

Omega-3-Acid Ethyl Esters A (Omtryg®)

National Drug Monograph

January 2015

**VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives**

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

Efficacy:

- Omega-3-acid ethyl esters A (Omtryg®) is an omega-3 fatty acid (omega-3 FA), containing $\geq 75\%$ omega-3-acid ethyl esters, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that has been approved by the Food and Drug Administration (FDA) as an adjunct to diet for the reduction of triglyceride (TG) levels in adults with severe hypertriglyceridemia (TG ≥ 500 mg/dL).
- The recommended daily dose is 4 capsules, (4.8g)/day, taken as a single dose or divided twice daily with food. Capsules should be swallowed whole. Each capsule contains at least 900 mg EPA+DHA.
- A randomized, double-blind, placebo-controlled trial of 254 patients with hypertriglyceridemia compared the efficacy of omega-3-acid ethyl esters A and omega-3-acid ethyl esters to placebo. Compared to placebo, omega-3-acid ethyl esters A demonstrated a statistically significant decrease in TG and VLDL-C, 12.2% and 28.7% respectively. Omega-3-Acid Ethyl esters also demonstrated a statistically significant decrease in TG and VLDL, reducing TG by 14% and VLDL-C by 23.7%. No significant change in other endpoints (Non-HDL-C, TC, and HDL-C) was demonstrated; except for a statistically significant increase in LDL-C for both omega-3-acid ethyl esters A (24.7%) and omega-3-acid ethyl esters (18.9%).
- The effect of omega-3-acid ethyl esters A on the risk for pancreatitis in patients with severely elevated TG levels (≥ 500 mg/dL) has not been evaluated.
- The effect of omega-3-acid ethyl esters A on cardiovascular morbidity or mortality has not been evaluated.
- There have been no studies comparing omega-3-acid ethyl esters A to other marketed TG lowering medications at this time (e.g. niacin, fibrates), aside from omega-3-acid ethyl esters.

Safety:

- Omega-3-acid ethyl esters A is generally well tolerated with a safety profile similar to placebo.
- Eructation, dyspepsia, and taste perversion were reported in 3-4% of patients receiving omega-3-acid ethyl esters A, occurring more frequently than those receiving placebo.
- It is unknown whether patients with fish and/or shellfish allergies are at an increased risk for allergic reactions with the use of omega-3-acid ethyl esters A and caution should be exercised in those with a known hypersensitivity.
- Safe and effective use has not been evaluated in pediatric patients, patients with renal or hepatic insufficiency, lactating women or pregnancy.
- LFTs should be monitored periodically in patients with hepatic impairment during omega-3-acid ethyl esters A therapy. In clinical trials, some patients experienced an increase in ALT without a simultaneous increase in AST levels.
- Omega-3-acid ethyl esters A may increase LDL levels and periodic monitoring is recommended.
- Omega-3 FA can inhibit cyclo-oxygenase, decreasing platelet aggregation and theoretically increasing the risk for bleeding. However, inconsistent results exist concerning the effects of fish oil supplements on bleeding risk. The FDA states that EPA and DHA demonstrate small, dose-related increases in bleeding time, which are of no clinical significance in doses of 3g/day or less

of EPA plus DHA. The effect of omega-3-acid ethyl esters A on bleeding time has not been studied. Therefore, patients on anticoagulation therapies or other drugs affecting coagulation should be periodically monitored while on omega-3-acid ethyl esters A.

- There is a potential correlation with omega-3-acid ethyl esters and higher rates of symptomatic atrial fibrillation or flutter recurrence in patients with a history of paroxysmal or persistent AF, especially within the initial 2-3 months of beginning therapy.
- ***Omtryg® has not been launched for marketing at the time the monograph was written. Launch date is unknown (personal communication with manufacturer).***

Introduction

Omega-3-acid ethyl esters A is an omega-3 fatty acid containing predominantly omega-3-acid ethyl esters, which gained FDA approval in 2014. It was approved as an adjunct to diet for reducing triglycerides in adult patients with severe hypertriglyceridemia (≥ 500 mg/dL).

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating omega-3-acid ethyl esters A for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in VA.

Pharmacology/Pharmacokinetics¹

The mechanism of action of omega-3-acid ethyl esters A is not completely understood. The following are the current proposed mechanisms of triglyceride lowering: inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase, increased β -oxidation due to enhanced action of mitochondria and peroxisomes in the liver, or enhanced plasma lipoprotein lipase activity. Additionally, omega-3-acid ethyl esters A are comprised of EPA and DHA, which may decrease synthesis of triglycerides through inhibition of esterification of fatty acids and inhibition of other enzymes involved in the production of triglycerides.

The only reported pharmacokinetic data available is bioavailability. Under fed conditions, patients on average experienced peak (C_{max}) and total (AUC_{0-72h}) exposure that was significantly greater than those observed under fasting conditions after administration of omega-3-acid ethyl esters A. Total plasma EPA demonstrated a 20 to 80-fold decrease and total DHA demonstrated a 2-4 fold decrease under fasting conditions.

FDA Approved Indication¹

Omega-3-acid ethyl esters A is FDA approved as an adjunct therapy to diet and exercise for the reduction of TG levels in adult patients with severe hypertriglyceridemia (≥ 500 mg/dL).

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. Address the VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Given similarities between omega-3-acid ethyl esters A and omega-3 FAs, potential off-label uses for this medication may include: prevention of cardiovascular disease, psoriasis, pancreatitis, macular degeneration, mood disorders, rheumatoid arthritis, glomerular kidney disease, dry eye syndrome, etc.

Cardiovascular Disease: There is conflicting evidence for the use of omega-3 FAs in the prevention and treatment of cardiovascular disease. A large, randomized clinical trial, a meta-analysis, and a systematic review demonstrated that the consumption of omega-3 FAs led to reductions in cardiovascular events (coronary heart disease and cardiovascular death).²⁻⁵ Alternatively, more recent studies and meta-analyses have not shown omega-FA supplementation to be associated with lower risks of mortality, cardiac death,

MI, or stroke. Based on the conflicting data mentioned above, the overall impact of omega-3 FAs on cardiovascular outcomes is unclear.^{6,7} Questions from researchers focus on whether the insignificant outcomes of some trials are a result of inadequate powering of studies, low event rates, improved medical therapies for cardiovascular events or if a true lack of benefit of omega-3 FA on cardiovascular health exists.⁸

The American Heart Association (AHA) supports daily consumption of 1 gram of EPA/DHA by patients with documented coronary heart disease, preferably by consumption of fatty fish. Individuals with low dietary intake of fatty fish may be recommended supplementation with omega-3 FAs. Dietary omega-3 FA is the preferred source versus supplementation due to the enhanced absorption offered from natural sources. The AHA recognizes conflicting evidence exists for omega-3 FA use to reduce and prevent cardiovascular disease, and recommend additional trials with broad objectives be conducted in order to determine if omega-3 FA supplementation benefits cardiovascular health.⁹

Other Uses: Omega-3 FAs have been studied as both primary and adjunctive therapy in disease states such as: rheumatoid arthritis, pancreatitis, macular degeneration, psoriasis, mood disorders, dry eye syndrome and glomerular kidney disease. The results demonstrating efficacy of omega-3 FAs in these particular diseases originate from a small number of trials and also from trials showing conflicting data. Further research must be conducted prior to considering omega-3 FAs or omega-3-acid ethyl esters A for use in treatment of these disease states as a result.¹⁰

Current VA National Formulary Alternatives

National formulary alternatives for the management of hypertriglyceridemia include fish oil, niacin and gemfibrozil. When triglyceride-reducing therapies are used in combination with statins, the PBM-MAP-VPEs recommend considering fish oil supplements. Fibrate + statin combinations are not recommended for use within the VA due to increased risk of adverse drug events, specifically muscle related events, and a lack of evidence suggesting benefit beyond treatment with statins.

Dosage and Administration¹

Lifestyle changes (e.g. cessation of alcohol, weight loss, exercise, dietary modification) should be instituted prior to initiation of omega-3-acid ethyl esters A. Additionally, elevated triglyceride levels should be carefully assessed and secondary causes of hypertriglyceridemia (e.g. poorly controlled diabetes mellitus, nephrotic syndrome, alcoholism, and hypothyroidism) should be managed as appropriate. Common drug-induced causes of hypertriglyceridemia should also be considered including protease inhibitors, corticosteroids, estrogens, beta-blockers, and thiazide diuretics.

The recommended daily dose of omega-3-acid ethyl esters A for the treatment of hypertriglyceridemia (TG \geq 500 mg/dL) is 4 capsules (each capsule containing at least 900 mg EPA+DHA) by mouth daily as a single or in a divided dose with meals. Capsules should be swallowed whole; do not crush, open, chew or dissolve.

Efficacy¹

Efficacy Measure

A randomized, double-blind, placebo-controlled trial evaluated the percent change in triglyceride levels from baseline to 12 weeks when omega-3-acid ethyl esters A was compared to placebo or omega-3-acid ethyl esters as their primary efficacy endpoint. Secondary endpoints included percent change in non-high density lipoprotein cholesterol (non-HDL-C), very low density lipoprotein cholesterol (VLDL-C), low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C).

Summary of efficacy finding¹

Omega-3-acid ethyl esters A contains ethyl esters of omega-3 FA of both EPA and DHA. The FDA approved this medication on April 23, 2014 as an adjunct to diet and exercise for the reduction of triglyceride levels in adult patients with severe hypertriglyceridemia (≥ 500 mg/dL). Despite omega-3-acid ethyl esters A reducing triglyceride levels, there is a lack of evidence supporting an association between consumption of omega-3-acid ethyl esters A and a reduction in the risk of pancreatitis or cardiovascular morbidity or mortality in patients with severe hypertriglyceridemia. The studies summarized below are not published but are included in the prescribing information.

A randomized, double-blind, placebo controlled study involving 254 patients with severe hypertriglyceridemia (500-1500 mg/dL) was conducted. In this study, there was an initial 6-week wash-out/dietary lead-in period for enrolled patients. After the lead in, patients were advanced to a 12-week treatment period and were randomized to three groups: omega-3-acid ethyl esters A, omega-3-acid ethyl esters, or placebo (vegetable oil) with each medication being administered as 4 capsules daily. Baseline characteristics showed that patients were predominantly Caucasian males (92% Caucasian, 72% male) with an average age of 51 years, an average BMI of 33 kg/m², and only 21% were on statin therapy. Baseline median TG was 675 mg/dL, mean HDL-C was 30 mg/dL, and mean LDL-C was 87 mg/dL.

The primary endpoint was the placebo-corrected median percent change in serum triglycerides (TG) from baseline to week 12. Secondary endpoints were percent change in non-HDL-C, VLDL-C, LDL-C, and HDL-C from baseline to week 12.

Results showed a statistically significant, placebo-corrected reduction in TGs in both the omega-3-acid ethyl esters A and omega-3-acid ethyl ester group (12.2% and 14.0% reduction respectively, $p < 0.05$ vs. placebo). Significant reductions in VLDL-C were also observed (28.7% [$p < 0.01$ vs. placebo] and 23.7%, [$p < 0.05$ vs. placebo], respectively. However, there was a statistically significant increase in placebo-corrected LDL-C in both the omega-3-acid ethyl esters A and omega-3-acid ethyl ester group (24.7% and 18.9% increase, $p < 0.01$ and $p < 0.05$ respectively vs. placebo).

This trial demonstrated that omega-3-acid ethyl esters A and omega-3-acid ethyl esters significantly reduce TG levels versus placebo and improve other lipid parameters but also caused a significant increase in LDL-C levels.

A second set of trials was conducted to assess the effects of omega-3-acid ethyl esters versus placebo. Eighty-four patients, with baseline hypertriglyceridemia (500-2000 mg/dL), were randomized to receive omega-3-acid ethyl esters (listed as Omtryg® or omega-3 FA) or placebo and followed for 6 weeks and 16 weeks. In the omega-3-acid ethyl esters group, TGs were reduced 44.9 % from baseline; 51.6% lower than placebo (placebo-corrected). The omega-3-acid ethyl esters group also showed a decrease from baseline in non-HDL-C, TC, and VLDL-C (-13.8%, -9.7%, and -41.7%, respectively), which was lower than placebo by -10.2%, -8.0%, and -40.8%, respectively. Omega-3-acid also increased HDL-C by 9.1% compared to placebo, which showed no change in HDL-C. Statistical significance was not reported.

Adverse Events (Safety Data)¹

Adverse Reactions Occurring in Clinical Studies of Omega-3-Acid Ethyl Esters

Body System Adverse Reaction	Omega-3-Acid Ethyl Esters* (N=665)	Placebo (N=370)
Eructation	4%	1%
Dyspepsia	3%	2%
Taste perversion	4%	<1%

*Includes both Omtryg® and omega-3-acid ethyl esters

Other adverse events reported in clinical trials included constipation, gastrointestinal disorder, vomiting, increased ALT and AST, pruritus, and rash, however frequency was not reported.

Contraindications¹

Omega-3-acid ethyl esters A is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to omega-3-acid ethyl esters or any component of omega-3-acid ethyl esters A.

Warnings and Precautions¹

Hypersensitivity: It is unknown whether patients with fish and/or shellfish allergies are at an increased risk of an allergic reaction to omega-3-acid ethyl esters A. This medication should be used with caution in this particular patient population.

Hepatic impairment: AST and ALT levels should be monitored periodically during therapy with omega-3-acid ethyl esters A in patients with hepatic impairment. In some cases, increases in ALT levels occurred without an observed increase in AST levels.

LDL cholesterol: It has been observed that some patients taking omega-3-acid ethyl esters A may have increases in LDL-cholesterol levels. LDL-cholesterol levels should be periodically monitored while taking this medication.

Recurrent Atrial Fibrillation (AF) or Flutter: Omega-3-acid ethyl esters A is not indicated for the treatment of AF or flutter. It has been observed that patients with pre-existing symptomatic paroxysmal AF or persistent AF had higher rates of recurrent AF or flutter while taking omega-3-acid ethyl esters versus placebo. There is a potential correlation with omega-3-acid ethyl esters and higher rates of symptomatic AF or flutter recurrence in patients with a history of paroxysmal or persistent AF, especially within the initial 2-3 months of beginning therapy.

Special Populations^{1,10}

Pregnancy: Pregnancy category C. No well-controlled studies have been conducted in pregnant women. Studies have been conducted in lab animals and demonstrated numerous fetal adverse events when doses were given that resulted in exposures seven times above the recommended human dose. Due to the overall lack of evidence-based studies focused on pregnant women, it is unknown if omega-3-acid ethyl esters A causes harm to the fetus or affects human reproduction. Risk versus benefits should be evaluated before considering omega-3-acid ethyl esters A use during pregnancy.

Lactation: Studies with omega-3-acid ethyl esters have shown excretion in human milk, yet the effect of this excretion on the infant is unknown. A study in lactating rats given oral gavage of 14-C-ethyl EPA determined that drug levels were 6-14 times higher in milk than plasma. Caution should be exercised when administering omega-3-acid ethyl esters A to nursing mothers.

Pediatrics: Use has not been established in pediatric patients.

Geriatrics: In subjects >60 years old, the safety and efficacy findings did not differ from findings in subjects <60 years old. However, it is important to note that older patients have potentially greater sensitivity to this medication.

Renal Impairment: Use has not been evaluated in patients with renal insufficiency. Neither EPA nor DHA are renally eliminated.

Hepatic Impairment: Use has not been evaluated in patients with hepatic insufficiency; however, limited evidence has shown increased LFTs. Periodic monitoring of ALT and AST is recommended in patients with known hepatic impairment.

Postmarketing Safety Experience (Optional)

No safety concerns were noted in the prescribing information that would require specific post-marketing safety evaluation. Spontaneous post-marketing reports of adverse reactions related to use of omega-3-acid ethyl esters, not specific to omega-3-acid ethyl esters A, include anaphylactic reaction and hemorrhagic diathesis.

Sentinel Events

After an extensive search of the literature, no sentinel events have been identified that were directly attributable to omega-3-acid ethyl esters A.

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

As part of a Joint Commission standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

LA/SA for generic name <Omega-3-acid ethyl esters>: <Omega-3 carboxylic acids>

LA/SA for trade name <Omtryg>: <Onglyza>

Drug Interactions^{1,11,12}

Drug-Drug Interactions:

Anticoagulants: Some studies involving omega-3-acids have resulted in prolonged bleeding times. The prolonged bleeding times from these studies did not exceed normal limits, nor did it cause clinically significant bleeding episodes. Clinical studies to thoroughly evaluate the effect of omega-3-acid ethyl esters A and concomitant anticoagulants have not been done. Patients receiving omega-3-acid ethyl esters A and an anticoagulant or other medication for coagulation (e.g., antiplatelets, NSAIDs, warfarin) should be monitored often.

Statins: No drug interactions were observed in healthy adults when 4 grams of omega-3-acid ethyl esters were co-administered with simvastatin, atorvastatin, or rosuvastatin.

Cytochrome P450: In vitro studies utilizing human liver microsomes did not find significant cytochrome P450 mediated inhibition by EPA/DHA.

Acquisition Costs

Refer to VA pricing sources for updated pricing

Pharmacoeconomic Analysis

There are no published pharmacoeconomic analyses available.

Conclusion

Omega-3-acid ethyl esters A (Omtryg®) is a combination product containing both EPA and DHA and was FDA approved as an adjunct therapy to diet and exercise for the reduction of triglyceride levels in adult patients with severe hypertriglyceridemia (≥ 500 mg/dL) at a dose of 4.8 g/day (4 capsules daily), taken once daily or in divided doses with meals.

A randomized, double-blind, placebo controlled study consisting of 254 patients with severe hypertriglyceridemia (≥ 500 to <1500 mg/dL) demonstrated a statistically significant reduction in triglyceride levels in patients taking 4 capsules/day of omega-3-acid ethyl esters A versus placebo. Patients were randomized to 4 capsules/day omega-3-acid ethyl esters A, omega-3-acid ethyl esters, or placebo for 12 weeks following an initial 6-week washout period. Omega-3-acid ethyl esters A use resulted in a 12.2% placebo-corrected median reduction in triglycerides from baseline at 12 weeks ($p<0.05$) and omega-3-acid ethyl esters reduced by 14% ($p<0.05$) from baseline. Also, this study showed a statistically significant placebo-corrected increase in LDL-C levels with use of omega-3-acid ethyl esters A and omega-3-acid ethyl esters versus placebo (24.7% $p<0.01$ and 18.9% $p<0.01$, respectively).

An additional randomized, double-blind, placebo controlled trial was conducted to assess the effects of omega-3-acid ethyl esters (Omtryg® and other omega-3-acid ethyl esters) versus placebo on lipids. Eighty-four patients, with baseline hypertriglyceridemia (500-2000 mg/dL), were randomized to receive omega-3-acid ethyl esters or placebo and followed for 6 weeks and 16 weeks. Those treated with 4 capsules/day of omega-3-ethyl esters showed a 51.6% decrease in TG compared to those treated with placebo. The omega-3-acid ethyl esters group also had a decrease in non-HDL-C, TC, and VLDL-C and an increase in HDL-C. Statistical significance was not reported.

Adverse events reported from pooled data across 23 clinical trials for omega-3-acid ethyl esters (including Omtryg® as well as omega-3-acid ethyl esters) were mostly gastrointestinal in nature and were reported at higher rates than placebo. Adverse events included: eructation (4%), dyspepsia (3%), and taste perversion (4%) as the most common adverse reactions. As with other fish oil products, patients receiving concomitant anticoagulants should be closely monitored because of the potential increased risk for bleeding.

There are no studies examining the effect of omega-3-acid ethyl esters A on cardiovascular outcomes or for the prevention of pancreatitis in patient with very high TG levels. There have been no studies comparing omega-3-acid ethyl esters A to any other marketed TG lowering medications (e.g., niacin or fibrates) at this time, aside from omega-3-acid ethyl esters.

References:

1. Omtryg® (omega-3-acid ethyl esters A) [prescribing information]. Arlington, VA: Trygg Pharma Inc; April 2014.
2. He K, Song Y, Daviglius ML, et al. Accumulated evidence on fish consumption and coronary heart disease mortality: a meta-analysis of cohort studies. *Circulation* 2004;109:2705-2711.
3. Leon H, Shibata MC, Sivakumaran S, et al. Effect of fish oil on arrhythmias and mortality: systematic review. *BMJ* 2008;337:a2931.
4. Marik PE, Varon J. Omega-3 dietary supplements and the risk of cardiovascular events: a systematic review. *Clin Cardiol* 2009;32:365-372.
5. Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med* 2009;169:659-669.
6. Rizos EC, Ntzani EE, Bika E, et al. Association Between Omega-3 Fatty Acid Supplementation and Risk of Major Cardiovascular Disease Events: A Systematic Review and Meta-analysis. *JAMA* 2012;308(10):1024-1033.
7. Kotwal S, Jun M, Sullivan D, et al. Omega 3 Fatty Acids and Cardiovascular Outcomes: Systematic Review and Meta-analysis. *Circ Cardiovasc Qual Outcomes* 2012;5(6):808-818.

8. Marchioli R, Levantesi G. n-3 PUTFAs in cardiovascular disease. *Int J Cardiol* 2013. <http://dx.doi.org/10.1016/j.ijcard.2013.06.042>. Accessed: November 10, 2014.
9. Smith Jr SC, 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. *Circulation* 2011;124:2458-2473.
10. Omega-3 fatty acids. Micromedex 2.0. http://www.micromedexsolutions.com/micromedex2/librarian/ND_T/evidencexpert/ND_PR/evidencexpert/CS/0B4CCD/ND_AppProduct/evidencexpert/DUPLICATIONSHIELDSYNC/3F1AC1/ND_PG/evidencexpert/ND_B/evidencexpert/ND_P/evidencexpert/PFActionId/evidencexpert.IntermediateToDocumentLink?docId=3899-v&contentSetId=30&title=Omega-3+Fatty+Acids&servicesTitle=Omega-3+Fatty+Acids. Accessed: November 10, 2014.
11. Vanschoonbeek K, Feijge M, Paquay M, et al. Variable Hypocoagulant Effect of Fish Oil Intake in Humans. Modulation of Fibrinogen Level and Thrombin Generation. *Sterioscler Thromb Vasc Biol* 2004;24:1734-1740.
12. Knapp HR. Dietary Fatty Acids in Human Thrombosis and Hemostatis. *Am J Clin Nutr* 1997;65(5 Suppl):1687S-1698S.

Prepared December 2014 by Megan Jacobson, PharmD; Evan Robb, PharmD; Megan Casares, PharmD; Jared Hrdy, PharmD; Michaela Hrdy, PharmD; and reviewed by Catherine Kelley, PharmD. PBM contact: Catherine.kelley@va.gov

For the purposes of clarification, Omega-3-Acid Ethyl Esters and Omega-3 fatty acids (FA) are interchangeable terms within this document. Omega-3-Acid Ethyl Esters A refers specifically to Omtryg®.