

Omega-3-acid Ethyl Esters (Lovaza) For Severe Hypertriglyceridemia

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INTRODUCTION

Hypertriglyceridemia is an independent risk factor for coronary heart disease (CHD), according to the guidelines from the Third Report of the National Cholesterol Education Program Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP III).¹ High triglyceride (TG) levels are frequently found in combination with insulin resistance, obesity, and low levels of high-density lipoprotein-cholesterol (HDL-C) in patients with the metabolic syndrome. Extremely high TG concentrations can cause a number of medical problems, including CHD and acute pancreatitis.

The primary causes of hypertriglyceridemia include cigarette smoking, very-high-carbohydrate diets, disease (i.e., diabetes, nephrotic syndrome), certain drugs (i.e., corticosteroids, protease inhibitors), and genetic factors. Excess acute alcohol intake can also raise TG levels, especially when alcohol is consumed with food.^{1,2}

TG levels are classified as follows: normal (below 150 mg/dL), borderline-high (150–199 mg/dL), high (200–499 mg/dL), or very high (500 mg/dL or more).¹

Approximately five to six million people in the U.S. have TG levels exceeding 500 mg/dL. NCEP ATP III guidelines endorse pharmacological treatment of hypertriglyceridemia above this value. The underlying principles in treating very high TG levels are to prevent acute

pancreatitis and CHD. Standard treatments include:¹

- diet and exercise
- smoking and alcohol cessation
- medications:
 - niacin (e.g., Niaspan, Kos)
 - fibric acids: gemfibrozil (Lopid, Pfizer); fenofibrate (TriCor, Abbott)
 - HMG-CoA reductase inhibitors (statins)
 - fish oil

For more than 30 years, it was recognized that certain ethnic populations, such as the Native Alaskans, had much lower mortality rates from cardiovascular disease (CVD). Further examination revealed that their diets were high in polyunsaturated fatty acids.^{3,4} Small observational and large epidemiological studies have since confirmed that ingesting omega-3 fatty acids (a type of long-chain polyunsaturated fatty acid) was associated with a reduced rate of premature deaths from CVD.^{5,6}

Omega-3 and omega-6 fatty acids are essential, because humans do not synthesize them. The omega-6 fatty acids include linolenic acid, gamma-linolenic acid, and arachidonic acid. The three main types of omega-3 fatty acids are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (Figure 1).

Chemically, ALA, EPA, and DHA are carboxylic acids with 18, 20, and 22 carbons and three, five, and six double bonds, respectively (see Figure 1).⁷ Humans produce only small amounts of omega-3 fatty acids via conversion of ALA to EPA and DHA. EPA and DHA are found in breast milk. Thus, omega-3 fatty acids must be ingested through the diet.

ALA omega-3 fatty acids occur naturally in plant foods such as flaxseed, walnuts, and canola oil. EPA and DHA omega-3 fatty acids are found in all fish, and the quantity is highest in oily fish (salmon, rainbow trout, mackerel, tuna, and herring). They are also available alone and in combination in over-the-counter dietary supplements.^{4,8–10}

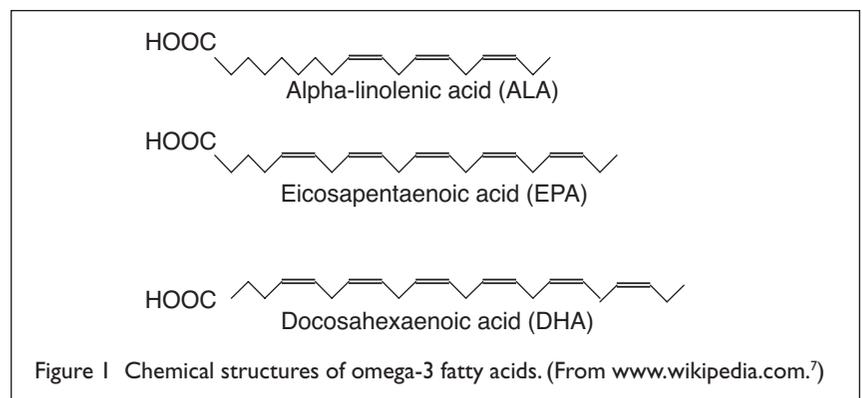
DHA, the primary structural fatty acid in the gray matter of the brain and the retina, is essential for mental functioning and vision.¹¹ Both DHA and EPA act as precursors for eicosanoids (prostaglandin, thromboxane, and leukotriene) and are thought to play a role in reducing inflammation. In clinical trials, they also worked together in reducing TG levels and mortality rates from CVD. It is unclear whether the effects on CVD would result if either agent were taken alone.⁷

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Disclosure: The author has no conflict of interest or financial interest with regard to this manuscript.

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This amount of fish provides approximately 250 to 300 mg/day of EPA and DHA. For patients with CHD, the AHA recommends 1,000 mg/day of EPA and DHA. In the U.S., the current DHA/EPA intake ranges from 130 to 150 mg/day, which is well below the recommended amount.¹²

In 2004, the Food and Drug Administration (FDA) approved Lovaza, a highly purified and concentrated omega-3 polyunsaturated fatty acid preparation, as the first prescription omega-3 product.⁸ Originally called Omacor, Lovaza was developed by Reliant Pharmaceuticals, which was acquired by Glaxo-SmithKline in December 2007.

PHARMACOLOGY

Each 1-g capsule of omega-3-acid ethyl esters (Lovaza) contains at least 900 mg (90% or more) of the ethyl esters of omega-3 fatty acids. The product is predominantly a combination of ethyl esters of EPA (465 mg) and DHA (375 mg). Each capsule contains 60 mg of other omega-3 fatty acids, and the remaining 10% comprises mostly omega-6 fatty acids. Lovaza reduces hepatic production of TG, but the mechanism of action is complex and not completely understood.⁹

In the liver, EPA and DHA inhibit acyl-CoA: 1,2-diacylglycerol acyltransferase (resulting in decreased TG synthesis) and they increase peroxisomal beta-oxidation, resulting in up-regulation of fatty acid metabolism. They also inhibit the esterification and release of other fatty acids, because they have a high affinity for, but are poor substrates of, the enzymes responsible for TG synthesis. In addition, EPA and DHA increase lipoprotein lipase activity, resulting in increased TG clearance.^{8-10,13}

Omega-3 fatty acids also decrease hepatic production of very-low-density lipoprotein-cholesterol (VLDL-C). The effects on HDL-C are minimal. Low-density lipoprotein-cholesterol (LDL-C) levels may increase, but LDL-C changes from small, dense atherogenic particles to larger, more buoyant and less atherogenic particles. Clinically, this latter cholesterol change could offset the increase in LDL-C that may occur. Also, the rise in LDL-C is usually less than the decrease in VLDL-C.^{8-10,13,14}

Other potential cardiovascular bene-

fits of omega-3 fatty acids are a decrease in platelet aggregation, a slight reduction in blood pressure and heart rate, and fewer arrhythmias. Omega-3 fatty acids (specifically, DHA and EPA) have been found to reduce sudden cardiac death in patients with or without a history of CHD.

The efficacy of these esters in reducing ventricular fibrillation or tachycardia in patients with implantable cardioverter defibrillators and atrial and ventricular premature complexes in patients with a history of cardiac arrhythmias have also been studied. So far, however, the results have been inconsistent.¹⁵⁻¹⁸

Because Lovaza is a fatty acid, it is incorporated into cell membranes; as a result, plasma levels are not detectable. Clinically significant drug interactions with this agent are not expected in humans.⁹

INDICATIONS AND USAGE

Lovaza is approved as an adjunct to diet to reduce very high TG levels of 500 mg/dL or greater in adults.⁹ Reliant received an approval letter for Lovaza for use in patients with TG levels of 200 to 499 mg/dL. This agent is also being evaluated for preventing CHD and for treating immunoglobulin A (IgA) nephropathy, inflammatory bowel disease, rheumatoid arthritis, renal disease, systemic lupus erythematosus, and osteoporosis.⁸⁻¹⁰ The clinical data are promising for CHD, but the evidence is insufficient to support its use in the other medical conditions listed. Lovaza is approved in most European countries for the treatment of high TG levels or the secondary prevention of CVD.¹⁹

Lovaza can be used as monotherapy or in combination with a statin. The manufacturer is currently working on a combination product of Lovaza and a statin.¹⁹

CLINICAL EFFICACY

Triglycerides and Cholesterol

Some small, prospective, randomized, placebo-controlled trials have been conducted to study the effect of omega-3-acid ethyl esters on very high TG levels. The trials lasted from 6 to 24 weeks. In most of the trials, the placebo was corn oil. The baseline TG levels for study subjects ranged from 500 to 2,000 mg/dL.

In these studies, Lovaza decreased TG levels by 26% to 47%, whereas corn oil

placebo increased them by an average of 6.7%. The higher the baseline TG level before therapy began, the greater the percentage reduction achieved after therapeutic drug levels were attained.

These trials also demonstrated a 10% to 46% increase in LDL-C levels and an increase of 11% to 14% in HDL-C levels with the active drug versus a 4.8% decrease in LDL-C levels and no change in HDL-C concentrations with placebo. Lovaza appeared to be well tolerated with few complications reported. Table 1 presents two pivotal trials that support the use of omega-3-acid ethyl esters for severe hypertriglyceridemia.^{20,21}

When compared with gemfibrozil 1,200 mg daily for the treatment of very high TG levels in two small, double-blind, randomized trials, Lovaza 4 g daily showed the following results. A study by Stalenhoef et al. included 30 patients with baseline TG levels between 354 and 2,480 mg/dL.²² No significant difference in TG reduction was noted between the two groups. Gemfibrozil decreased TG levels by 40.4%, whereas Lovaza decreased them by 37.1%. Gemfibrozil increased HDL-C levels by 17.1%, and Lovaza increased them by 11%. In the second study,²³ gemfibrozil decreased TG levels more than Lovaza did (51.2% vs. 28.9%, respectively). Gemfibrozil increased HDL-C levels by 27.9%, but Lovaza increased them by only 1.2%.

Lovaza has also been studied in combination with statins.^{24,25} In a study by Durrington et al., a dose of 4 g daily decreased TG levels by 23% at 24 weeks in patients whose levels remained elevated (above 200 mg/dL) despite taking simvastatin (Zocor, Merck) 10 to 40 mg daily. The results were sustained in patients who continued therapy for an additional 24 weeks of open-label treatment.²⁴

In a study by Nordoy et al., 4 g daily decreased TG concentrations by an additional 27.9% in patients with elevated TG levels (177-1,327 mg/dL) who were taking simvastatin 20 mg daily.²⁵

The effects of Lovaza on other biomarkers or risk factors for CVD have been studied as well. Calabresi et al. discovered that Lovaza 4 g daily for eight weeks both decreased VLDL-C and changed LDL-C into more buoyant and cholesterol-rich particles.²⁶ In two trials, Lovaza did not significantly cause a change in lipoprotein A (LpA) levels.^{15,27}

Table 1 Pivotal Studies of Omega-3-Acid Ethyl Esters (Lovaza) For the Treatment of Very High Triglyceride Levels

| | Study 1 (Harris) | Study 2 (Pownall) |
|--------------------|---|---|
| No. of patients | 42 | 40 |
| Inclusion criteria | TG 500–2,000 mg/dL | TG 500–2,000 mg/dL |
| Treatment | Esters 4 g daily or corn oil placebo | Esters 4 g daily or corn oil placebo |
| Duration | 16 weeks | 6 weeks |
| Results | Change from baseline results of Esters/placebo | Change from baseline results of Esters/placebo |
| Total cholesterol | ↓ 15% / ↓ 2% | ↓ 10% / 0% |
| Triglycerides | ↓ 45% / ↑ 15% | ↓ 39% / ↑ 8% |
| LDL-C | ↑ 31% / ↓ 5% | ↑ 17% / ↓ 4% |
| HDL-C | ↑ 13% / 0% | ↑ 6% / ↓ 6% |

LDL-C = low-density lipoprotein-cholesterol; HDL-C = high-density lipoprotein-cholesterol; TG = triglyceride.
 Data from Harris et al. *J Cardiovasc Risk* 1997;4:385–391;²⁰ and Pownall HJ, et al. *Atherosclerosis* 1999;143:285–297.²¹

Blood Pressure

Lovaza was compared with placebo for its effects on blood pressure (BP) in three studies. In a study of 57 patients, Grundt et al. noted that giving omega-3-acid ethyl esters resulted in a reduction of 8 mm Hg in systolic BP and a reduction of 4 mm Hg in diastolic BP.²⁸

Lungerhausen et al. included 43 hypertensive patients who were taking diuretics, beta blockers, or both. The study drug decreased systolic BP by 3.1 mm Hg and diastolic BP by 1.8 mm Hg.²⁹ Russo et al. found that the study drug had no effect on lowering BP or heart rate.³⁰

C-reactive Protein

Chan et al. compared the effects of Lovaza 4 g daily and atorvastatin (Lipitor, Pfizer) 40 mg daily for six weeks on high-sensitivity C-reactive protein (hs-CRP) levels in 48 men.³¹ Atorvastatin significantly reduced hs-CRP levels, whereas Lovaza had no effect.

Other Clinical Endpoints

Trials that evaluated the effects of Lovaza on clinical endpoints have also been published. Nilson et al. performed a randomized, double-blind, placebo-controlled trial to determine the effects of the study drug at a dose of 4 g daily on cardiac events and serum lipids in those

patients who had had an acute myocardial infarction (AMI) within eight days of study entry.³² The results showed a significant benefit on lipids but no difference in the rate of cardiac events.

In a study by Eritsland et al., Lovaza reduced the incidence of vein graft occlusion in patients admitted to the hospital for coronary artery bypass graft.³³ Johansen et al. noted that Lovaza did not lower the incidence of restenosis in patients undergoing elective coronary angioplasty.³⁴

GISSI-Prevenzione (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) was a randomized, open label, placebo-controlled study that included 11,324 patients who had an AMI within three months prior to enrollment in the study. Omega-3 fatty acids 1 g daily for approximately 3.5 years significantly improved survival in post-MI patients.³⁵

Mortality Rates

The effect of omega-3 fatty acids on mortality have been assessed in three published meta-analyses. Bucher et al. noted a risk ratio of 0.77 (95% confidence interval [CI], 0.63–0.94) for overall mortality with omega-3 fatty acids.³⁶

Studer et al. found a relative risk of 0.87 (95% CI, 0.73–1.03) for patients randomly assigned to receive omega-3 fatty acids. The authors stated that the non-

significant finding was mostly a result of inclusion of one large study that showed an increase in mortality with omega-3 fatty acid supplementation.³⁷ In the third meta-analysis, Hooper et al. noted a risk ratio of 0.8 (95% CI, 0.7–0.9) for overall mortality.³⁸

Limitations to the trials in these meta-analyses included, but were not limited to, variations in sample size (leading to differences in effect size) and variations in fish oil intake.^{36–38} In interpreting the findings of these studies, it seems likely that the benefits of fish oil for CHD were multifactorial and were not caused by lowering of TG alone. Several large-scale trials are now ongoing, with thousands of patients in each trial, to evaluate the effect of omega-3 fatty acids on the risk of CVD.³⁹

WARNINGS AND ADVERSE EFFECTS

Patients with a known sensitivity or an allergy to fish should use Lovaza with caution. This product was associated with a low frequency of side effects that led to discontinuation of therapy during trials (3.5% vs. 2.6% with placebo, respectively). Adverse effects that were reported more frequently with Lovaza versus placebo included eructation (belching, 4.9% vs. 2.2%), infection (4.4% vs. 2.2%), taste perversion (fishy taste, 2.7% vs. 0%), and rash (1.8% vs. 0.4%). Some patients experienced elevated alanine aminotransferase (ALT) levels; therefore, liver enzymes should be monitored periodically.^{8–10}

Unlike niacin and fibric acids, Lovaza has not been found to increase the risk of rhabdomyolysis when combined with a statin.^{8–10} Studies with larger numbers of participants taking the combination are needed to assess this risk.

McKenney et al. found that administering simvastatin and Lovaza together did not appear to affect the pharmacokinetics of simvastatin tablets.⁴⁰

Some studies have shown a prolonged bleeding time with omega-3 fatty acids but no resulting bleeding episodes of clinical significance. In animal studies, omega-3 fatty acids decreased the level of vitamin K–dependent clotting factors and reduced platelet arachidonic acid and thromboxane A₂ levels. Clinical studies have not been conducted to thoroughly examine the effect of combining Lovaza and anticoagulants.^{8–10}

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Table 2 Characteristics of Drugs Used to Treat Very High Triglyceride Levels

| | Lovaza | Niacin (Niaspan) | Gemfibrozil (Lopid) | Fenofibrate (TriCor) |
|-------------------|---------------|-------------------------|----------------------------|-----------------------------|
| Dose | 4 g daily | 1–2 g at bedtime | 600 mg twice daily | 145 mg daily |
| Price* | \$153.98 | \$120.98–\$241.97 | \$15.99 | \$118.52 |
| Total cholesterol | ↓9.7% | ↓25% | ↓15% | ↓15% |
| Triglycerides | ↓44.9% | ↓20%–50% | ↓20%–50% | ↓20%–50% |
| LDL-C | ↑44.5% | ↓5%–25% | ↓5%–20% | ↓5%–20% |
| HDL-C | ↑9.1% | ↑15%–35% | ↑10%–20% | ↑10%–20% |

LDL-C = low-density lipoprotein-cholesterol; HDL-C = high-density lipoprotein-cholesterol.
 * Cash price for a 30-day supply of the stated dose as of April 14, 2008. (From Drugstore.com.⁴⁸)
 Data from prescribing information for Lovaza, TriCor, Lopid, and Niaspan.^{9,43–45}

McClaskey and Michalets reported on a subdermal hematoma that developed after a fall in an elderly patient who had been taking high-dose omega-3 fatty acids (6 g/day) with warfarin (Coumadin, Bristol-Myers Squibb) and aspirin. Patients receiving this combination should be monitored carefully.⁴¹

It is unknown whether Lovaza, a Pregnancy Category C agent, is excreted in human milk. Caution must be exercised for women who are breast-feeding.^{8–10}

DOSAGE AND ADMINISTRATION

Lovaza is available as a 1-g oil-filled capsule. In addition to containing omega-3 and omega-6 fatty acids, it includes alpha-tocopherol 4 mg in a carrier of partially hydrogenated vegetable oils (2.2 mg per 1-mg capsule), including soybean oil.⁴² The recommended dose is 4 g by mouth daily with meals for the treatment of very high TG levels. The dose can be taken as 4 g once daily or 2 g twice daily. Dividing doses and taking the medication with meals can help reduce gastrointestinal adverse effects.^{8–10} The dose is 1 to 2 g daily for the off-label use of preventing CHD.¹⁹

Table 2 lists therapeutic agents that can reduce very high TG levels, along with their doses, retail prices for a one-month supply, and the effects on lipids.

ALTERNATIVE THERAPIES

NCEP ATP III guidelines recommend therapeutic lifestyle changes, including a decreased intake of saturated fats and cholesterol, exercise, smoking and alcohol cessation, niacin, fibric acids, omega-3 fatty acids, and statins—all as options for treating hypertriglyceridemia. It is unlikely that diet and lifestyle changes alone can lower very high TG levels to less than 500 mg/dL.¹

Fibric Acids

The mechanism of action by which fibric acids reduce TG remains unclear, but it may be mediated by peroxisome proliferator-activated receptors (PPARs), which regulate gene transcription. This results in increased TG clearance and decreased hepatic TG synthesis.^{43,44}

Niacin

Niacin's mechanism of action is not well defined, but it may involve several actions that result in lower TG, higher HDL-C, and a lower prevalence of small, dense particles of LDL-C. Niacin inhibits access of free fatty acid to adipose tissue, suppresses hepatic assembly and release of VLDL-C, and increases lipoprotein lipase activity.⁴⁵

There are less expensive over-the-counter niacin products than Niaspan, a prescription product, but they cause considerably more flushing. Flushing is a prostaglandin-mediated response and may be reduced by taking a sustained-release formulation product like Niaspan or an aspirin, 81 to 325 mg, at a minimum of 30 minutes before the niacin dose.⁴⁵

Statins

Statins reduce TG levels by only 7% to 30%, so they can be used when TG levels are below 400 mg/dL.¹

Dietary Supplements

Several nonprescription omega-3 fatty acid products are classified as dietary supplements. Because the FDA does not regulate these supplements, the potency and purity of ingredients are not guaranteed. Fish oil used in the manufacture of Lovaza undergoes an intense purification process that includes removal of pesticides, cholesterol, fatty acids, and by-products. Most

dietary supplements of fish oils do not undergo as rigorous a purification process and have a “fishier” taste.

Because nonprescription fish oils do not contain the same high levels of EPA and DHA, they are less potent than Lovaza; an average of 12 to 20 capsules is equal to four capsules of Lovaza. Taking more capsules has the potential to increase caloric consumption by approximately 100 calories per day.⁴⁶ For example, the amount of EPA and DHA in four capsules of Lovaza is equivalent to 12 capsules of Member's Mark Omega 3 Fish Oil (Sam's Club), to 16 capsules of Walgreen's Fish Oil Concentrate or General Nutrition Centers Fish Body Oil, and to 20 capsules of Nature's Bounty Salmon Oil. Fish consumption is another option, but the amount needed to consume to equal 4 g of Lovaza would be extreme and not feasible because of safety concerns regarding exposure to environmental pollutants such as mercury.⁴⁶

FORMULARY CONSIDERATIONS

Gemfibrozil (Lopid) is a safe, cost-effective therapy for hypertriglyceridemia, and it should be recommended as a first-line therapy for TG levels above 500 mg/dL. Advantages of gemfibrozil include low cost, less need for titration, and good tolerability. A disadvantage is its potential drug interaction with statins.

Because of their higher cost, fenofibrate (TriCor), niacin (Niaspan), and Lovaza are all reasonable second-line options in patients who do not respond to or who are intolerant of gemfibrozil. For very high TG levels, the ATP III guidelines recommend a fibric acid to be used as a first-line drug, niacin as a second-line drug, and omega-3 fatty acids as an adjunct.¹ If a patient's TG level is 200 to 499

mg/dL, the primary aim is to achieve the goal LDL-C. Statins are preferred; they are safe and efficacious for lowering both LDL-C and TG levels, and they are generally well tolerated. Other options for lowering LDL-C levels include niacin, ezetimibe (Zetia, Merck), and bile acid resins.¹

After patients achieve targeted LDL-C levels, if TG levels still exceed 200 mg/dL, non-HDL (total cholesterol minus HDL) should be calculated. If non-HDL is above goal (LDL-C goal plus 30 mg/dL), either LDL-C or TG values should be lowered.

If a patient is taking a statin and if increasing the dose is not effective or is not an option, combination therapy is necessary. Fibric acids (especially fenofibrate) and niacin are possible options, but Lovaza may also be a reasonable choice; it does not interact with statins or increase the risk of rhabdomyolysis.¹

For patients with acquired or genetic disorders of combined hyperlipidemia (e.g., high LDL-C and high TG), combination therapy is required to attain goal lipid levels.¹ Based on current information, it is safe to combine Lovaza with a statin to treat dyslipidemia.

COST

The cost of Lovaza is comparable to that of niacin, slightly more than that of fenofibrate, and significantly more than that of gemfibrozil (see Table 2).⁴⁷ An increasing number of insurance companies are covering Lovaza, usually in Tier 3 or with a prior authorization.⁴⁸

CONCLUSION

Lovaza 4 g daily is an option for the treatment of very high TG levels. Safe and effective, it may reduce the risk of acute pancreatitis and the long-term risk of CVD. Patients using Lovaza should be counseled about compliance with diet and lifestyle modifications.

Acknowledgment: The author would like to thank Joan Rider, PharmD, CDE, for reviewing the manuscript.

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