, the last sentence should include "However at higher doses evidence of maternal toxicity is observed (4 times human systemic exposure following an oral dose of 4 g/day based on a body surface area comparison)".
- The Agency and the sponsor agreed on the **CLINICAL PHARMACOLOGY** and **PRECAUTIONS** sections of the PI.
- The Division recognized the data submitted to the application however noted that it was not the same level of degree as other lipid lowering products. Moreover, Omacor is a promising drug with no issues of safety, however must be held to the same standard as other lipid lowering drugs. Therefore, the Division recommends that the language in the clinical pharmacology section of the PI should be removed.
- The sponsor proposed using the terms '[ ]' as opposed to the [ ] It was also noted that NECP guidelines uses tables and numbers. The sponsor reasoned that it gives physicians a greater option for regulation for patients who cannot tolerate Niaspan. However, the issue would be discussed with the Division Director.
- The Division stated that the proposed use [ ] (Table 2) designation is similar to a [ ] in addition to [ ] and could not agree to the proposal, however, the issue would be discussed with the Division Director.
- The sponsor then inquired [ ]
- The Agency responded [ ] A follow-up teleconference to discuss the sponsor's proposed PI modifications has been scheduled for Tuesday, November 9, 2004.

/S/

Valerie Jimenez
Regulatory Project Manager

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/s/

Valerie Jimenez
11/9/04 03:23:15 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-654

11/3/04

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, 1gm.

We also refer to your October 22, 2004, submission containing your request to change the established name, omega-3-acid ethyl esters, to '[ ]

We have reviewed your submission and have concluded that the USAN name, omega-3-acid ethyl esters, should be used as the established name for the drug substance. The proposed established name [ ]' is not acceptable for the following reasons:

1. [ ] is NOT a recommended International Name (rINN) for the drug substance, but consists of the rINN's for the pure individual components, EPA and DHA ethyl esters. INN's are not typically adopted for mixtures. As of this time there is no provisional International Name (pINN) or rINN for the drug substance.

2. The proposed established name, [ ] implies that there are no other components to the drug substance, when, in fact, there are

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, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

David Orloff
11/3/04 03:19:37 PM

8/17/04

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.

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. [ ]

4. Provide solubility profiles of Omacor as well as dissolution profiles for capsules from [ ] batches (12 unit/batch) under the current proposed condition and two other conditions such as various concentrations of [ ] different apparatus or agitation.

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}

/S/

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

6/4/04

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 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}

/S/

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
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