Clinical Overview of Omacor: A Concentrated Formulation of Omega-3 Polyunsaturated Fatty Acids

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Omacor (omega-3-acid ethyl esters; Reliant Pharmaceuticals, Inc., Liberty Corner, NJ) is a highly purified, prescription omega-3 fatty acid formulation with high concentrations of eicosapentaenoic acid (EPA) (465 mg) and docosahexaenoic acid (DHA) (375 mg) in each 1-g capsule, along with 4 mg (6 IU) of vitamin E. At a typical dose of 4 capsules/day, Omacor significantly lowers plasma triglyceride levels either as monotherapy or in combination with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) or fibrates. Omacor also modestly increases plasma levels of low-density lipoprotein cholesterol, increases high-density lipoprotein cholesterol levels, and has favorable effects on lipoprotein particle size and subclass distribution. Omacor is well tolerated, with few side effects other than mild gastrointestinal symptoms. Hyperglycemia, abnormal bleeding, elevations in muscle or liver enzymes, and/or abnormalities in kidney or nerve function have not been reported. Through its intensive purification process, Omacor has minimal "fishy" smell and taste, and it has not been reported to cause hypervitaminosis or illness due to exposure to environmental toxins. Omacor provides a safe, effective, well-tolerated approach to management of hypertriglyceridemia. **(Am J Cardiol 2006;98[suppl]:71i–76i)**

The American Heart Association (AHA) has recommended that patients with coronary artery disease (CAD) take ≥1 g/day of eicosapentaenoic acid (EPA) plus docosahexaenoic acid (DHA) and those with elevated plasma triglyceride (TG) levels take 2 to 4 g/day (Table 1).[1] Omega-3 fatty acid intake can be achieved through the consumption of either fish (Table 2),[2] a concentrated liquid formulation, or omega-3 fish oil powder. An additional therapeutic option is the use of fish oil therapy, such as Omacor (omega-3-acid ethyl esters; Reliant Pharmaceuticals, Inc., Liberty Corner, NJ), which is a prescription fish oil preparation. Omacor is composed of approximately 90% omega-3 fatty acids (465 mg EPA, 375 mg DHA, and ≥60 mg other omega-3 fatty acid esters), for a total of ≥900 mg of omega-3 fatty acids per 1-g capsule.

Clinical Trials

Clinical trials have specifically evaluated the efficacy and safety of Omacor and have included efficacy trials of Omacor on hypertriglyceridemia (Table 3), biomarkers or risk factors for cardiovascular disease (Table 4), and clinical end points (Table 5). For example, for a mean of 3.5 years, the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico (GISSI)–Prevenzione study[3] evaluated 11,323 patients who had a myocardial infarction (MI) within 3 months prior to study entry. The 4 equal groups included 3 treatment groups—(1) Omacor omega-3 fatty acid supplements (1 g/day) alone, (2) vitamin E alone (300 mg/day), and (3) omega-3 fatty acid supplements (1 g/day) and vitamin E (300 mg/day)—and (4) a control group. Other drugs were prescribed according to standard practice (such as angiotensin-converting enzyme inhibitors, antiplatelet drugs, β-adrenergic blockers, and lipid-lowering agents). All patients were encouraged to adhere to a Mediterranean-style diet. The results demonstrated that

- Vitamin E had no effect on outcomes;
- Omacor resulted in a 14% risk reduction ($p < 0.05$) for the end point of death, nonfatal MI, or nonfatal stroke;
- Omacor resulted in a 11% risk reduction for the end point of cardiovascular death plus nonfatal MI and nonfatal stroke ($p < 0.01$);
- Omacor's benefits were statistically significant within 3 to 6 months;
- Omacor's benefit was in addition to concurrent cardiac medications and diet; and
- Omacor was well tolerated.

During its clinical trial development, Omacor had previously been referred to as "omega-3 fatty acid concentrate K-85" because it contained ≥85% omega-3 fatty acids. Lipid efficacy clinical trials have shown Omacor to reduce TG levels in various patient populations by 19% to 47% (Table 3).[4–15] With regard to cardiovascular biomarkers, Omacor has been shown to downregulate platelet-derived growth factor gene expression, lower blood pressure incon-

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sistently, decrease the number of endothelial adhesion molecules, and improve lipoprotein particle size (Table 4).[4,8,13,16–18] Finally, clinical trials have shown Omacor to reduce all-cause mortality as well as the incidence of nonfatal MI and nonfatal stroke in patients with a recent history of MI, to decrease the incidence of vein graft occlusion in patients after undergoing coronary artery bypass surgery, and to slow the progression of renal insufficiency in patients with immunoglobulin A nephropathy (Table 5).[3,5,10,19]

Safety and Tolerability of Omacor

Omacor has been shown in clinical trials to be generally well tolerated. Adverse experiences are rare; if they do occur, they usually involve belching or eructation or perhaps taste perversion. Omacor has not been shown in clinical trials to have an adverse effect on plasma glucose levels, bleeding, or levels of muscle or liver enzymes or to cause abnormalities in kidney or nerve function. No case of hypervitaminosis or illness due to exposure to environmental toxin (Table 6)[20] has been reported, likely because of Omacor's extensive purification and concentration process (Figure 1).[21] This production process results in a content of <90 mg of omega-6, -7, and -9 fatty acids; undetectable concentrations of heavy metals, halogenated polycarbons, and dioxins; and <0.05% of *trans* fatty acids.

With regard to tolerability, each 1-g capsule of Omacor contains 4 mg (6 IU) of vitamin E. The addition of this antioxidant, coupled with the extensive purification process, results in reduced "fishy" taste or belching, the most common tolerability issue in clinical practice.

Indications, Contraindications, and Directions for Use

Omacor is indicated as an adjunct to diet to reduce very high (≥5.65 mmol/L [500 mg/dL]) plasma TG levels in adult patients.[22] Omacor has also been shown to be effective in reducing plasma TG levels when used in combination with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins),[14] and increase the production of the larger, more buoyant (and potentially less atherogenic) low-density lipoprotein (LDL) particles with a decrease in the smaller, more dense (and potentially more atherogenic) LDL particles.[11–13] Before the use of any drug therapy to treat hypertriglyceridemia, appropriate diet, exercise, and weight management should be initiated, as well as avoidance of excessive alcohol intake, because these may be important factors in hypertriglyceridemia. Other potential secondary causes of hypertriglyceridemia should be evaluated and treated if necessary, such as hypothyroidism and diabetes mellitus, and the use of certain concomitant drugs, such as estrogen therapy, thiazide diuretics, and rarely β-blockers. Omacor is contraindicated in patients who exhibit hypersensitivity to any component of the medication.

Table 1
Summary of the American Heart Association recommendations for omega-3 fatty acid intake

Population	Recommendation
Patients without documented CAD	Eat a variety of (preferably fatty) fish at least twice a week Include oils and foods rich in α-linolenic acid (flaxseed, canola, and soybean oils; flaxseed and walnuts)
Patients with documented CAD	Consume about 1 g/day of EPA plus DHA, preferably from fatty fish EPA plus DHA supplements could be considered in consultation with the physician
Patients who need to lower triglycerides	2–4 g/day of EPA plus DHA provided as capsules under a physician's care

CAD = coronary artery disease.
Adapted from American Heart Association.[1]

Table 2
Approximate levels of EPA plus DHA in dry heat cooked fish*

Fish	EPA plus DHA (mg/100 g eaten)
Salmon (Atlantic)	2,100
Salmon (chinook)	1,700
Salmon (coho, farmed)	1,300
Herring (Atlantic)	2,000
Herring (Pacific)	2,100
Mackerel (Pacific and jack)	1,800
Mackerel (Atlantic)	1,200
Mackerel (King)	400
Halibut (Atlantic and Pacific)	470
Halibut (Greenland)	1,200
Tuna (bluefin)	1,500
Tuna (yellowfin)	280
Tuna (skipjack)	330
Bluefish	990
Whitefish	1,600
Trout (mixed species)	900
Trout (farmed, rainbow)	1,200
Bass (striped)	970
Bass (sea bass, mixed species)	760
Bass (freshwater, mixed species)	760
Sablefish (black cod)†	1,800
Cod (Atlantic)	160
Cod (Pacific)	280

DHA = docosahexaenoic acid (22:6 n-3); EPA = eicosapentaenoic acid (20:5 n-3).
* Cooked fish (dry heat) often has less omega-3 fatty acid content than raw fish: 100 g of fish would be approximately 4 ozs, which would be a bit larger than a deck of playing cards or cassette tape. The amount of omega-3 fatty acids varies considerably in the same type of fish, depending on the environment and location.
† Sablefish or "black cod" is not part of the codfish family.
Adapted from USDA Agricultural Research Service.[2]

Some studies with omega-3 fatty acids demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies did not exceed normal limits and did not produce clinically significant bleeding episodes.

Table 3
Clinical studies of hypertriglyceridemia (HTG) treatment with Omacor

Study	Patient Population	Study Design	N	Dose (g/day)	Duration (wk)	Placebo	Baseline TG, mmol/L (mg/dL)	Change from Baseline (%)			Safety Comments
								TG	LDL-C	HDL-C	
Grundt et al (1995)[4]	Combined hyperlipidemia	RCT: double blind, parallel	57	4	12	Corn oil	4.0 (356)	−28	No data	NS	3% reduction in platelet count; no change in blood sugar, insulin, or proinsulin
Eritsland et al (1996)[5]	Coronary artery bypass grafting	RCT: 2×2 factorial	610	4	52	No	2.0 (178)	−19	+10	+10	No bleeding complication or GI complaint when taken with aspirin or warfarin vs aspirin or warfarin alone; may have increased dysphagia
Harris et al (1997)[6]	Severe HTG	RCT: double blind, parallel	42	4	16	Corn oil	10.4 (926)	−45	+31	+13	GI complaints comparable with placebo, no serious side effects; no impact on glucose, HbA_{1c}, liver enzymes, kidney function, and platelet count
McKeone et al, (1997)[7]	Severe HTG	RCT: double blind, parallel	40	4	6	Corn oil	5.6–22.6 (500–2,000)	−26	No data	+14	Safety data not reported
Abe et al (1998)[8]	Severe HTG	RCT: parallel	27	4	>28	Yes	9.8 (876)	−47	No data	NS	Safety data not reported
Pownall et al (1999)[9]	Severe HTG	RCT: double blind, parallel	40	4	6	Corn oil	9.0 (801)	−39	+17	NS	FPG maintained in those with type 2 DM and impaired glucose tolerance; no serious side effects; AST, BP, and glucose remained within enrollment criteria
Johansen et al (1999)[10]	Coronary angioplasty	RCT: double blind, parallel	500	6	2 Before + 24 after	Corn oil	2.2 (196)	−27	No data	NS	3 of 196 patients in the Omacor group and 2 of 192 in the placebo group had diarrhea or nausea; no other adverse effect noted
Calabresi et al (2000)[11]	Familial combined hyperlipidemia	RCT: double blind, crossover	14	4	8	Corn oil	2.8 (251)	−27	+21	NS	No effect on glucose, uric acid, liver enzymes, kidney function, or platelets
Westphal et al (2000)[12]	Severe HTG	Parallel	12	4	6	No	13.6 (1,210)	−40	+46	NS	Reduced CM, late postprandial CM remnants; no adverse event
Stalenhoef et al (2000)[13]	Primary HTG	RCT: double blind, double dummy, parallel	28	4	12	Corn oil	9.8 (872)	−37	+30	+11	FPG and HbA_{1c} unchanged; no significant side effect observed
Durrington et al (2001)[14]	Persistent HTG while treated with simvastatin	RCT: double blind, parallel	59	4	24	Corn oil	4.6 (409)	−20 to −30	NS	NS	No significant change in FPG or HbA_{1c} in patients with or without DM; no difference in blood chemistry, fibrinogen, or BP
Calabresi et al (2004)[15]	Familial combined hyperlipidemia	RCT: double blind, crossover	14	4	8	Corn oil	4.3 (378)	−44	+25	NS	Well tolerated

AST = aspartate aminotransferase; BP = blood pressure; CM = chylomicron; DM = diabetes mellitus; FPG = fasting plasma glucose; GI = gastrointestinal; HbA_{1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NS = not significant; RCT = randomized controlled trial; TG = triglycerides.

Table 4
Effects of Omacor on biomarkers or other risk factors for cardiovascular disease

Study	Risk Factor	Population	Result
Kaminski et al (1993)[16]	PDGF	Healthy men	Downregulated gene expression of PDGF-A and PDGF-B
Eritsland et al (1995)[17]	Lp(a)	6 mo after coronary artery bypass surgery	Did not change Lp(a) levels
Grundt et al (1995)[4]	BP	Normal BP and severe HTG	Lowered systolic and diastolic BP and heart rate
Russo et al (1995)[18]	BP	Hypertension	Did not lower BP or heart rate
Abe et al (1998)[8]	Endothelial adhesion molecules	HTG	At baseline, patients with HTG and low HDL-C had increased ICAM-1, VCAM-1, and E-selectin Omacor reduced TG levels by 47% and reduced levels of ICAM-1 and E-selectin
Stalenhoef et al (2000)[13]	LDL oxidation	Primary HTG	Omacor reduced TG levels similar to gemfibrozil; improved LDL subfractions, but increased the susceptibility of LDL to oxidation in vitro*

BP = blood pressure; HTG = hypertriglyceridemia; ICAM-1 = intercellular adhesion molecule–1; LDL = low-density lipoprotein; Lp(a) = lipoprotein(a); PDGF = platelet-derived growth factor; TG = triglycerides; VCAM-1 = vascular cell adhesion molecule to 1.
* Significance unclear regarding effects that may be found in vivo.

Table 5
Effects of Omacor on clinical end points

Study	End Point	Patients	Result
Eritsland et al (1996)[5]	Coronary artery bypass graft patency	Admitted for coronary artery bypass grafting without concomitant cardiac surgery (such as valve implantation or aneurysmectomy)	Reduced the incidence of vein graft occlusion
GISSI-Prevenzione (1999)[3]	Mortality and morbidity	MI within 3 months prior to study entry	Reduced all-cause mortality plus nonfatal MI and nonfatal stroke
Johansen et al (1999)[10]	Restenosis	Elective coronary angioplasty	Did not reduce the incidence of restenosis
Donadio et al (2001)[19]	Serum creatinine	Renal insufficiency with biopsy-proven immunoglobulin A nephropathy	Slowed the progression of renal insufficiency

MI = myocardial infarction.

Table 6
2004 Environmental Protection Agency (EPA) and US Food and Drug Administration (FDA) advice for women who might become pregnant, women who are pregnant, nursing mothers, and young children

- Do not eat shark, swordfish, king mackerel, or tilefish, because they contain high levels of mercury.
- Eat ≤12 oz (2 average meals) a week of a variety of fish and shellfish that are lower in mercury.
  - —5 of the most commonly eaten fish that are low in mercury are shrimp, canned light tuna, salmon, pollock, and catfish.
  - —Another commonly eaten fish, albacore (white) tuna has more mercury than canned light tuna. Albacore tuna should be limited to ≤6 oz (1 average meal) per week.
- Check local advisories about the safety of fish caught by family and friends in your local lakes, rivers, and coastal areas. If no advice is available, eat ≤6 oz (1 average meal) per week of fish you catch from local waters but don't consume any other fish during that week.
- Follow these same recommendations when feeding fish and shellfish to children, but serve smaller portions.

Adapted from US Department of Health and Human Resources and US EPA.[20]

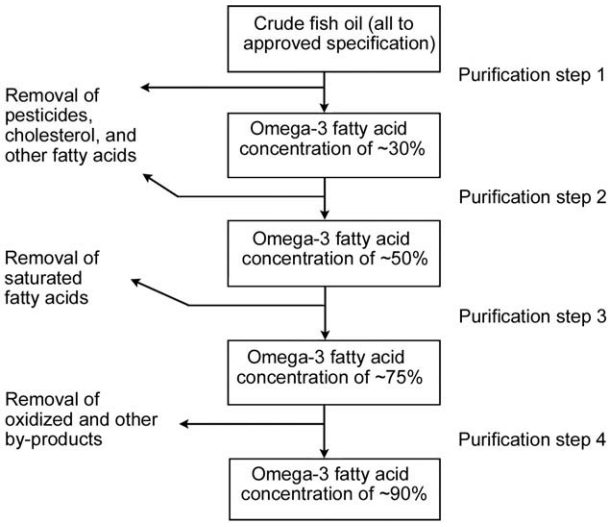

Figure 1. Process of manufacturing Omacor. (Reprinted with permission from Solvay Healthcare Limited.[21])

Clinical studies have not thoroughly examined the effect of Omacor and concomitant anticoagulants, although ≥1 trial has reported no bleeding complications when Omacor has been taken with warfarin or aspirin.[5] Nonetheless, patients receiving treatment with both Omacor and anticoagulants should be monitored periodically for abnormal bleeding. Otherwise, Omacor has no known drug interaction.

Omacor is a pregnancy category C drug, which means that there is no adequate and well-controlled study in pregnant women. It is unknown whether Omacor either can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Thus, Omacor should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Caution should be exercised when Omacor is administered to a woman who is breast-feeding, and safety and effectiveness in pediatric patients (aged <18 years) have not been established. Although the number of patients aged >65 years who enrolled in the clinical studies is limited, the safety and efficacy findings in subjects aged >60 years (approximately 25% of the study population) does not appear to differ from those of subjects aged <60 years. Therefore, there is no specific dosing difference in older persons.

Omacor was administered with meals during clinical trials. It is supplied as 1-g transparent, soft gelatin capsules filled with light yellow oil and bearing the designation Omacor. The daily dose of Omacor is 4 g, which can be taken as a single 4-g dose (4 capsules) or as 2 doses of 2 g (2 capsules given twice daily).

Conclusions

Omacor is a US Food and Drug Administration (FDA)–approved prescription omega-3 fatty acid preparation with a therapeutic indication for use as an adjunct to diet to reduce very high (≥5.65 mmol/L [500 mg/dL]) TG levels in adult patients. Because Omacor is the result of an extensive purification and concentration process, each capsule has ~90% omega-3 fatty acids such as EPA and DHA, undetectable concentrations of environmental toxins, and markedly reduced potential for fishy taste or belching. Clinical trials with Omacor have shown a marked reduction in TG levels (20% to >40%), especially with the recommended treatment dose of 4 capsules/day. Omacor has also been shown to be safe and generally well tolerated. Omacor represents a therapeutic option for the treatment of hypertriglyceridemia.

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