National PBM Drug Monograph
Omega-3-acid ethyl esters (Lovaza®, formerly Omacor®)
October 2005
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary

Efficacy:

- Omacor is the first marine-derived omega-3 polyunsaturated fatty acid product (n-3 PUFA, fish oil, omega-3 fatty acid) to be approved by the FDA.
- It was approved as an adjunct to diet in patients with very high triglyceride (TG) levels (≥500 mg/dL). The manufacturers of Omacor have received an approvable letter for use in patients with TG levels between 200-499 mg/dL. Omacor may increase LDL-C in patients with elevated TG levels. Since LDL-C is the primary target for treating dyslipidemia, the FDA has stated that it is likely that these patients (with TG within this range) will also be receiving statins. As a result, the FDA has requested additional information on the effect of Omacor in combination with statins.
- The initial dose is 4 grams daily given as 4 capsules once daily or 2 capsules twice daily.
- To date there have been eight prospective, randomized clinical trials examining the effect of Omacor on TGs and LDL-C in patients with elevated TG levels. In general, four grams per day of Omacor reduces TG levels 20-45%. The TG lowering response appears to correlate with baseline TG levels (e.g. patients with higher baseline TG levels will generally have a greater TG lowering response). Low-density lipoprotein was increased in four of the eight studies ranging from approximately 16.7 to 31%. Increases in LDL-C also appear to correlate with baseline TG levels. In three studies, Omacor added to existing statin treatment did not result in a significant increase in LDL-C.
- Studies involving fish oil supplements, other than Omacor, have demonstrated a 20-30% reduction in TG levels with doses of 2-4 grams/day.
- In the GISSI Prevenzione study, 11,324 survivors of a recent MI (<3 months) were randomized to receive an n-3 PUFA supplement (Omacor) 1gram daily (n=2836), vitamin E 300 mg daily (n=2830), both (n=2830) or neither (n=2828) for 3.5 years. Treatment was not blinded. The primary composite endpoint was the cumulative rate of all cause mortality, non-fatal MI, and non-fatal stroke and the cumulative rate of cardiovascular death, non-fatal MI, and non-fatal stroke. The authors concluded that in patients surviving a recent MI and who were receiving other post-MI preventative therapies {e.g. beta-blockers, aspirin and angiotensin converting enzyme inhibitors} and who were also consuming a Mediterranean-type diet, long-term administration of n-3 PUFA in a dose of 1 gram daily was beneficial in reducing all cause mortality and combined death, nonfatal MI and stroke. The observed benefit of n-3 PUFAs supplementation was attributed solely to the reduction in all-cause and cardiovascular related death.

Safety:

- Omacor appears to be well tolerated with gastrointestinal adverse events (e.g. nausea, eructation, and taste perversion-fishy taste) being the most commonly reported.
- Elevation in LDL-C has been observed during Omacor treatment and should be monitored periodically.
- Increases in ALT have been observed. ALT should be monitored periodically during treatment with Omacor.
- Although there have been some inconsistencies in the available evidence for fish oils and risk for bleeding, bleeding risk does not appear to be increased at the doses (4 grams daily) used for managing very high TG levels.
- There have been case reports of INR elevation after the addition of fish oils to patients stabilized on warfarin therapy. However, studies have not been done to determine the effect of concomitant anticoagulants and Omacor. As a result, patients receiving Omacor and anticoagulants should be closely monitored.
- Drug-drug interactions involving the cytochrome P450 isoenzyme system are not expected.

Introduction

Over the past few years, there has been increasing interest in using omega-3 polyunsaturated fatty acids (n-3 PUFAs) or fish oil supplements in combination with statins in patients with elevated triglyceride levels. The MAP and VISN formulary leaders have recommended that fish oil supplements be available because of their effectiveness in reducing elevated triglyceride levels and their greater safety in combination with statins (as an alternative to fibrates). In November 2004, Omacor® became the first FDA approved prescription marine derived omega-3 product.

Pharmacology/Pharmacokinetics[2]

The exact mechanism of action responsible for reducing triglycerides with n-3 PUFAs is not completely known. However, potential mechanisms may include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase and increased peroxisomal β-oxidation in the liver. In addition, since EPA and DHA (omega-3 fatty acids) are poor substrates for the enzymes responsible for triglyceride synthesis, triglyceride synthesis is reduced. Finally, EPA and DHA inhibit esterification of other fatty acids.

Since Omacor is a fatty acid, information on pharmacokinetics are not applicable. Omega-3 fatty acids are incorporated into cell membranes and as a result, plasma levels are not detectable.

FDA Approved Indication(s) and Off-Label Uses[2]

FDA Approved

Omacor® is FDA approved as an adjunct to diet to reduce very high triglyceride levels (≥500 mg/dL) in adult patients.

Approvable Letter

The sponsors of Omacor have received an approvable letter for the use of their product in patients whose triglyceride levels fall between 200 and 499 mg/dL. Some patients with triglycerides levels in this range may experience increased LDL-C levels when omega-3s are consumed. However, it is anticipated that most of these patients would already be receiving statins since LDL-C is the primary lipoprotein targeted for the management of dyslipidemia. However, the FDA has requested additional information in these patients to determine the effect of combination therapy (statins and n-3 PUFAs) on the total lipid profile (e.g. LDL-C, TG and non-HDL-C). These studies are reported to be underway.

Off-Label Uses

a. Prevention of Coronary Heart Disease (CHD): There is a growing body of epidemiologic and clinical trial evidence supporting a beneficial effect of omega-3 fatty acids (n-3 polyunsaturated fatty acids, n-3 PUFAs, fish oils, or omega-3 fatty acids) on cardiovascular morbidity and mortality. Within the past few years, several reviews of the available evidence supporting a role of n-3 PUFAs for the prevention of CHD have been published.[3-9] However, not all of the available evidence provides support for a role of n-3 PUFAs in the prevention of CHD.[10-13] Authors have speculated that the inconsistencies in the data may be explained by differences in baseline consumption of fish, types of fish consumed or method of preparation, population differences, etc.[5]

In 2002, the American Heart Association (AHA) published a scientific statement and review of the literature pertaining to the relationship between fish consumption, fish oil, omega-3 fatty acids and cardiovascular disease.[5] In their statement, the AHA provided guidance on fish consumption and use of fish oil supplements. In patients with known CHD, the AHA recommended consuming approximately 1 gram of EPA+DHA per day, preferable from oily fish. However, also stated that supplements containing n-3 PUFAs could be considered in collaboration with a physician for patients either unwilling or unable to eat fish. In patients without known CHD, the AHA recommends eating a variety of fish at least twice a week. Finally, for the management of elevated triglyceride (TG) levels, they recommend 2-4 grams of n-3 PUFAs supplements daily under the supervision of a physician.

In the third report of the Expert Panel for Detection, Evaluation and Treatment of High Blood Cholesterol [Adult Treatment Panel III (ATP III)], the use of n-3 PUFAs is discussed briefly. As part of the report, n-3 PUFAs (e.g. fish, fish oils, or high alpha-linolenic acid oils) in lower doses (1-2 g/day) are mentioned for the prevention of CHD. ATP III concluded that the strength of the available clinical trial evidence [14-16] for this use was moderate and state that more definitive clinical trials are needed prior to strongly recommending n-3 PUFAs for primary or secondary prevention of CHD.[17]

Authors of a recent systematic review examined the effect of different lipid-lowering medications and diets on mortality. They found that statins and n-3 PUFAs were associated with a lower risk of overall and cardiac mortality. The authors concluded that statins and n-3 PUFAs were the most favorable antilipidemic agents.[48]

b. IgA Nephropathy: Several studies have been conducted evaluating the effect of omega-3 fatty acids on renal function in patients with IgA nephropathy. IgA nephropathy is a chronic kidney disease which can lead to end-stage renal disease. It has been hypothesized that omega-3 fatty acids may stabilize renal function in these patients. The evidence has not demonstrated a consistent benefit of omega-3 fatty acids for this indication.[18-23]

c. Other Uses: In March 2004, the Agency for Healthcare Research and Quality (AHRQ) published a report on their findings with regard to the effect of omega-3 polyunsaturated fatty acids in inflammatory bowel disease, rheumatoid arthritis, renal disease, systemic lupus erythematosus, and osteoporosis. In this report, it was determined that insufficient evidence existed to make recommendations for the use of omega-3s in these conditions.[24]

Current VA National Formulary Alternatives

For the management of hypertriglyceridemia, formulary alternatives include niacin and gemfibrozil. In combination with statins, the PBM-MAP recommends considering niacin or fish oil supplements prior to fibrates because of their greater safety in combination with statins.

Dosage and Administration[2]

Therapeutic lifestyle changes (e.g. cessation of alcohol, weight loss, exercise, dietary changes) should be instituted and secondary causes of hypertriglyceridemia (e.g. poorly controlled diabetes mellitus, nephrotic syndrome, alcoholism, hypothyroidism, and medications [Especially protease inhibitors. Others may include corticosteroids, estrogens, beta-blockers, and thiazide diuretics]) should be considered prior to initiating any drug therapy.

The recommended daily dose of Omacor for very high triglycerides (≥500 mg/dL) is 4 grams (4 capsules) once daily or two grams (2 capsules) twice daily. In many of the clinical trials, Omacor was given with a meal.

Each capsule of Omacor contains at least 900 mg of the ethyl esters of omega-3 fatty acids (465 mg eicosapentaenoic acid [EPA] and 375 mg docosahexaenoic acid [DHA]).

Efficacy

This section includes only those prospective, randomized clinical trials in which one treatment arm involved Omacor. The trials will be limited to Omacor in patients with hypertriglyceridemia or for the prevention of CHD events. Although n-3 PUFAs have been studied in other diseases, the data are either lacking or inconsistent.

Efficacy Measures:

a. Triglyceride (TG) (FDA approved indication) and LDL-C Levels

The primary lipid altering effect of Omacor or n-3 PUFAs is a reduction in elevated TG levels. As a result, TGs are the primary endpoint in the included clinical trials. N-3 PUFAs may also increase LDL-C levels in some patients, especially in those patients with elevated TGs.[25-26] However, LDL particles, formed in the presence of n-3 fatty acids, are believed to be larger and more buoyant than the smaller more dense LDL particles and are considered to be less atherogenic.[27]

Summary of the data: To date there have been eight prospective, randomized clinical trials examining the effect of Omacor on TGs and LDL-C in patients with elevated TG levels. In general, four grams per day of Omacor reduces TG levels 20-45%. The TG lowering response appears to correlate with baseline TG levels (e.g. patients with higher baseline TG levels will generally have a greater TG lowering response). Low-density lipoprotein was increased in four of the eight studies ranging from approximately 16.7 to 31%. Increases in LDL-C also appear to correlate with baseline TG levels. In three studies, Omacor added to existing statin treatment did not result in a significant increase in LDL-C.

Table 1.	**Omacor vs. Placebo or Fibrate (# of studies)**	**Omacor + Statin vs. Statin alone (# of studies)**
% TG Reduction	27-45% (5 studies)	20-30% (3 studies)*
% LDL-C Elevation	16.7-31% (4/5 studies LDL increased)	Not significant (3 studies)

In one study, addition of Omacor 1.68 g to atorvastatin did not significantly reduce TG.
For additional information on the included studies, see Appendix A.

The manufacturer of Omacor recommends discontinuation if an adequate response is not observed within 2 months.

b. Cardiovascular Outcomes: (non-FDA approved indication)

There have been several prospective, randomized clinical trials in which the effect of n-3 fatty acid supplements on cardiovascular outcomes (e.g. cardiac death, non-fatal myocardial infarction [MI], and stroke) has been examined. There have also been numerous epidemiologic and observational studies in which consumption of fish rich in n-3 fatty acids has been associated with a reduction in cardiovascular events. However, for the purpose of reviewing Omacor, only those studies utilizing Omacor have been included.

Summary of the data:

The effects of n-3 PUFAs (Omacor) and vitamin E were examined individually and in combination in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarcto miocardico (GISSI)-Prevenzione Trial.[36] In the GISSI Prevenzione study, 11,324 survivors of a recent MI (<3 months) were randomized to receive an n-3 PUFA supplement (Omacor) 1gram daily (n=2836), vitamin E 300 mg daily (n=2830), both (n=2830) or neither (n=2828) for 3.5 years. Treatment was not blinded. The primary composite endpoint was the cumulative rate of all cause mortality, non-fatal MI, and non-fatal stroke and the cumulative rate of cardiovascular death, non-fatal MI, and non-fatal stroke. Secondary analyses included rates of individual components of the combined endpoints and reason for death. Primary events were adjudicated by cardiologists and neurologists blinded to the patients' assigned treatment. See Table 2 for results with Omacor.

Table 2. GISSI Prevenzione Trial Results (Overall Efficacy)

Endpoint	n-3 PUFA (n=2836)	Control (n=2828)	RRR/ARR/NNT	95% CI
Primary: All cause mortality, non-fatal MI and stroke	356 (12.3%)	414 (14.6%)	RRR=15% ARR=2.3% NNT=43	0.74-0.98
Primary: CV death, non-fatal MI and stroke	262 (9.2%)	322 (11.4%)	RRR=20% ARR=2.2% NNT=45	0.68-0.95
All Fatal Events	236 (8.3%)	293 (10.4%)	RRR=20% ARR=2.1% NNT=48	0.87-0.94
CV Deaths	136 (4.8%)	193 (6.8%)	RRR=30% ARR=2% NNT=50	0.56-0.87
Cardiac Death	108 (3.8%)	165 (5.8)	RRR=35% ARR=2% NNT=50	0.51-0.82
Coronary Death	100 (3.5%)	151 (5.3%)	RRR=35% ARR=1.8% NNT=55	0.51-0.84
Sudden Death	55 (1.9%)	99 (3.5%)	RRR=45% ARR=1.6% NNT=62.5	0.40-0.76
Other Deaths	100 (3.5%)	100 (3.5%)	NS	0.75-1.30
Non-fatal CV Events	140 (4.9%)	144 (5.1%)	NS	0.76-1.21
CHD Death/Non-fatal MI	196 (6.9%)	259 (9.2%)	RRR=25% ARR=2.3% NNT=43	0.62-0.90
Fatal and Non-fatal stroke	54 (1.9%)	41 (1.5%)	RR 1.30 (NS)	0.87-1.96

Table adapted from GISSI Prevenzione Study: Lancet 1999;354:447-455. Data based upon the four-way analysis
ARR=absolute risk reduction, CI=confidence interval, MI=myocardial infarction, NNT-number needed to treat, RRR=relative risk reduction
By the end of the trial, 28.5% and 26.2% of patients assigned to n-3 PUFA and vitamin E, respectively, were no longer taking their assigned supplement. Only a small number of patients not assigned to vitamin E or n-3 PUFA began taking them.

There was no apparent benefit of vitamin E supplementation. Possible limitations of the study include no blinding (investigators or patients) and a drop out rate nearing 30% by study completion. The authors concluded that in patients surviving a recent MI and who were receiving other post-MI preventative therapies {e.g. beta-blockers, aspirin and angiotensin converting enzyme inhibitors} and who were also consuming a Mediterranean-type diet, long-term administration of n-3 PUFA in a dose of 1 gram daily was beneficial in reducing all cause mortality and combined death, nonfatal MI and stroke. However, the observed benefit of n-3 PUFAs supplementation was attributed solely to the reduction in all cause and cardiovascular related death.

In a second open-label study, 160 patients scheduled for coronary artery bypass (CABG) surgery were randomized to a control group or Omacor 2 grams daily for at least 5 days prior to surgery. [37] Omacor was continued until the day of hospital discharge. The primary endpoint was the rate of postoperative atrial fibrillation, which is reported to be a common complication after CABG surgery. Postoperative atrial fibrillation occurred in 27 (33.3%) control subjects vs. 12 (15.7%) Omacor recipients (p=0.013). The authors also report a statistical reduction in the number of hospital days in favor of Omacor (8.2 vs 7.3 days, respectively).

Finally, patients having had an acute MI were randomly assigned to receive double-blind treatment with Omacor 4 grams daily or corn oil placebo.[55] Patients were randomized within 8 days of their MI and followed for a median of 1.5 years. The primary endpoint was occurrence of cardiac events (e.g. cardiac death, resuscitation, recurrent MI, and unstable angina). There was no difference in the rate of cardiac events between groups (42 or 28% in fish oil vs. 36 or 24% in corn oil group). The authors concluded that

despite the improvement in lipid levels, there was no difference in outcomes between treatments. The lack of difference was largely attributed to inclusion of Norwegian patients living in a coastal region whose diets already consisted of a high content of fish.

Considerations: Fish Oil Supplements vs. Omacor

There have been numerous clinical trials evaluating the effect of n-3 PUFAs on TG levels. Many of these studies utilized n-3 PUFA supplements other than Omacor. In these trials, a reduction in TG levels ranging from 20-30% was observed with doses between 2-4 grams/day. From this evidence, one can conclude that n-3 PUFA supplements are effective TG reducing agents. There have also been several cardiovascular outcome studies that have examined the effect of n-3 PUFA supplements (other than Omacor) or dietary fish consumption in which a benefit was observed. [38-40]

There are several issues to consider when comparing Omacor to a non-FDA approved n-3 PUFA supplement. One issue pertains to considering the potency of a particular product. For example, a 1 gram capsule of Omacor contains >90% n-3 PUFAs and <10% of "other fatty acids" while a 1 gram capsule of an n-3 PUFA supplement may contain only 60% n-3 PUFAs and 40% of "other fatty acids". Supplement manufacturers aren't required to list what the "other fatty acids" may include (e.g. omega-6 fatty acids, saturated fats, trans fats, etc.). Will these potency differences produce a variable effect on lipids assuming that equal amounts of EPA and DHA are provided? Will there be a difference in outcomes? Since there are no head to head trials comparing Omacor to other n-3 PUFA products, the answer is unknown. However, in studies providing n-3 PUFAs in doses between 2-4 grams daily, TG lowering was similar to that seen with Omacor in separate studies. A final issue with regard to potency is the number of capsules necessary to produce the desired TG reduction.

A second issue relates to the lack of FDA oversight of current good manufacturing practices (cGMP) of dietary supplement manufacturers. As a result, there may be questions with regard to batch-to-batch consistency of n-3 PUFAs or other ingredients contained in the product as well as its purity and freshness. There have been several reports in which groups have selected a number of different n-3 PUFA products to test whether or not they contain the primary ingredient(s) in quantities close to what is listed on the label. In addition, testing for contaminants such as mercury and organochlorines (e.g. polychlorinated byphenyls (PCBs), dioxins and furans) has been completed (Table 3. for summary).

Table 3. Laboratory Testing of n-3 PUFA Products: (Summary)

Organization or Investigator	# Products Tested	# Products Containing Labeled Amount of EPA/DHA	# Products Not Containing Labeled Amount of EPA/DHA	Products with Unsafe or Detectable Levels of Mercury[a] or Organochlorines	Testing Conclusion
Consumer Labs[41] Consumer Labs chose 16 products for testing. The remaining 25 were tested at the manufacturer or distributors request through Consumer Labs voluntary certification program.	41	40 (95%)	1 (2.4 %) (Pet supplement)	0	Consumer Labs found 1/41 product (2.4%) to be spoiled. Spoiled products have an unpleasant odor and may have reduced effectiveness.
Melanson SF, et al.[42]	5	Not Tested	Not Tested	0	PCBs and Organochlorines tested. All were below detectable limits. Authors conclude fish oils may be safer than fish consumption.
Foran SE, et al. [43]	5	Not Tested	Not Tested	0	Mercury Levels were found to be either non detectable or negligible. Authors conclude fish oils may be safer than fish consumption.

Consumer Reports [44]	16	16 (100%)	0	0	All products were reported to contain "roughly" labeled amounts of n-3 PUFAs and none were spoiled.
National Medical Services of Willow Grove, PA[45]	9	Not Tested	Not Tested	0	No detectable levels of mercury. Sponsor of study was a stockholder of vitacost.com who assisted with support for the study.

[a]Mercury in fish typically ranges from 10 parts per billion (ppb) up to 1,000 ppb. 10 ppb is considered to be a detectable level of mercury. Levels of mercury in fish are dependent upon the type of fish consumed. Mercury is believed to accumulate in the meat of the fish (not the fish oil) and is mostly removed during the distillation process.

In 2004, the FDA outlined a science-based plan for dietary supplement enforcement.[46] The major components of this plan include: 1) developing rules for the dietary supplement industry on good manufacturing practices (GMPs) to protect consumers from impurities or contaminants resulting from their manufacturing process; 2) closer scrutiny of dietary supplement labeling; and 3) systematic evaluation of the safety evidence of dietary supplements (published literature, evidence-based reviews and adverse event data) similar to the process used to determine the FDA's recent decision pertaining to ephedra.[47]

Although there is currently no direct oversight of the supplement industry by the FDA, in the case of fish oil supplements, there is evidence to support that they are free from contamination and generally contain quantities of n-3 PUFAs stated on the label. Additionally, the FDA has put forth a plan to monitor the activities of dietary supplement manufacturers. This plan includes developing rules and guidelines for demonstrating and maintaining cGMP as well as oversight of the manufacturing process. In addition, there is an increasing demand by consumers for the manufacture of consistent and uncontaminated, quality supplement products. As a result, the supplement manufacturers are facing increasing pressures to produce a safe quality product.

Adverse Events (Safety Data) [2]

In patients with elevated TG levels, consumption of fish oils, including Omacor can be associated with an increase in LDL-C. However, in studies involving patients on background statins, administration of fish oils did not result in a significant effect on LDL-C. As a result, LDL-C should be monitored periodically during therapy with Omacor.

In some patients, elevation of ALT had been witnessed. As a result, ALT should be monitored periodically during Omacor treatment. The manufacturer does not provide details on the frequency or time to occurrence of ALT elevation and do not offer guidance for monitoring.

The effect of fish and fish oil supplements on bleeding and hemostatic factors has been examined and the data are inconsistent.[49-53] However, the risk of bleeding is considered to be low at the doses recommended (e.g. 2-4 g/day) for lowering TG levels.[5,54]

Table 4. Adverse Events: Clinical Trials Involving Omacor 4 g/day for Elevated TGs

Adverse Event	Omacor (%)	Placebo (corn oil) (%)
Withdrawal Due to Adverse Event	3.5	2.6
Patients with 1 Adverse Event	35.4	27.6
Back Pain	2.2	1.3
Flu Syndrome	3.5	1.3
Infection	4.4	2.2
Dyspepsia	3.1	2.6
Eructation	4.9	2.2
Rash	1.8	0.4
Taste Perversion	2.7	0

Table adapted from the product label.

In the GISSI Prevenzione study, gastrointestinal complaints and nausea were reported by 4.9% and 1.4%, respectively in those receiving Omacor vs. 2.9% vs. 0.4%, respectively in those taking vitamin E.[36]

Precautions/Contraindications[2]

Precautions:
Clinicians are advised to consider and address secondary causes of hypertriglyceridemia including excessive alcohol ingestion, hypothyroidism, poorly controlled diabetes mellitus, nephrotic syndrome and medications (e.g. Especially protease inhibitors. Others may include corticosteroids, estrogens, beta-blockers and thiazide diuretics). In addition, diet, exercise and weight loss should be instituted prior to treatment with Omacor.

Omacor should be discontinued if an adequate reduction in TG is not observed within 2 months of initiation of treatment.

Omacor should not be given to patients with a known sensitivity or allergy to fish.

ALT and LDL-C should be monitored periodically during treatment with Omacor (see adverse event section).

Contraindications:
Omacor is contraindicated in patients who exhibit hypersensitivity to any component of it.

Look-Alike/Sound Alike (LA/SA) Error Risk Potential

Omega-3 fatty acid ethyl esters (generic name):
Potential name confusion: omeprazole and Orap (pimozide)
Potential severity: Minor
Probability: Occasional

Omacor® (brand name)
Potential name confusion: omeprazole, Mevacor (lovastatin), Orap (pimozide), Amicar
Potential severity: Moderate for Amicar and minor for others
Probability: Occasional
Recommendations: There has already been one reported sound alike error with Omacor and Amicar. The patient was intended to receive Omacor 1 g twice daily but instead received Amicar 1 g. Match indications to patient's diagnosis to avoid this error.[58]

Lovaza®(new brand name)
Potential name confusion: lovastatin, Lovenox, Levitra, Lokara, Lunesta, lorazepam (mix-up already reported in ISMP), Lopid, Sonata, Lofibra, Rowasa, Zavesca.
Potential severity: Moderate for lorazepam, Sonata and Lunesta, mild for others
Recommendations: There has already been one reported sound alike error with lorazepam and Lovaza (ISMP newsletter).

Drug Interactions [2]

There have been case reports of significant elevation of INR (international normalized ratio) after the addition of fish oil supplementation in patients previously stabilized on warfarin.[56] There was one small study (n=16) in patients stabilized on chronic warfarin therapy in which patients were randomly assigned to placebo, 3 grams of fish oils or 6 grams of fish oils for 4 weeks. Although there was a fairly large drop out rate (n=5 or 33.3%) due to noncompliance and unstable INR values, there was no difference in the remaining group's INRs after the addition of 3 or 6 grams of fish oils to background warfarin.[57]

The manufacturer of Omacor states that clinical studies have not been completed examining the effect of Omacor on INR in patients receiving anticoagulants. As a result, patients receiving anticoagulation who are considered for treatment with Omacor should be closely monitored.

The manufacturer states that since the free forms of EPA and DHA are not detectable in the circulation, clinically important interactions involving the cytochrome P450 isoenzyme system are not expected.

Acquisition Costs (prices as of 10-1-05)

Product	Usual Daily Dose	Cost per Capsule ($)	Cost/Day ($)	Cost/30 Days ($)
Omacor	4 grams[a]	0.71	2.84	85.20
Fish Oil Supplement	4 grams[c]	0.08	0.64	19.20
Niaspan	1-2 grams	0.42	0.42-0.84	12.60-25.20
Gemfibrozil [b]	600 mg twice daily	0.10	0.20	6.00
Fenofibrate [b]	130 mg (Antara) or 145 mg (Tricor)	2.10-1.09	2.10-1.36	63.00-32.70

[a]Dose for TGs ≥500 mg/dL, given as 2 grams twice a day or 4 grams once. FSS cost per capsule is $0.71
[b]In patients receiving statins, the statin-fibrate combination can increase the risk for muscle toxicity (http://www.vapbm.org/Safety%20Reports/87ry38statin-fibrate-Final.pdf). Niacin and fish oils should be considered first.
[c]SeaOmega 50 pricing, 8 capsules/day provides 4 grams of n-3 PUFAs.

Pharmacoeconomic Analysis-Cost Impact Analysis

Time Frame: 5/05-7/05 (3 months)

Use Patterns of n-3 PUFAs in VHA	**Pharmacy Uniques**	**%**	**Average Dose/Day (MG)**
N-3 FATTY ACID	15,784		4,682
N-3 FATTY ACID+STATIN	9,048	57.32%	
N-3 FATTY ACID+NIACIN/FIBRATE	4,128	26.15%	
N-3 FATTY ACID+STATIN+NIACIN/FIBRATE	2,432	15.41%	

From the information provided, it is not possible to determine which fish oil supplements have been dispensed and whether they were for 30 or 90 days. However, the following calculation assumes we are dispensing all SEA OMEGA 50 capsules for 30 days. So, for the most recent three-month period, we spent $21.60 for each individual 30-day prescription for SEA OMEGA 4.5 grams (EPA+DHA). If we were to use Omacor at a dose of 4 grams daily for 30 days, we would need to spend an additional $63.60 per patient. So an additional $63.60 per month for 15,784 patients would result in an additional expenditure of $1,003,862.40 per month for Omacor or $12,046,348 annually. This estimate assumes current levels of fish oil consumption. It is likely that demand for fish oils will increase as Omacor is promoted.

Conclusions

Omacor is the first marine-derived n-3 polyunsaturated fatty acid (n-3 PUFA, fish oil or omega-3 fatty acid) to be approved by the FDA. It was approved as an adjunct to diet in patients with very high triglyceride levels (≥500 mg/dL) at a dose of 4 grams daily. The manufacturers of Omacor have also received an approvable letter from the FDA for treating patients with triglyceride levels between 200 and 499 mg/dL. In the GISSI Prevenzione study, Omacor 1 gram daily was observed in an unblinded study to reduce the risk of a composite endpoint consisting of major cardiac events. Similar to Omacor, there is evidence to support a triglyceride lowering effect of other fish oil supplements. In addition, a beneficial effect on cardiac events has been observed with increased consumption of fish and fish oil supplements, other than Omacor.

There are several issues to contemplate when considering use of Omacor vs. other non-FDA approved fish oil supplements. The first is FDA oversight of current good manufacturing practices (cGMP), to ensure batch-to-batch consistency of the primary ingredients and production of a quality product. Although there is currently no direct oversight of the supplement industry by the FDA, in the case of fish oil supplements, there is evidence to support that they are free from contamination and generally contain quantities of n-3 PUFAs stated on the label. Additionally, the FDA has put forth a plan to monitor the activities of dietary supplement manufacturers. This plan includes developing rules and guidelines for demonstrating and maintaining cGMP as well as oversight of the manufacturing process. In addition, there is increasing demand by consumers for the manufacture of consistent and uncontaminated, quality supplement products. As a result, the supplement manufacturers are facing increasing pressures to produce a safe quality product.

Recommendations

Develop nonformulary criteria for Omacor to include patients with very high triglyceride levels (≥500 mg/dL) who have either not had an adequate TG lowering response, are not a candidate for (e.g. history of confirmed peptic ulcer disease [perforation, ulceration or upper GI bleeding] gouty attacks [as evidenced by the presence of intra-articular uric acid crystals in the affected joint] and/or poorly controlled diabetes) or are unable to tolerate niacin. In those patients not receiving statins, a therapeutic trial of monotherapy with each a fibrate and niacin is recommended.

References

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Appendix A. Clinical Trials Involving Omacor in Patients With Elevated Triglyceride Levels

Author	Population/Intervention	N	Dose (grams/d)**	Mean TG after Treatment/ %Reduction	LDL-C Elevation	Comments
Harris, etal [28] Omacor vs. Pla 4 months	TG: 500-2000 mg/dL Mean TG baseline: Pla: 876 mgdL O: 919 mg/dL	42	3.4	Pla 1007 mg/dL O : 505 mg/dL 45% (p<0.00001)	31% (p=0.0014)	Seven patients noted burping a fishy taste (3 Pla, 4 Omacor)
Nordoy, etal [29] Atorva 10 mg/d plus either Omacor or Pla for 5 weeks	TG: 177-1329 mg/dL Mean TG baseline (on atorva): Pla: 303 mg/dL O: 217 mg/dL	42	1.68	NS	NS	None
Durrington, etal [30] Simvastatin 10-40 mg/d plus either Omacor or Pla 24-48 weeks	TG: >204 mg/dL Mean TG baseline: Pla: 336 mg/dL O: 407	59	3.4	Pla: 345 mg/dL O: 310 mg/dL at 24 weeks and 265 at 28 weeks. 20-30% at 3, 6 and 12 months (p<0.005)	Unchanged	22 Omacor vs. 17 Pla patients reported ADEs, mostly minor.
Stalenfoef, etal [31] Omacor vs. gemfibrozil 1200 mg/d 12 weeks	TG: 354-2480 mg/dL Mean TG baseline: O: 867 mg/dL G: 619 mg/dL	30	3.4	O: 464 G: 317 Omacor: 37.1% Gemfibrozil: 40.4% NS between groups	Omacor: 29.7% Gemfibrozil: 33.6 % NS between groups	None
Mackness, etal[32] R, DB, PC Omacor vs. Corn oil (pla) for 14 weeks	Type IV or Type IIb dyslipidemia with TG: 177-886 mg/dL Mean TG baseline: O: 354 mg/dL Pla: 328 mg/dL Omacor 2 g or corn oil 2 g twice daily	95	4	O: 254 mg/dL (median) Pla: no change	NS	TG reduction was greater in patients with LDL-C >174 mg/dL (Type IIb dyslipidemia) 16 patients withdrew (6 O/10 Pla)
Nordoy, et al[33] R, DB, PC Simva + Omacor vs. Simva + corn oil (Pla) 15 weeks, only 5 weeks with Omacor	Patients with combined dyslidemia and TG: 177-1329 mg/dL Mean TG baseline: 391-450 mg/dL Simva 20 mg vs. placebo X5 weeks, then all patients given simva 20 mg. Then randomized to Omacor or Pla for 5 weeks	41	4	O: TG reduced a mean of 68 mg/dL (27.9%) after addition to simva (p<0.01) Pla: TG increased by 41 mg/dL	NS	Compliance with medications was reported to be excellent and reported no ADEs with Omacor or simva
Pownall, etal[34]	Patients with severe Type IV hyper-	40	4	O: 512 mg/dL (median) 38.9%	Omacor: 16.7%	Compliance exceeded 95% and no serious

R, DB, PC Omacor vs. Corn oil (Pla) 6 weeks	triglyceridemia and TG: 500-2000 mg/dL Mean TG baseline: O: 801 mg/dL Pla: 786mg/dL			reduction in TG (p=0.001) Pla: 664 mg/dL (median) 7.5% reduction in TG (NS)	(p=0.007) Pla: -4.2% (NS)	ADEs were reported.
Calabresi, etal[35] R, DB, PC, CO Omacor vs. Corn oil (Pla) 16 weeks	Patients with familial combined hyperlipidemia (FCHL) Range of baseline TG: O: 141-779 mg/dL, mean 251 mg/dL One-half randomized to Omacor or Pla for 8 weeks and then crossed over to the alternate treatment	14	4	O: Mean: 183.5 mg.dL , Range: 75-407 mg/dL, (27% from baseline,p<0.05) Pla: Mean: 231.8 mg/dL, Range: 149-1030 mg/dL (NS)	Omacor: 25% (p<0.05) Pla: NS	LDL-C particle size did not change in the presence of Omacor. However, the increased production of LDL-C was in the form of larger, more buoyant particles. The degree of TG lowering and LDL-C elevation correlated with baseline TGs (e.g. the higher, the more significant TG reduction and LDL-C elevation).
Borthwick L, et al						

ADE=adverse events, CO=cross-over, DB=double-blind, G=gemfibrozil, NS=not significant, O=Omacor, Pla=placebo, R=randomized, TG=triglyceride
Omacor contains 4 mg of Vit E in each capsule.
** EPA plus DHA (n-3 fatty acids)