Therapeutic Class Overview
Omega-3 Fatty Acids

INTRODUCTION

- The independent relationship of triglycerides (TGs) to the risk of future cardiovascular disease (CVD) events has long been controversial (Miller et al, 2011).
- Rich sources of omega-3-fatty acids come from fatty fish and plant sources, and fish oil has eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).
    - When administered at high doses, they can reduce levels of TGs by approximately 50% (National Cholesterol Education Program [NCEP], 2002; Rosensen, 2013; Tangney, 2013).
    - Select clinical trials suggest that relatively high doses of omega-3-fatty acids, in the form of fish, fish oils or high-linolenic acid oils, will reduce the risk for major coronary events in persons with established coronary heart disease; however, the overall body of literature does not offer convincing evidence that fish oil supplements are beneficial for preventing cardiovascular disease or improving outcomes (NCEP, 2002; Institute for Clinical Systems Improvement, 2017; Smith et al, 2011).
- The scope of this review will focus on LOVAZA®, OMTRYG™ and TRIKLO (omega-3-acid ethyl esters), VASCEPA® (icosapent ethyl), and EPANOVA® (omega-3-carboxylic acids) for their respective Food and Drug administration (FDA)-approved indications, which are outlined in Table 1.
- LOVAZA, OMTRYG and TRIKLO (omega-3-acid ethyl esters), VASCEPA (icosapent ethyl), and EPANOVA (omega-3 carboxylic acids) are FDA-approved prescription omega-3 fatty acids. These products are approved as adjunct therapy to diet to reduce TGs in adults with severe (≥500 mg/dL) hypertriglyceridemia.
    - LOVAZA (omega-3-acid ethyl esters) is available as a 1 gram soft-gelatin capsule, containing approximately 375 mg and 465 mg of DHA and EPA, respectively. TRIKLO is a branded generic product for LOVAZA.
    - VASCEPA (icosapent ethyl) is available as a soft-gelatin capsule, containing ≥95% icosapent ethyl, an esterified formation of EPA (Rosensen, 2013).
    - EPANOVA (omega-3 carboxylic acids) is available as a coated, soft-gelatin capsule, containing at least 850 mg of polyunsaturated fatty acids, including multiple omega-3 fatty acids (predominantly EPA and DHA).
    - OMTRYG (omega-3-acid ethyl esters) is available as a 1.2 gram, transparent, soft-gelatin capsule filled with yellow oil containing 375 mg and 465 mg of DHA and EPA, respectively.
    - Of note, there are several over-the-counter products containing omega-3 fatty acids that are marketed as nutritional supplements. These products do not have FDA-approved indications and may not contain the same amount of the active ingredient (Facts and Comparisons, 2017).
- Omega-3 fatty acids have the potential to be used off-label for the treatment of coronary arteriosclerosis, familial combined hyperlipidemia, heart failure and hyperlipidemia with TG levels < 500 mg/dL (Micromedex, 2017).
- The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults focuses more heavily on a patient's overall atherosclerotic cardiovascular disease (ASCVD) risk versus achieving target LDL-C and/or non-HDL-C levels to guide appropriate treatment. The guidelines also state that adherence to lifestyle and to statin therapy should be re-emphasized before considering the addition of a non-statin drug (Stone et al, 2014). Recent ACC/AHA recommendations on non-statin use do not consider the use of omega-3 fatty acids as they did not include therapies for severe hypertriglyceridemia (Lloyd-Jones et al, 2016; Lloyd-Jones et al, 2017).
- The National Lipid Association recommends omega-3 fatty acids, fibric acid derivatives, or niacin as first-line agents for patients with TG levels of 1000 mg/dL or greater. These agents may also be considered for patients with contraindications for, or intolerance to, statin therapy (Jacobson et al, 2015).
- The Endocrine Society Clinical Practice Guidelines state that omega-3 fatty acids, fibrates, and niacin may be considered as monotherapy or in combination with statins in patients with TG levels that are moderate (200 to 999 mg/dL, based on the Endocrine Society criteria) to severe (1,000 to 1999 mg/dL, based on the Endocrine Society criteria) (Berglund et al, 2012).

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
EPANOVA (omega-3-carboxylic acids capsule)	AstraZeneca	05/05/2014	-
LOVAZA (omega-3-acid ethyl esters capsule)	GlaxoSmithKline	11/10/2004	✔
OMTRYG (omega-3-acid ethyl esters Type A capsule)	Trygg Pharma, Inc.	04/23/2014	-*
TRIKLO (omega-3-acid ethyl esters capsule)	Key Therapeutics, LLC	08/08/2017	✔ **
VASCEPA (icosapent ethyl capsule)	Amarin Pharma, Inc.	07/26/2012	-

*OMTRYG was FDA-approved in 2014, but current availability of the product is unclear.
**Branded generic for LOVAZA.
(Drugs@FDA, 2017; Facts and Comparisons, 2017; Clinical Pharmacology, 2017; TRIKLO prescribing information, 2017)

INDICATIONS

Table 2. FDA-Approved Indications

Indication	EPANOVA (omega-3-carboxylic acids)	LOVAZA (omega-3-acid ethyl esters)	TRIKLO (omega-3-acid ethyl esters)	OMTRYG (omega-3-acid ethyl esters)	VASCEPA (icosapent ethyl)
Adjunctive treatment to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia	✔	✔	✔	✔	✔

(Prescribing information: EPANOVA, 2017; LOVAZA, 2015; OMTRYG, 2016; TRIKLO, 2017; VASCEPA, 2017)

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- There are currently no head-to-head efficacy trials comparing EPANOVA (omega-3-carboxylic acids), LOVAZA and OMTRYG (omega-3-acid ethyl esters), or VASCEPA (icosapent ethyl). One study compared the effects of an acylglycerol omega-3 formulation, which is often available in non-prescription omega-3 supplements to LOVAZA. In this double-blind trial in patients with TG concentrations of 150 to 500 mg/dL, 120 patients were randomized to 5563 mg acylglycerol omega-3 daily, LOVAZA 4 g daily, or placebo (olive oil). Both omega-3 groups had decreased TG concentrations compared with placebo (P<0.001), but no difference was found between active treatments (28% reduction with acylglycerol omega-3 and 22% with LOVAZA; P=0.785). Unfortunately, patients included in this study had mild to moderate elevations in TG at baseline, and it is unclear if the acylglycerol omega-3 formulation would have similar results in patients with severe hypertriglyceridemia (Hedengran et al, 2015).
- EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) was a 12-week, double-blind, placebo (olive oil)-controlled, randomized trial that evaluated the safety and lipid-altering efficacy of EPANOVA (omega-3-carboxylic acids) in 399 adult patients with average serum TG concentrations of ≥500 mg/dL but <2,000 mg/dL at screening (one and two weeks before random assignment). Patients were either treatment-naïve for dyslipidemia or using a stable (for at least six weeks before the first qualifying lipid measurement) dosage of a statin, cholesterol absorption inhibitor (CAI), or their combination. They were randomized to one of four treatment groups: placebo (olive oil) (n=99), or EPANOVA 2 g (n=100), 3 g (n=101), or 4 g (n=99). The EPANOVA 3 g group demonstrated a lower TG reduction than the other two active treatment groups. Treatment with EPANOVA 2 g and EPANOVA 4 g compared to placebo led to statistically significant reductions in fasting TG levels (P<0.01 and P<0.001, respectively) and in non-HDL-C levels (P<0.05 and

P<0.01, respectively). However, there was a statistically significant increase in LDL-C levels in both active treatment groups (P<0.001 for both) (Kastelein et al, 2014).

- The ESPRIT trial was a six-week, double-blind, parallel-group trial of 647 diet-stable patients with fasting TG levels ≥200 mg/ dL and <500 mg/dL (treated with a maximally tolerated dose of statin or statin with ezetimibe) and at high risk for CVD who were randomized to receive placebo (olive oil) capsules (n=216), EPANOVA 2 g daily (n=215), or EPANOVA 4 g daily (n=216) to assess the TG and non-HDL-C lowering efficacy of adding EPANOVA to existing statin therapy. Compared to placebo, both EPANOVA 2 g and 4 g treatment groups demonstrated significant reductions in non-HDL-C levels (P<0.05 for both) and TG levels (P<0.001 for both). LDL-C was significantly increased compared to placebo in the EPANOVA 2 g group only (P<0.025) (Maki et al, 2013).
- LOVAZA (omega-3-acid ethyl esters) and VASCEPA (icosapent ethyl) (studied under the investigational name, AMR-101) were consistently associated with decreases in TG levels from baseline compared to placebo in studies of hypertriglyceridemia (Ballantyne et al, 2012; Bays et al, 2011; Bays, Maki et al, 2010; Bays, McKenny et al, 2010; Calabresi et al, 2000; Calabresi et al, 2004; Davidson et al, 2007; Durrington et al, 2001; Eritsland et al, 1996; GISSI-Prevenzione Investigators,1999; Johansen et al,1999; Koh et al, 2012; Macchia et al, 2013; Maki et al, 2008; Maki et al, 2010; McKeone et al,1997; Nilsen et al, 2001; Nordoy et al, 1998; Peters et al, 2012; Pownall et al,1999; Risk and Prevention Study Collaborative Group et al, 2013; Roth et al, 2009; Stalenhoef et al, 2000; Van Dam et al, 2001).
- In select placebo-controlled trials, LOVAZA (omega-3-acid ethyl esters) was associated with an increase in low density lipoprotein cholesterol (LDL-C) levels from baseline compared to placebo (Bays, Maki et al, 2010; Calabresi et al, 2000; Calabresi et al, 2004; Koh et al, 2012; Maki et al, 2010; Pownall et al, 1999; Roth et al, 2009; Stalenhoef et al, 2000).
- LOVAZA (omega-3-acid ethyl esters) was generally associated with an additive decrease in TG and total cholesterol (TC) levels when added to a regimen containing a statin or a fibric acid derivative (Bays, Maki et al, 2010 COMBOS; Bays, McKenny et al, 2010; Davidson et al, 2007; Durrington et al, 2001; Maki et al, 2008; Maki et al, 2010 COMBOS; Nordoy et al, 1998; Peters et al, 2012; Roth et al, 2009).
- When compared in head-to-head trials, LOVAZA (omega-3-acid ethyl esters) was associated with similar decreases in cholesterol parameters from baseline compared to fenofibrate. When compared to gemfibrozil, one randomized controlled trial demonstrated similar cholesterol decreases. However, a second randomized controlled trial demonstrated that this agent was associated with a significantly smaller decrease in TG levels from baseline (–28.9 vs –51.2%, respectively; P=0.007) (Koh et al, 2012; Stalenhoef et al, 2000; Van Dam et al, 2001).
- In placebo-controlled trials, VASCEPA (icosapent ethyl) was not associated with an increase in LDL-C levels from baseline compared to placebo (Ballantyne et al, 2012; Bays et al, 2011).
- Outcomes data with LOVAZA (omega-3-acid ethyl esters) have demonstrated mixed results when evaluating reduction in the risk of cardiovascular events.
    - The GISSI-Prevenzione trial demonstrated the beneficial effects of omega-3 acid ethyl esters in patients who have experienced a recent myocardial infarction (MI); omega-3-acid ethyl esters significantly reduced the risk of death, nonfatal MI, and nonfatal stroke compared to vitamin E. Treatment with omega-3 poly unsaturated fatty acids (PUFA), but not vitamin E, significantly lowered the risk of the composite of death, nonfatal MI, and nonfatal stroke (relative risk [RR], 0.10; 95% confidence interval [CI], 0.01 to 0.18; P=0.048 by 2-way analysis and RR, 0.15; 95% CI, 0.20 to 0.25; P=0.023 by 4-way analysis) (GISSI-Prevenzione Investigators, 1999).
    - A randomized controlled trial comparing LOVAZA (omega-3-acid ethyl esters) to dietary therapy in patients admitted for coronary artery bypass grafting demonstrated a lower incidence of vein graft occlusion rate in the treatment group. After one year of therapy, the vein graft occlusion rate per distal anastomoses was 27% in the group receiving LOVAZA (omega-3-acid ethyl esters) compared to 33% in the control group (odds ratio [OR], 0.77; 95% CI, 0.60 to 0.99; P=0.034) (Eritsland et al, 1996).
    - A randomized controlled trial comparing LOVAZA (omega-3-acid ethyl esters) to placebo in patients who were scheduled for elective coronary angioplasty demonstrated no difference in the rate of restenosis. This event occurred in 40.6% of the treated stenoses in the LOVAZA (omega-3-acid ethyl esters) group and in 35.4% of the treated stenoses in the placebo group (OR, 1.25; 95% CI, 0.87 to 1.80; P=0.21) (Johansen et al, 1999).
    - A randomized, controlled trial comparing LOVAZA (omega-3-acid ethyl esters) to placebo in patients with an acute MI demonstrated no difference in the rate of cardiovascular events and revascularizations. Of the patients receiving LOVAZA (omega-3-acid ethyl esters), 28% experienced at least one cardiac event compared to 24% of patients in the placebo group (P=0.74). There was no significant difference between the groups with regards to the number, type, or severity of cardiac events (Nilsen et al, 2001).

- The Risk and Prevention Study compared LOVAZA (omega-3-acid ethyl esters) to placebo in patients evaluated to be at a high cardiovascular risk and demonstrated no difference in the rate of death, nonfatal MI, and nonfatal stroke. The primary end point occurred in 1,478 of 12,505 patients included in the analysis (11.8%), of whom 733 of 6,239 (11.7%) had received omega-3 PUFA and 745 of 6,266 (11.9%) had received placebo (hazard ratio [HR], 0.97; 95% CI, 0.88 to 1.08; P=0.58) (Risk and Prevention Study Collaborative Group et al, 2013).
- A randomized controlled trial comparing LOVAZA (omega-3-acid ethyl esters) to placebo in patients with confirmed symptomatic paroxysmal atrial fibrillation (AF) that required cardioversion, who had at least two episodes of AF in the six months before randomization, or both, demonstrated no significant difference in the rate of recurrence of symptomatic AF. At 12 months, 56 of 297 participants (18.9%) in the placebo group and 69 of 289 participants (24%) in the omega-3 PUFA group had a recurrent symptomatic AF (HR, 1.28; 95% CI, 0.90 to 1.83; P=0.17) (Macchia et al, 2013).

- There are no published trials evaluating VASCEPA (icosapent ethyl) as an adjunctive therapy to treat hypercholesterolemia or evaluating the cardiovascular outcomes with this agent. However, a formulation of icosapent ethyl has been marketed in Japan since 1994 under the trade name EPADEL® (ethyl-eicosapentaenoic acid, the active metabolite of icosapent ethyl). Published studies have evaluated this formulation as an adjunctive therapy with estriol and statins and the cardiovascular outcomes of this agent.
  - In a prospective observational, 48-week trial, EPADEL (ethyl-eicosapentaenoic acid) 1,800 mg daily added to estriol 2 mg daily was compared to estriol 2 mg daily alone. TC decreased significantly from baseline in both groups. Serum levels of TGs decreased significantly from 194.5 to 141.5 mg/dL (-27. 2%; P=0.001) in the study group but increased slightly from 192.9 to 207.4 mg/dL (+7.5%) in the control group at week 48 in the women whose level of TGs was not <150 mg/dL (Kurabayashi et al, 2000).
  - In an open-label trial, 900 to 1,800 mg/day of EPADEL (ethyl-eicosapentaenoic acid) was administered to patients with hyperlipidemia who had been treated with statins for an average of 30 months. Serum TC and TG concentrations were significantly decreased three months after the administration of EPADEL (ethyl-eicosapentaenoic acid) (from 5.63 to 5.02 mmol/L, P<0.05; from 2.07 to 1.08 mmol/L; P<0.01, respectively) (Nakamura et al, 1999).
  - In the Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS), a prospective, open label, blinded endpoint trial, 18,645 patients were randomly assigned to receive either 1,800 mg of EPADEL (ethyl-eicosapentaenoic acid) daily with a statin or statin therapy alone. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal MI, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. At mean follow-up of 4.6 years, the primary endpoint occurred less frequently in the EPADEL (ethyl-eicosapentaenoic acid) group compared to the control group (262 [2.8%] vs. 324 [3.5%], respectively; RR=0.19; P=0.011) (Yokoyama et al, 2007).
  - Seven sub-analyses have been published of the JELIS study.
    - The reduction in cardiovascular risk was greater in the EPADEL (ethyl-eicosapentaenoic acid) group compared to the control group in patients unable to attain LDL-C and/or high density lipoprotein cholesterol (HDL-C) goals (-38% reduced risk; P=0.007), those with peripheral artery disease (HR, 0.44, 95% CI, 0.19 to 0.97; P=0.041), those with preexisting coronary artery disease (CAD) and a TC ≥250 mg/dL (8.7% vs. 10.7%, respectively; HR, 0.77, 95% CI, 0.63 to 0.96; P=0.017) and regardless of the number of cardiovascular risk factors (hypercholesterolemia, obesity, high TG or low HDL-C, diabetes, and hypertension) (P<0.05 for all comparisons) (Ishikawa et al, 2010; Matsuzaki et al, 2009; Saito et al, 2008, Sasaki et al, 2012).
    - The use of EPADEL (ethyl-eicosapentaenoic acid) was associated with a significantly greater decrease in CAD compared to the control group in patients with impaired glucose metabolism, but not normoglycemic patients (P=0.048 and P=0.062, respectively) (Oikawa et al, 2009).
    - Adherence to ≥80% of the medication regimen was associated with a decreased incidence of cardiovascular endpoints compared to those exhibiting <80% adherence to study medications (P=0.041) (Origasa et al, 2010).
    - The incidence of secondary stroke was lower in the EPADEL (ethyl-eicosapentaenoic acid) group compared to the control group (6.8 vs 10.5%, respectively; HR, 0.80; 95% CI, 0.64 to 0.997; P=0.047); however, there was no difference between groups in the incidence of primary stroke (1.5 vs 1.3%, respectively; HR, 1.08; 95% CI, 0.95 to 1.22; P=0.244) (Tanaka et al, 2008).

- The authors of a Cochrane systematic review that examined the effects of omega-3 fatty acids on the prevention and treatment of CVD concluded that it is unclear whether dietary or supplemental omega-3 fats reduce or increase total mortality or combined cardiovascular events in people with, or at risk of, CVD or in the general population (Hooper et al, 2004).
- The 2013 ACC/AHA guidelines emphasize adherence to lifestyle and to statin therapy before considering the addition of a nonstatin drug (Stone et al, 2013). Other guidelines suggest a potential role for other lipid-lowering therapies when treating hypertriglyceridemia including fibric acid derivatives, niacin, and omega-3 fatty acids (Jellinger et al, 2012; Jacobson et al, 2015).

SAFETY SUMMARY

- Omega-3 fatty acids have precautions for use in patients with hepatic impairment and fish allergy. LOVAZA, TRIKLO, OMTRYG (omega-3 acid ethyl esters) and EPANOVA (omega-3-carboxylic acids) may be associated with increases in LDL-C. Additionally, LOVAZA, TRIKLO, and OMTRYG have a possible association with atrial fibrillation or flutter.
- The most common adverse reactions associated with LOVAZA, TRIKLO, and OMTRYG (incidence >3% and greater than placebo) were eructation, dyspepsia, and taste perversion.
- The most common adverse reactions with EPANOVA (incidence ≥ 3% and greater than placebo) were eructation, nausea, diarrhea, and abdominal pain. Additional adverse reactions include vomiting, flatulence, and taste perversion.
- The most common adverse reaction associated with VASCEPA (incidence >2% and greater than placebo) was arthralgia.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
EPANOVA (omega-3-carboxylic acids)	Coated soft gelatin capsule: 1 g	Adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia: 2 g or 4 g once daily depending on individual patient response and tolerability	Assess TG levels carefully before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high TG levels and manage as appropriate. Patients should be placed on an appropriate lipid-lowering diet prior to receiving treatment and should continue diet during therapy.	In clinical trials, this agent was administered without regard to meals. Swallow capsules whole. Do not break open, crush, dissolve, or chew. Gelatin source: porcine
LOVAZA and TRIKLO (omega-3-acid ethyl esters)	Soft-gelatin capsule: 1 g	Adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia: 4 g/day administered once daily or in two divided doses	Assess TG levels carefully before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high TG levels and manage as appropriate. Patients should be placed on an appropriate lipid-lowering diet prior to receiving treatment and should continue diet during therapy.	In clinical trials, this agent was administered with meals. Swallow capsules whole. Do not break open, crush, dissolve, or chew.
OMTRYG (omega-3-acid ethyl esters)	Soft-gelatin capsule: 1.2 g (containing	Adjunct to diet to reduce TG levels in adult patients with severe	Assess TG levels carefully before initiating therapy. Identify other causes (e.g.,	Should be administered with food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	≥900 mg ethyl esters of omega-3 fatty acids)	(≥500 mg/dL) hypertriglyceridemia: 4 capsules/day administered once daily or in two divided doses	diabetes mellitus, hypothyroidism, or medications) of high TG levels and manage as appropriate. Patients should be placed on an appropriate lipid-lowering diet prior to receiving treatment and should continue diet during therapy.	Swallow capsules whole. Do not break open, crush, dissolve, or chew.
VASCEPA (icosapent ethyl)	Soft-gelatin capsule: 0.5 g, 1 g	Adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia: 4 g/day administered in two divided doses	Assess TG levels carefully before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high TG levels and manage as appropriate. Patients should be placed on an appropriate lipid-lowering diet prior to receiving treatment and should continue diet during therapy.	Should be administered with food. Swallow capsules whole. Do not break open, crush, dissolve, or chew.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
EPANOVA (omega-3-carboxylic acids)	Clinical trials did not include sufficient numbers of patients ≥65 years of age to determine if they have a different response than younger patients. In general, therapy should be initiated at the lower end of the dosing range for elderly patients.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Unclassified† No studies in pregnant women: data insufficient to inform risk. No information regarding presence in human breast milk or effects on breast-fed infants. Limited studies show that omega-3 fatty acids are present in human milk at levels higher than plasma concentrations.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
LOVAZA, TRIKLO, and OMTRYG (omega-3-acid ethyl esters)	The efficacy and safety profile among those ≥60 years of age did not appear to differ from the efficacy and safety profile observed in younger patients.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Pregnancy Category C Caution should be exercised in lactating mothers.
VASCEPA (icosapent ethyl)	No overall differences in safety or effectiveness were observed between subjects ≥65 years of age and younger subjects.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Pregnancy Category C Caution should be exercised in lactating mothers.

*Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

CONCLUSION

- Prescription omega-3 fatty acids are approved by the FDA for the treatment of severe hypertriglyceridemia. There is a generic formulation of LOVAZA (omega-3-acid ethyl esters) currently available, as well as a branded generic product (TRIKLO).
- In patients with an elevated TG level (≥500 mg/dL), a fibric acid derivative or niacin should be initiated before LDL-C lowering therapy to prevent pancreatitis. Omega-3-acid fatty acids represent an alternative to fibric acid derivatives and niacin for the treatment of hypertriglyceridemia. Select clinical trials suggest that relatively high doses of omega-3-fatty acids, in the form of fish, fish oils or high-linolenic acid oils, will reduce the risk for major coronary events in persons with established coronary heart disease; however, the overall body of literature does not offer convincing evidence that fish oil supplements are beneficial for preventing cardiovascular disease or improving outcomes.
- Clinical trials have demonstrated that prescription omega-3 acid ethyl esters can effectively lower TGs, as well as positively impact other lipid/lipoprotein parameters when used as monotherapy or in combination with fenofibrate or statins.
- In select placebo-controlled trials, both LOVAZA and OMTRYG (omega-3-acid ethyl esters) and EPANOVA (omega-3 carboxylic acids) were associated with an increase in LDL-C levels from baseline compared to placebo.
- In placebo-controlled trials, VASCEPA (icosapent ethyl) was not associated with an increase in LDL-C levels from baseline compared to placebo.
- Select cardiovascular outcomes studies have suggested a decrease in cardiovascular outcomes with LOVAZA (omega-3 acid ethyl esters) and VASCEPA (icosapent ethyl); however, certain trials have demonstrated no benefit compared to a control group.
- EPANOVA (omega-3-carboxylic acids) is the first FDA-approved prescription omega-3 in free fatty acid form, which produces higher bioavailability than esterified forms. Unlike the other prescription omega-3 fatty acids, EPANOVA can be taken without regard to meals. It does have a similar safety profile as the existing available products.
- The 2013 ACC/AHA guidelines emphasize adherence to lifestyle and to statin therapy before considering the addition of a nonstatin drug. When EPA and/or DHA are used to treat severe hypertriglyceridemia, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding (Stone et al, 2013).

Table 5. Advantages and Disadvantages of Omega-3 Fatty Acids

Drug	Advantages	Disadvantages
EPANOVA (omega-3-carboxylic acids)	• First FDA-approved prescription omega-3 in free fatty acid form • Can be taken with or without food • Dosing option may be as few as two capsules once daily	• May be associated with an increase in LDL-C levels • The effects of the agent on the risk of pancreatitis or cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia have not been determined.
LOVAZA, TRIKLO, and OMTRYG (omega-3-acid ethyl esters)	• Clinical trials have established that this agent is associated with a decrease in TG levels and select other lipid parameters.	• May be associated with an increase in LDL-C levels • The effects of the agent on the risk of pancreatitis or cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia have not been determined. • The absorption is greater when given with high-fat high-calorie meals. Since many patients with hypertriglyceridemia are advised to stick to a low-fat diet, this could negatively affect absorption.
VASCEPA (icosapent ethyl)	• Clinical trials have established that this agent is associated with a decrease in TG levels and select other lipid parameters. • May not be associated with an increase in LDL-C levels	• The effects of the agent on the risk of pancreatitis or cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia have not been determined.

REFERENCES

- Ballantyne CM, Bays HE, Kastelein JJ, et al. Efficacy and safety of eicosapentaenoic acid ethyl ester (AMR101) therapy in statin-treated patients with persistent high TGs (from the ANCHOR study). Am J Cardiol. 2012 Oct 1;110(7):984-92.
- Bays HE, Ballantyne CM, Kastelein JJ, et al. Eicosapentaenoic acid ethyl ester (AMR101) therapy in patients with very high triglyceride levels (from the Multi-center, plAcebo-controlled, Randomized, double-blINd, 12-week study with an open-label Extension [MARINE] trial). Am J Cardiol. 2011;108(5):682-90.
- Bays HE, Maki KC, McKenny J, et al. Long-term up to 24-month efficacy and safety of concomitant prescription omega-3-acid ethyl esters and simvastatin in hypertriglyceridemic patients. Curr Med Res Opin. 2010 Apr;26(4):907-15.
- Bays HE, McKenny J, Maki KC, et al. Effects of prescription omega-3-acid ethyl esters on non-high-density lipoprotein cholesterol when coadministered with escalating doses of atorvastatin. Mayo Clin Proc. 2010 Feb;85(2):122-8.
- Berglund L, Brunzell JD, Goldberg AC. Evaluation and treatment of hypertriglyceridemia: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2012;97(9):2969-2989.
- Calabresi L, Donati D, Pazzucconi F, et al. Omacor in familial combined hyperlipidemia: effects on lipids and low density lipoprotein subclasses. Atherosclerosis. 2000;148:387-96.
- Calabresi L, Villa B, Canavesi M, et al. An omega-3 polyunsaturated fatty acid concentrate increases plasma high-density lipoprotein 2 cholesterol and paraoxonase levels in patients with familial combined hyperlipidemia. Metabolism. 2004 Feb;53(2):153-8.
- Clinical Pharmacology [database on the Internet]. Gold Standard, 2017. Available from www.clinicalpharmacology.com. Accessed November 10, 2017.
- Davidson MH, Stein EA, Bays HE, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. Clin Ther. 2007 Jul;29(7):1354-67.
- Durrington PN, Bhatnagar D, Mackness MI, et al. An omega-3 polyunsaturated fatty acid concentrate administered for one year decreased triglycerides in simvastatin treated patients with coronary heart disease and persisting hypertriglyceridemia. Heart. 2001;85:544–548.
- Drugs@FDA [database on the Internet]. Rockville (MD): Food and Drug Administration (US), Center for Drug Evaluation and Research; 2017. Available from: http://www.accessdata.fda.gov/scripts/cder/daf/. Accessed November 10, 2017.
- EPANOVA prescribing information. AstraZeneca. Wilmington, DE. March 2017.
- Eritsland L, Arnesen H, Gronseth K, et al. Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. Am J Cardiol. 1996;77:31–36.
- Facts & Comparisons eAnswers [database on the Internet]. St. Louis, MO: Wolters Kluwer; 2017. Available from: https://fco.factsandcomparisons.com/. Accessed November 13, 2017.
- GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet. 1999 Aug 7;354(9177):447-55.
- Grundy SM, Cleeman JI, Merz NB, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation. 2004; 110:227-39.
- Hedengran A, Szecsi PB, Dyerberg J, Harris WS, Stender S. n-3 PUFA esterified to glycerol or as ethyl esters reduce non-fasting plasma triacylglycerol in subjects with hypertriglyceridemia: a randomized trial. Lipids. 2015;50(2):165-175.
- Hooper L, Harrison RA, Summerbell CD. Omega 3 fatty acids for prevention and treatment of cardiovascular disease. Cochrane Database Syst Rev. 2004;10:CD003177.

- Ishikawa Y, Yokoyama M, Saito Y, et al. Preventive effects of eicosapentaenoic acid on coronary artery disease in patients with peripheral artery disease. Circ J. 2010 Jul;74(7):1451-7.
- Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1—full report. J Clin Lipidol. 2015;9(2):129-169.
- Jellinger PS, Smith DA, Mehta AE, et al. American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis. Endocr Pract. 2012 Mar-Apr;18 Suppl 1:1-78.
- Johansen O, Brekke M, Seljeflot I, et al., Coronary Angioplasty Restenosis Trial. n-3 fatty acids do not prevent re stenosis after coronary angioplasty: Results from the CART study. J Am Coll Cardiol. 1999; 33:1619–1626.
- Kastelein JJ, Maki KC, Susekov A, et al. Omega-3 free fatty acids for the treatment of severe hypertriglyceridemia: the EpanoVa fOr Lowering Very high triglyceridEs (EVOLVE) trial. J Clin Lipidol. 2014;8(1):94-106. doi: 10.1016/j.jacl.2013.10.003.
- Koh KK, Quon MJ, Shin KC, et al. Significant differential effects of omega-3 fatty acids and fenofibrate in patients with hypertriglyceridemia. Atherosclerosis. 2012;220:537-44.
- Kurabayashi T, Okada M, Tanaka K. Eicosapentaenoic acid effect on hyperlipidemia in menopausal Japanese women. The Niigata Epadel Study Group. Obstet Gynecol. 2000 Oct;96(4):521-8.
- Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular risk. J Am Coll Cardiol. 2016;68(1):92-125.
- Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *J Am Coll Cardiol*. 2017 Oct;70(14):1785-1822.
- LOVAZA prescribing information. GlaxoSmithKline, Research Triangle Park, NC. September 2015.
- Macchia A, Grancelli H, Varini S, et al. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) trial. J Am Coll Cardiol. 2013 Jan 29;61(4):463-8. doi: 10.1016/j.jacc.2012.11.021.
- Maki KC, Dicklin MR, Davidson MH, et al. COMBination of prescription omega-3 with simvastatin (COMBOS) Investigators. Am J Cardiol. 2010 May;105(10):1409-12.
- Maki KC, McKenny JM, Reeves MS, et al. Effects of adding prescription omega-3 acid ethyl esters to simvastatin (20 mg/day) on lipids and lipoprotein particles in men and women with mixed dyslipidemia. Am J Cardiol. 2008;102:429-33.
- Maki KC, Orloff DG, Nicholls SJ, et al. A highly bioavailable omega-3 free fatty acid formulation improves the cardiovascular risk profile in high-risk, statin-treated patients with residual hypertriglyceridemia (the ESPRIT trial). Clin Ther. 2013;35(9):1400-11.e1-3. doi: 10.1016/j.clinthera.2013.07.420.
- Matsuzaki M, Yokoyama M, Saito Y, et al. Incremental effects of eicosapentaenoic acid on cardiovascular events in statin-treated patients with coronary artery disease. Circ J. 2009 Jul;73(7):1283-90.
- McCrindle BW, Urbina EM, Dennison BA, et al. Drug therapy of high-risk lipid abnormalities in children and adolescents: a scientific statement from the American Heart Association Atherosclerosis, Hypertension, and Obesity in Youth Committee, Council of Cardiovascular Disease in the Young, with the Council on Cardiovascular Nursing. Circulation. 2007 Apr;115(14):1948-67.
- McKeone BJ, Osmundsen K, Brauchi D, Pao Q, Payton-Ross C, Kilinc C, et al. Alterations in serum phosphatidylcholine fatty acyl species by eicosapentaenoic and docosahexaenoic ethyl esters in patients with severe hypertriglyceridemia. J Lipid Res. 1997;38:429-36.
- Micromedex [database on the Internet]. Greenwood Village, CO: Truven Health Analytics; 2017. Available from: http://www.micromedexsolutions.com. Accessed November 13, 2017.
- Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011;123(20):2292-2333.
- Nakamura N, Hamazaki T, Ohta M, et al. Joint effects of HMG-CoA reductase inhibitors and eicosapentaenoic acids on serum lipid profile and plasma fatty acid concentrations in patients with hyperlipidemia. Int J Clin Lab Res. 1999;29(1):22-5.
- National Cholesterol Education Program (NCEP). Detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III) final report, 2002 [guideline on the internet]. Available at: https://www.nhlbi.nih.gov/files/docs/guidelines/atp3xsum.pdf. Accessed November 13, 2017.
- Nilsen DWT, Albrelasen G, Landmark K, et al. Effects of a high-dose concentration of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. Am J Clin Nutr. 2001;74:50–56.
- Nordoy A, Bonaa KH, Nilsen H, et al. Effects of simvastatin and omega-3 fatty acids on plasma lipoproteins and lipid peroxidation in patients with combined hyperlipidemia. J Intern Med. 1998;243:163–170.
- Oikawa S, Yokoyama M, Origasa H, et al. Suppressive effect of EPA on the incidence of coronary events in hypercholesterolemia with impaired glucose metabolism: Sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis. 2009 Oct;206(2):535-9. doi: 10.1016/j.atherosclerosis.2009.03.029.
- OMTRYG prescribing information. Trygg Pharma, Inc. Arlington, VA. March 2016.
- Origasa H, Yokoyama M, Matsuzaki M, et al. JELIS Investigators. Clinical importance of adherence to treatment with eicosapentaenoic acid by patients with hypercholesterolemia. Circ J. 2010 Mar;74(3):510-7.
- Peters BS, Wierzbicki AS, Moyle G, et al. The effect of a 12-week course of omega-3 polyunsaturated fatty acids on lipid parameters in hypertriglyceridemic adult HIV-infected patients undergoing HAART: a randomized, placebo-controlled pilot trial. Clin Ther. 2012;34:67-76.
- Pownall HJ, Brauchi D, Kilinc C, et al. Correlation of serum triglyceride and its reduction by omega-3 fatty acids with lipid transfer activity and the neutral lipid compositions of high-density and low-density lipoproteins. Atherosclerosis. 1999;143:285-97.
- Risk and Prevention Study Collaborative Group, Roncaglioni MC, Tombesi M, Avanzini F, et al. n-3 fatty acids in patients with multiple cardiovascular risk factors. N Engl J Med. 2013 May 9;368(19):1800-8. doi: 10.1056/NEJMoa1205409.
- Roth EM, Bays HE, Forker AD, et al. Prescription omega-3 fatty acid as an adjunct to fenofibrate therapy in hypertriglyceridemic patients. J Cardiovasc Pharmacol. 2009;54:196-203.

- Saito Y, Yokoyama M, Origasa H, et al. Effects of EPA on coronary artery disease in hypercholesterolemic patients with multiple risk factors: sub-analysis of primary prevention cases from the Japan EPA Lipid Intervention Study (JELIS). Atherosclerosis. 2008 Sep;200(1):135-40. doi: 10.1016/j.atherosclerosis.2008.06.003.
- Sasaki J, Yokoyama M, Matsuzaki M, et al. Relationship between coronary artery disease and non-HDL-C, and effect of highly purified EPA on the risk of coronary artery disease in hypercholesterolemic patients treated with statins: sub-analysis of the Japan EPA Lipid Intervention Study (JELIS). J Atheroscler Thromb. 2012;19(2):194-204.
- Smith SC Jr, Benjamin EJ, Bonow RO, et al. AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. J Am Coll Cardiol. 2011 Nov 29;58(23):2432-46.
- Stalenhoef AFH, de Graaf J, Wittekoek ME, et al. The effect of concentrated n-3 fatty acids vs gemfibrozil on plasma lipoproteins, low density lipoprotein heterogeneity and oxidizability in patients with hypertriglyceridemia. Atherosclerosis. 2000;153:129-38.
- Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American College of Cardiology/American Heart Association. Circulation. 204;129(25 Suppl 2):S1-S45.
- Tanaka K, Ishikawa Y, Yokoyama M, et al. Reduction in the recurrence of stroke by eicosapentaenoic acid for hypercholesterolemic patients: subanalysis of the JELIS trial. Stroke. 2008 Jul;39(7):2052-8. doi: 10.1161/STROKEAHA.107.509455.
- TRIKLO prescribing information. Key Therapeutics, LLC. Flowood, MS. August 2017.
- Van Dam M, Stalenhoef AFH, Wittekoek J, et al. Efficacy of concentrated omega-3 fatty acids in hypertriglyceridemia: A comparison with gemfibrozil. Clin Drug Invest. 2001;21:175–181.
- VASCEPA prescribing information. Amarin Pharma Inc. Bedminster, NJ. February 2017.
- Woolley T, Canoniero M, Conroy W, et al. Institute for Clinical Systems Improvement. Lipid Management in Adults. Updated February 2017. Available at: https://www.icsi.org/_asset/qz5ydq/LipidMgmt-Interactive1111.pdf. Accessed November 13, 2017.
- Yokoyama M, Origasa H, Matsuzaki M, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007 Mar 31;369(9567):1090-8.

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