CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-853

21654s016

OFFICE DIRECTOR MEMO

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; 21-853
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 with Fredrickson type I [redacted] V (marked b(4)

hypertriglyceridemia/hyperchylomicronemia). 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) ; [ ] the application has been administratively split with the Type V remaining as NDA 21-654 and the other indications being placed under 21-853. b(4)

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. b(4)

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. b(4)

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 a phase 4 commitment looking at this potential effect in vitro. 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. [b(4)

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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. In sum, these data suggest that, at a minimum, additional information is needed to determine whether the lipoprotein changes in association with Omacor treatment in patients with atherogenic dyslipidemias are proatherogenic, antiatherogenic, or simply neutral. Alternatively, it may be that adding Omacor to a statin may have a favorable effect in all important lipid parameters and therefore Omacor may only be useful in such patients when used in combination with a statin. This will need to be further investigated and is the basis for the limited approval. Since patients with mixed dyslipidemia (type IIb) and isolated hypertriglyceridemia (type IV) are not, per se, at risk for pancreatitis due to elevated TG, [b(4)

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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 [b(4)] 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. 1) The sponsor wanted to place into the labeling a discussion on [ ] While this may be true, there were insufficient data to assure this, particularly in light of OCPB's concerns over the induction of 3A4 by fish oils (though, as above, I do not feel that induction is clearly clinically important). 2) The sponsor wanted to [ ] b(4)

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 with type V be approved at this time, and I concur.

1. Indication to lower plasma TG in patients with Fredrickson type V hyperlipidemia: **Approval – NDA 21-654**

2. Indications to lower plasma TG in patients with [ ] hyperlipidemia: **Approvable – NDA 21-853**. More data are needed either to show that the apparent deleterious effects on the lipid profile in these patients is not clinically important or that addition of Omacor to a statin leads to clinically favorable lipid profile changes in these patients. b(4)

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/s/

Robert Meyer
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