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 Documents will be placed in the Archive section when the information is deemed to be no longer current.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 carboxylic acids (OM3-CA [Epanova®]) is the first omega-3 free fatty acid to be approved by the Food and Drug Administration (FDA) as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe hypertriglyceridemia (≥ 500mg/dL).
- OM3-CA is comprised of a combination of polyunsaturated fatty acids, including 50-60% eicosapentaenoic acid (EPA) and 15-25% docosahexaenoic acid (DHA). Each capsule contains at least 850 mg polyunsaturated fatty acids with EPA and DHA being most plentiful.
- The recommended daily dosage of OM3-CA is 2 grams (2 capsules) or 4 grams (4 capsules) once daily without regard to meals. Capsules should be swallowed whole; crushing, chewing, and dissolving should be avoided.
- The ECLIPSE study assessed the bioavailability of OM3-CA 4g daily and omega-3-acid ethyl esters (OM3-EE [Lovaza®]) 4g daily with regards to low- and high-fat meal consumption. The relative bioavailability was greater in the group receiving OM3-CA with a high-fat meal.
- EVOLVE, a phase 2/3 trial, evaluated the efficacy of olive oil 4g/d, OM3-CA 2g/d plus olive oil 2g/d, OM3-CA 3g/d plus olive oil 1g/d, and OM3-CA 4g/d for the treatment of severe hypertriglyceridemia (≥ 500 but < 2000mg/dL). There were significant reductions in triglyceride (TG) levels from baseline (ranging from 25-30%) for the active treatments vs. olive oil (4.3%); however, low-density lipoprotein cholesterol (LDL-C) levels were increased in all dose groups. Significant reductions in non-high density lipoprotein cholesterol (non-HDL-C) and a number of other serum lipid levels were observed in the active treatments vs. control, including very low density lipoprotein cholesterol (VLDL-C).
- ESPRIT, a phase 3 trial, investigated OM3-CA (2- or 4-g daily) in statin-treated patients, who were at an increased risk for cardiovascular disease, for the treatment of persistent hypertriglyceridemia (≥ 200 but < 500mg/dL). The results demonstrated that treatment with OM3-CA significantly decreased non-HDL-C levels (2 grams: -3.9% and 4 grams: -6.9% vs. -0.9% control) and TG levels (2 grams: -14% and 4 grams: -20.6% vs. -5.9% control, p<0.001); however, in the patients receiving 2g daily, LDL-C levels were statistically increased versus control (4.6% vs. 1.1%, p=0.025) but not in the 4g daily group.
- The effect of OM3-CA on reducing the risk of pancreatitis in adults with severe hypertriglyceridemia (≥ 500mg/dL) has yet to be determined.
- Currently, no data exist to support an effect of OM3-CA on cardiovascular morbidity and mortality. In October 2014, a phase III, randomized, double-blind study began to recruit patients with hypertriglyceridemia and a high risk for cardiovascular disease. The STRENGTH trial will enroll approximately 13,000 patients to evaluate the efficacy of OM3-CA in combination with statin therapy compared to corn oil in reducing the risk of major adverse events, including cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, emergent/elective coronary revascularization and hospitalization for unstable angina. Results are expected in June 2019.
- EVOLVE II is a phase 3 study that is currently recruiting patients in an effort to assess the efficacy and safety of OM3-CA as an adjunct to diet for reducing TG levels in adult patients with severe hypertriglyceridemia (500 to <2500 mg/dL). The estimated date of completion is December 2015.
• There are currently no studies directly comparing OM3-CA with other omega-3 fatty acid formulations or other triglyceride lowering therapies (e.g., niacin or fibrates) in patients with severe hypertriglyceridemia.

Safety:
• OM3-CA is generally well tolerated with a safety profile similar to olive oil.
• According to adverse event data pooled from the EVOLVE and ESPRIT trials, diarrhea, nausea, abdominal pain or discomfort and eructation were reported in > 3% of patients receiving OM3-CA acids.
• It is not known whether patients with fish and/or shellfish allergies are at an increased risk for experiencing allergic reactions to OM3-CA. Caution should be exercised when using in patients with a known hypersensitivity to fish and/or shellfish.
• Safe and effective use has not been established in patients with hepatic or renal insufficiency.
• Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels should be monitored periodically in patients with hepatic dysfunction.
• In the ESPRIT trial, patients who received 2g daily of OM3-CA plus 2g daily of olive oil experienced significantly higher LDL-C levels than those receiving OM3-CA 4g daily or olive oil 4g daily. As a result, it is recommended to occasionally monitor LDL-C levels in patients receiving therapy with OM3-CA.
• Results published from previous studies demonstrated prolonged bleeding time with omega-3 fatty acids. Thus, patients receiving single agent OM3-CA or in combination with other medications affecting coagulation should be monitored periodically.
• OM3-CA is pregnancy category C and should only be used during pregnancy if the potential benefit to the patient is greater than the potential risk to the fetus. Safety and efficacy has not been established in patients who are pregnant or in patients who are nursing.
• *Epanova®* has not been launched for marketing at the time the monograph was completed. Launch date is unknown (personal communication with manufacturer).

**Introduction**

In 2014, omega-3 carboxylic acids (OM3-CA) became the first free fatty acid form of the long-chain omega-3 fatty acids (EPA and DHA) to gain FDA approval as an adjunct to diet to reduce triglyceride levels in adult patients with severe hypertriglyceridemia (≥ 500mg/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 carboxylic acids for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

**Pharmacology/Pharmacokinetics**

The mechanism of action of omega-3 carboxylic acid is not fully known; however, several mechanisms have been proposed to explain the lipid-reducing properties of OM3-CA. These include acyl coenzyme A (CoA)-1,2 diacylglycerol acyltransferase (DGAT) inhibition, increased activity of plasma lipoprotein lipase, increased mitochondrial and peroxisomal beta-oxidation in the liver, and decreased lipogenesis in the liver. EPA and DHA are weak substrates for the enzymes associated with TG synthesis in the liver; subsequently, TG synthesis occurring in the liver may be decreased by OM3-CA.

Following oral administration of OM3-CA, it is absorbed in the small intestine and enters systemic circulation through the thoracic duct lymphatic system. After 2 weeks of continuous administration with OM3-CA 4g daily in combination with a reduced-fat diet, the peak plasma concentrations are reached after 5-8 hours for total EPA and 5-9 hours for total DHA. Plasma steady-state concentrations of EPA and DHA are generally achieved following 2 weeks of continuous administration of OM3-CA.
ECLIPSE I and ECLIPSE II were two pharmacokinetic studies conducted to assess the relative bioavailability of EPA and DHA. ECLIPSE I compared a single 4g dose of OM3-CA to OM3-EE (Lovaza®) 4g/d with regards to high- and low-fat meal consumption. The intent of the study was to show that OM3-CA exhibited a greater bioavailability during low-fat meal consumption vs. OM3-EE. During a low fat meal, AUC(0-T) for total EPA+DHA was 4-fold higher with OM3-CA vs. OME-EE (P<0.0001) but only 1.3 fold higher when consumed with a high fat meal (p<0.0001). ECLIPSE II compared OM3-CA 4g daily vs OM3-EE 4g daily for 14 days in healthy volunteers and demonstrated that the AUC of EPA and DHA was significantly greater with OM3-CA than OM3-EE (approximately 733%, 309%, and 576% of the values for total EPA, DHA, and EPA + DHA, respectively). Triglycerides were reduced from baseline by a mean of 22% in the OM3-CA group versus 7.5% in the OM3-EE group. However, baseline TGs were not equal between groups with higher baseline values in the OM3-CA vs. OM3-EE group (185.8 vs. 145.3 mg/dL, respectively). Although the difference in mean reduction in TG from baseline was significant between groups, the end of study TG was actually lower in the OM3-EE vs. OM3-CA group (approx. 134.4 mg/dL vs. 144.9 mg/dL, respectively). Therefore, the data do not support an advantage of OM3-CA over OM3-EE in reducing TGs since baseline values were not equal.

Similar to fatty acids derived from dietary intake, EPA and DHA are primarily metabolized via oxidation in the liver. Following concomitant administration of OM3-CA with reduced-fat diets, the total plasma clearance and half-life of EPA and DHA at steady-state are 548 ml/hr and 37 hours and 518 ml/hr and 46 hours, respectively.

OM3-CA and its metabolites are not renally eliminated.

In all clinical trials, OM3-CA was administered without regard to meals.

**FDA Approved Indication(s)**

OM3-CA is indicated as an adjunct to diet to reduce triglyceride levels in adult patients with severe (>500mg/dL) hypertriglyceridemia.

**Potential Off-label Uses**

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

Due to similarities between OM3-CA and omega-3 FAs, the off label uses for OM3-CA can include: prevention of cardiovascular disease, rheumatoid arthritis, psoriasis, pancreatitis, macular degeneration, dry eye syndrome, mood disorders, and glomerular kidney disease.

**Cardiovascular Disease**

Conflicting data currently exists for the clinical utilization of omega-3 fatty acids in the prevention and treatment of cardiovascular disease. Evidence obtained from previously conducted studies (randomized control trial, meta-analysis, and systematic review) showed that the use of omega-3 fatty acids resulted in decreased in cardiovascular events, such as coronary heart disease and cardiovascular death. However, more recent meta-analyses and clinical trials have since been published demonstrating that the use of omega-3 fatty acids did not reduce the overall risks of mortality, cardiac death, MI, or stroke. As a result of the conflicting evidence, the association between use of omega-3 fatty acids and improvement in cardiovascular outcomes is unclear.

Patients consuming an inadequate amount of dietary EPA and DHA may benefit from further supplementation with omega-3 fatty acids, preferably in the form of fatty fish. Currently, the American Heart Association (AHA) suggests that individuals previously diagnosed with coronary heart disease should receive 1-gram of EPA/DHA daily. The AHA recommends consumption of dietary omega-3 fatty acids over supplementation due to improved absorption from natural sources. However, the American Heart Association acknowledges limitations regarding the current evidence and believes that additional
trials should be conducted in order to determine if omega-3 fatty acid supplementation provides a benefit in improving cardiovascular health.

Other Uses: Omega-3 fatty acids (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 OM3-CA for use in treatment of these disease states.

Current VA National Formulary Alternatives

Fish oil, niacin and gemfibrozil are currently the national formulary alternatives for the management of hypertriglyceridemia. The PBM-MAP-VPEs recommend considering fish oil supplements in combination with statins to reduce triglyceride levels >500 mg/dL. Use of fibrate + statin combinations are not recommended within the VA due to an increased risk of adverse events and limited benefit beyond treatment with statins.

Dosage and Administration

Each OM3-CA capsule consists of ≥ 850 mg of polyunsaturated fatty acids (EPA, DHA, and other omega-3 fatty acids). The recommended daily dose of OM3-CA for the treatment of severe hypertriglyceridemia is 2 grams (2 capsules) or 4 grams (4 capsules) once daily, individualized based on clinical efficacy and tolerability. It can be taken without regard to meals. Patients should swallow OM3-CA capsules whole and not break open, crush, dissolve or chew.

Before starting OM3-CA, patients should institute a lipid-lowering diet and continue it throughout the treatment period. Other lifestyle changes including cessation of alcohol, weight loss and exercise should also be instituted. Additionally, secondary causes of hypertriglyceridemia should be ruled out (diabetes mellitus, hypothyroidism, or alcoholism) and managed as appropriate, as well as consideration of medications that may be contributing to elevated triglycerides (protease inhibitors, corticosteroids, beta blockers, thiazide diuretics, and estrogens).

Efficacy

Efficacy Measures

Two trials have been performed to evaluate the efficacy and safety of OM3-CA (EVOLVE and ESPRIT) in patients with elevated TGs. The primary endpoint in EVOLVE was the percent change from baseline in TG levels with OM3-CA (2, 3, and 4 g/d) in subjects with severe hypertriglyceridemia (≥ 500 to <2000 mg/dL). The primary endpoint in the ESPRIT trial was the difference in mean percent change from baseline to end-of-treatment in non-HDL cholesterol between olive oil 4g/d, OM3-CA 2g/day plus olive oil 2g/d or OM3-CA 4g/day in patients at high risk for cardiovascular disease and TGs <500 mg/dL on statins.

Summary of efficacy findings

EVOLVE Trial

The EVOLVE trial was a 12-week, phase III, randomized, double-blind, placebo-controlled, multicenter trial. For at least 4 weeks prior to randomization, patients were advised to follow the National Cholesterol Education Program Therapeutic Lifestyle Changes (TLC) diet. Patients that met the study inclusion criteria were randomized to receive control (olive oil 4g/d), OM3-CA 2g/d plus olive oil 2g/d, OM3-CA 3g/d plus olive oil 1 g/d, or OM3-CA 4g/d for 12 weeks in combination with the TLC diet. Additionally, a stratified randomization scheme was used to ensure balance between the treatment groups for patients who were using statins, cholesterol absorption inhibitors or a combination of the two. Baseline demographics and characteristics were similar between the treatment groups. A majority of the patients were white (92%) and men (77%) with an average age of 51.5 years and body mass index of 31.2 kg/m². Of the 399 patients
enrolled in the study, 364 patients completed the study. Thirty-five patients did not complete the study due to adverse events, non-compliance, follow-up issues, or withdrawal.

The primary endpoints were the differences in mean percent changes in triglycerides from baseline to week 12 between olive oil 4g/d, OM3-CA 2g/d plus olive oil 2g/d, OM3-CA 3g/d plus olive oil 1g/d, and OM3-CA 4g/d groups. The secondary endpoints were non-HDL-C and HDL-C percentage changes from baseline. Tertiary end points included changes or percentage changes in serum concentrations of lipids (triglycerides [TG], total cholesterol [total-C], low-density lipoprotein [LDL]-C, high-density lipoprotein [HDL]-C, calculated non-HDL-C [total-C minus HDL-C], very-low density lipoprotein [VLDL]-C, and the total-C-to-HDL-C ratio), Apo AI, Apo B, Apo CIII, remnant-like particle (RLP)-C, lipoprotein-associated phospholipase A2 (Lp-PLA2), and high-sensitivity C-reactive protein (hs-CRP); and plasma levels of EPA, DHA, and arachidonic acid (AA).

Results showed TG reduction from baseline of OM3-CA 2, 3 and 4-g/d compared to olive oil was 25.9% ($P < 0.01$), 25.5% ($P < 0.01$) and 30.9% ($P < 0.001$), respectively, compared with a reduction of 4.3% with olive oil. Total-C, Non-HDL-C, total-C-to-HDL-C ratio, VLDL-C, RLP-C and Apo CIII concentrations were all significantly reduced in all OM3-CA treatment groups. LDL-C was significantly increased in the 2- and 4-g/d OM3-CA group when compared to olive oil. HDL-C increased in all treatment groups; however, the change was not statistically significant.

Investigators from the EVOLVE trial concluded that OM3-CA produced statistically significant lowering of triglycerides and non-HDL-C concentrations at 2-, 3-, and 4-g/d in patients with severe hypertriglyceridemia.

**ESPRIT Trial**

The ESPRIT trial was a randomized, double-blind, placebo-controlled, parallel-group trial of men and women with elevated triglycerides and at high risk for cardiovascular disease. All subjects (n=647) were receiving maximally tolerated statins or statins plus ezetimibe and the National Cholesterol Education Program Therapeutic Lifestyle Changes diet. Subjects with fasting triglyceride levels ≥200 and <500 mg/dL were randomized to receive either olive oil 4g/d, OM3-CA 2g/d plus olive oil 2g/d, or OM3-CA 4g/d for 6 weeks in combination with a stable dose of statin they were taking during the diet/statin lead-in period. Baseline characteristics were similar between groups. Subjects were mostly non-Hispanic/non-Latino (82.6%), white (94.1%), and men (59.1%). The average age of the subjects was 60.8 years. Most of the patients used a statin alone (95.3%) while 4.7% used a statin with ezetimibe. Out of the 647 subjects that were randomized to receive treatment, there were 20 patients that did not finish the study due to noncompliance, adverse events, were lost to follow-up or withdrew consent.

The primary endpoint was the percent change from baseline in non-HDL-C and secondary endpoints were TG and HDL-C percent changes from baseline to end of treatment. Percent changes from baseline to end of treatment in total cholesterol, LDL-C, VLDL-C, the total cholesterol/HDL-C ratio, apolipoprotein (apo) AI, apoB, EPA, DHA, docosapentaenoic acid and arachidonic acid were also evaluated. The results of the ESPRIT trial showed that OM3-CA added to statin monotherapy demonstrated a statistically significant reduction in non-HDL-C with OM3-CA 2g/d and 4g/d (3.9% and 6.9%, respectively) compared with olive oil (0.9%) ($P < 0.05$ and $P < 0.001$, respectively vs. olive oil). A statistically significant reduction in TG levels (14.6% and 20.6%, respectively, verse olive oil [5.9%]; $P < 0.001$) in both active treatment groups was also observed. There was a statistically significant reduction in TC, VLDL-C and reductions from baseline in the total cholesterol/HDL-C ratio. Apo AI and apo B concentrations were significantly greater in the OM3-CA 4g/d cohort. LDL-C was significantly increased in the OM3-CA 2g/d cohort when compared to olive oil (4.6% vs 1.1%; $P < 0.05$), however, the change with the OM3-CA 4g/d cohort did not differ significantly (1.3% vs 1.1%). Plasma levels of EPA and DHA were significantly increased with both doses of OM3-CA.

Investigators from the ESPRIT trial concluded that patients with persistent hypertriglyceridemia (<500 mg/dL) while on a statin or statin + ezetimibe and who took OM3-CA at doses of 2 or 4-g/d had statistically lower non-HDL and TG levels versus control.
In both EVOLVE and ESPRIT, funding for each study was provided through the manufacturer of Epanova® and the authors of each study disclose potential conflicts of interest that may be considered to be significant.

**Adverse Events (Safety Data)**

The EVOLVE and ESPRIT trials evaluated the safety of OM3-CA in addition to efficacy.

**EVOLVE Trial**

OM3-CA was generally well tolerated during the EVOLVE trial. Adverse events identified are listed below in Table 1.

| Table 1. Treatment-emergent adverse events occurring in >3% of subjects (safety population) |
|---------------------------------------------|----------------------------------|----------------------------------|----------------------------------|
| System Organ Class, Preferred Term         | Olive Oil 4g/d (n=99)            | OM3-CA 2g/d (n=100)              | OM3-CA 3g/d (n=101)              | OM3-CA 4g/d (n=99)              |
| Gastrointestinal disorders                 |                                  |                                  |                                  |                                  |
| All                                         | 7 (7.1)                          | 19 (19.0)                        | 21 (20.8)                        | 27 (27.3)                        |
| Upper abdominal pain                        | 1 (1.0)                          | 4 (4.0)                          | 1 (1.0)                          | 1 (1.0)                          |
| Diarrhea                                     | 2 (2.0)                          | 10 (10.0)                        | 6 (5.9)                          | 10 (10.1)                        |
| Eruption                                     | 1 (1.0)                          | 3 (3.0)                          | 4 (4.0)                          | 4 (4.0)                          |
| Nausea                                       | 1 (1.0)                          | 6 (6.0)                          | 9 (8.9)                          | 5 (5.1)                          |
| Vomiting                                     | 1 (1.0)                          | 2 (2.0)                          | 4 (4.0)                          | 0 (0.0)                          |
| General Disorders                            |                                  |                                  |                                  |                                  |
| All                                         | 1 (1.0)                          | 5 (5.0)                          | 7 (6.9)                          | 1 (1.0)                          |
| Infections and infestations                  |                                  |                                  |                                  |                                  |
| All                                         | 11 (11.1)                        | 14 (14.0)                        | 7 (6.9)                          | 12 (12.1)                        |
| Nasopharyngitis                              | 2 (2.0)                          | 7 (7.0)                          | 3 (3.0)                          | 1 (1.0)                          |
| Investigations                               |                                  |                                  |                                  |                                  |
| All                                         | 4 (4.0)                          | 5 (5.0)                          | 4 (4.0)                          | 9 (9.1)                          |
| Metabolism and nutrition disorders           |                                  |                                  |                                  |                                  |
| All                                         | 2 (2.0)                          | 0 (0.0)                          | 1 (1.0)                          | 4 (4.0)                          |
| Musculoskeletal and connective tissue disorders |                                  |                                  |                                  |                                  |
| All                                         | 6 (6.1)                          | 5 (5.0)                          | 6 (5.9)                          | 3 (3.0)                          |
| Nervous system disorders                     |                                  |                                  |                                  |                                  |
| All                                         | 0 (0.0)                          | 6 (6.0)                          | 5 (5.0)                          | 4 (4.0)                          |
| Skin and subcutaneous tissue disorders       |                                  |                                  |                                  |                                  |
| All                                         | 0 (0.0)                          | 4 (4.0)                          | 1 (1.0)                          | 2 (2.0)                          |

Table reproduced from Kastelstein, et al.4

Patients randomized to OM3-CA reported more side effects than patients randomized to olive oil; however, the reports were of mild or moderate severity. There were 5% of patients who discontinued OM3-CA due to adverse effects (mostly gastrointestinal effects). There were nine subjects that withdrew from the study because of the gastrointestinal (GI) effects. Gastrointestinal disorders, infections and infestations, investigations, and nervous system disorders occurred more frequently in patients who were taking OM3-CA. Nervous system disorders were predominately headache and dysgeusia while diarrhea and nausea were the most common GI side effects reported. There were no deaths that occurred during the EVOLVE trial.

**ESPRIT Trial**

The ESPRIT trial recorded adverse events of OM3-CA during the study. Listed in Table 2 are the reported adverse events.
Table 2. Treatment-emergent adverse events occurring in >3% of subjects (safety population)*

<table>
<thead>
<tr>
<th>System Organ Class, Preferred Term</th>
<th>Statin + Olive Oil 4g/d (n=215)</th>
<th>Statin + OM3-CA 2g/d (n=215)</th>
<th>Statin + OM3-CA 4g/d (n=216)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>19 (8.8)</td>
<td>29 (13.5)</td>
<td>58 (26.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (2.3)</td>
<td>13 (6.0)</td>
<td>36 (16.7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (1.4)</td>
<td>6 (2.8)</td>
<td>13 (6.0)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>21 (9.8)</td>
<td>14 (6.5)</td>
<td>17 (7.9)</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>5 (2.3)</td>
<td>7 (3.3)</td>
<td>5 (2.3)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>11 (5.1)</td>
<td>7 (3.3)</td>
<td>10 (4.6)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>3 (1.4)</td>
<td>2 (0.9)</td>
<td>8 (3.7)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>3 (1.4)</td>
<td>7 (3.3)</td>
<td>8 (3.7)</td>
</tr>
</tbody>
</table>

*If a patient experienced the same adverse event more than once, only the first occurrence was reported*

*Table reproduced from Maki, et al.*

OM3-CA was generally well tolerated and considered safe according to the ESPRIT trial. Diarrhea and nausea were the side effects that were most commonly reported but were only mild and temporary. There were 12 patients that had adverse events that led to discontinuation from the study. There were no deaths reported in the ESPRIT trial.

Deaths and Other Serious Adverse Events
The EVOLVE and ESPRIT trials had 18 reported adverse events classified as serious (EVOLVE: olive oil, n=5; OM3-CA 2g/d, n=2; OM3-CA 3g/d, n=3; OM3-CA 4g/d, n=1; ESPRIT: olive oil, n=3; OM3-CA 2g/d, n=3, OM3-CA 4g/d, n=1). Serious adverse events reported include: myocarditis, abdominal pain, acute sinusitis, ear infection, microalbuminuria, urticaria, coronary artery disease, pulmonary embolism, implantable defibrillator insertion, diarrhea, intestinal obstruction, bronchitis, hyperglycemia, diverticular perforations, musculoskeletal chest pain, and osteoarthritis. Investigators concluded no serious adverse events were due to the treatment.

Common Adverse Events
Diarrhea and nausea were the most common adverse events reported in both the EVOLVE and ESPRIT trials.

Contraindications
OM3-CA is contraindicated in patients with known hypersensitivity to OM3-CA or any of its components.

Warnings and Precautions

Hypersensitivity: Because OM3-CA contains polyunsaturated free fatty acids derived from fish oils, patients with an allergy to fish and/or shellfish should use caution.

Hepatic Impairment: In patients with hepatic insufficiency, AST and ALT levels should be monitored periodically during therapy with OM3-CA.

Special Populations

Pregnancy: Pregnancy Category C. No clinical studies have been conducted to assess the safety and efficacy of OM3-CA administration in pregnant women. Studies performed in pregnant rats and rabbits showed late embryonic deaths, embryos with skeletal variations, and fetal malformations. As a result of the limited evidence for use in pregnancy and the potential for fetal adverse effects, OM3-CA should only be used if the potential benefit outweighs the potential risk to the fetus.
**Labor and Delivery:** There have been no studies performed in humans that have investigated the effects of OM3-CA on preterm labor or labor at term.

**Breastfeeding:** According to the manufacturers, caution should be used when administering OM3-CA to nursing mothers as studies with omega-3 fatty acids derived from fish oil have demonstrated excretion in breast milk at levels higher than in plasma. It is unknown how this excretion would affect the infant.

**Pediatrics:** OM3-CA in pediatric patients has not yet been studied.

**Elderly:** Studies evaluating safety did not include sufficient numbers of patients aged 65 years and over, so caution is advised when used in elderly patients. It is recommended to start at the low end of the dosage range and titrate upward as tolerated.

**Renal Impairment:** Use of OM3-CA in patients with renal impairment has not yet been studied.

**Hepatic Impairment:**
Limited data exists to suggest safe and effective use in patients with hepatic insufficiency. As a result, AST and ALT levels should be monitored periodically in patients receiving OM3-CA.

**Postmarketing Safety Experience (Optional)**
No data

**Sentinel Events**
No data

**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 &lt;Omega-3-carboxylic acids&gt;: &lt;Omega-3-acid ethyl esters&gt;
LA/SA for trade name &lt;Epanova&gt;: &lt;None&gt;

**Drug-Drug Interactions**

**Simvastatin:**
According the results of a 14-day study with 52 subjects, AUC and Cmax of simvastatin 40mg daily were unchanged with 4 grams daily OM3-CA co-administration.

**Warfarin:**
According the results of a 14-day study with 52 subjects, AUC, Cmax, and anticoagulation pharmacodynamics of warfarin 25mg daily were unchanged with 4 grams daily OM3-CA co-administration.

**In Vitro Studies:**
Studies have not shown any major impact on cytochrome enzymes or drug transporters.

**Acquisition Costs**
Please refer to VA pricing sources for updated information.

**Pharmacoeconomic Analysis**
There have not been any pharmacoeconomic analyses published.
Conclusions

Omega-3-carboxylic acids (OM3-CA, EPANOVA®) is the first omega-3 fatty acid product to be available in a "free fatty acid" formulation. Omega-3-carboxylic acids was approved by the FDA as an adjunct to diet to decrease triglyceride levels in adult patients with severe (≥500mg/dL) hypertriglyceridemia. The effect of OM3-CA on the risk of pancreatitis in patients with severe hypertriglyceridemia or its effect on cardiovascular morbidity or mortality has not been established.

There have been two published trials examining the efficacy and safety of OM3-CA in reducing elevated TGs (EVOLVE and ESPRIT). In the EVOLVE study, 399 patients with severe baseline hypertriglyceridemia (>500 to <2000 mg/dL) were assigned to receive control (olive oil 4g/d), OM3-CA 2g/d plus olive oil 2g/d, OM3-CA 3g/d plus olive oil 1 g/d, or OM3-CA 4g/d for 12 weeks in combination with the TLC diet. Triglycerides were reduced from baseline as follows: OM3-CA 2, 3 and 4-g/d 25.9% (**P** < 0.01), 25.5% (**P** < 0.01) and 30.9% (**P** < 0.001), respectively, compared with 4.3% with olive oil. The ESPRIT trial randomized 647 subjects with elevated TGs (>200 to <500 mg/dL) to receive olive oil 4g/d, OM3-CA 2g/d plus olive oil 2g/d, or OM3-CA 4g/d for 6 weeks in combination with a stable dose of statin they were taking during the diet/statin lead-in period. The primary endpoint (non-HDL-C) was reduced with OM3-CA 2g/d and 4g/d (3.9% and 6.9%, respectively) dose compared with olive oil (0.9%) (**P**<0.05 and **P** <0.001, respectively). Triglycerides were also significantly reduced (14.6% and 20.6%, respectively vs. 5.9% with control, **P**<0.001). At this time, there are no published studies evaluating the impact of OM3-CA on clinical outcomes. However, the Outcomes Study to Assess STatin Residual Risk Reduction With EpaNova in HiGh CV Risk PatienTs With Hypertriglyceridemia (STRENGTH) trial aims to determine whether OM3-CA will improve cardiovascular outcomes. Completion of the STRENGTH trial is expected by June 2019.

With regard to safety, OM3-CA is generally well tolerated with a safety profile similar to olive oil. According to adverse event data pooled from the EVOLVE and ESPRIT trials, diarrhea, nausea, abdominal pain or discomfort, and eructation was reported in > 3% of patients receiving OM3-CA. It is not known whether patients with fish and/or shellfish allergies are at an increased risk for experiencing allergic reactions to OM3-CA. Thus, it should be used cautiously in patients with known hypersensitivity to fish and/or shellfish. The ESPRIT trial concluded that patients who received 2 g daily or OM3-CA experienced significantly higher LDL-C levels than those receiving 4 g daily or olive oil. As a result, LDL-C levels should be monitored periodically in patients receiving therapy with OM3-CA. Safe and effective use has not been established in patients with hepatic or renal insufficiency. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels should be monitored periodically in patients with hepatic dysfunction.

At this time, there are no direct comparisons of OM3-CA and other omega-3 fatty acid formulations or other triglyceride lowering therapies (e.g., niacin or fibrates) in patients with severe hypertriglyceridemia; therefore, any advantage or disadvantage of OM3-CA in comparison to these other therapies is unknown.

References


March 2015: Adam Crabbe, PharmD; Janelle Weber, PharmD; Megan Casares, PharmD; Jared Hrdy, PharmD; and Michaela Hrdy, PharmD. PBM contact: Cathy Kelley Catherine.kelley@va.gov

**PRESCRIPTION FISH OIL PRODUCTS** (excluding formulary fish oil)

<table>
<thead>
<tr>
<th>Fish Oil Product</th>
<th>Omega-3 Fatty Acid Content (EPA+DHA)</th>
<th>Dosing Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulary Fish Oil</td>
<td>500 mg/cap</td>
<td>Up to 4 grams daily (8 capsules), as a single dose or divided twice daily.</td>
</tr>
<tr>
<td>Epanova®</td>
<td>At least 850 mg/cap</td>
<td>2-4 capsules once daily, without regard to meals</td>
</tr>
<tr>
<td>Lovaza®</td>
<td>At least 900 mg/cap</td>
<td>4 grams daily, given as 4 caps once daily or 2 capsules twice daily</td>
</tr>
<tr>
<td>Omtryg®</td>
<td>At least 900 mg/cap</td>
<td>4 grams daily, given as 4 capsules with a meal or 2 capsules twice daily with meals</td>
</tr>
<tr>
<td>Vascepa®</td>
<td>At least 900 mg EPA/cap</td>
<td>4 grams daily, given as 2 capsules twice daily with or following a meal.</td>
</tr>
</tbody>
</table>
### FDA-APPROVED INDICATIONS: SUMMARY OF EVIDENCE

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Population Size (N)</th>
<th>Treatment Groups</th>
<th>Inclusion/Exclusion Criteria</th>
<th>Results/Conclusions</th>
</tr>
</thead>
</table>
| The ECLIPSE Study | Prospective, randomized, open-label, single dose, 4-way crossover, bioavailability study | N = 54 | Patients underwent randomization to receive four single-dose alternating treatments starting with OM3-CA low-fat diet, OM3-CA high-fat diet, OM3-EE low-fat diet, or OM3-EE high-fat diet. Treatments had at least a 7 day wash-out in between each. | Inclusion Criteria:  
- Men or women, aged ≥18.  
- Normal healthy volunteers based on medical history, clinical assessments, and laboratory assessments.  
- Body mass index 25-35 kg/m².  
- Willingness to maintain current activity level.  
- Willingness to adhere to the Therapeutic Lifestyle Changes (TLC) diet during screening and treatment washout periods. | Primary objective: Compare the bioavailability of EPA and DHA following administration of OM3-CA and OM3-EE as single 4-gram doses with low- or high-fat diets.  
Total EPA + DHA AUC₀-t during the low-fat diet period:  
- OM3-CA: 2650.16 nmol•h/mL  
- OM3-EE: 662.95 nmol•h/mL  
(P < 0.0001) after adjustment for baseline change.  
Total EPA + DHA AUC₀-t during high-fat diet period:  
- OM3-CA: 4604.02  
- OM3-EE: 3589.47  
(P < 0.0001) after adjustment for baseline change.  
When administered to overweight patients consuming a low fat meal, the bioavailability of OM3-CA is significantly improved compared to OM3-EE. |

Exclusion Criteria:  
- Intolerance to omega-3 fatty acids, ethyl esters, or fish.  
- Unable or unwilling to eat the study meals.  
- Use of fish oil, other EPA or DHA containing supplements, or EPA and/or DHA fortified foods within 60 days of Visit 2, or during the study.  
- Consumption of any fish within 7 days of Visit 2, or during the study.  
- Use of flaxseed, perilla seed, hemp, spirulina, or black currant oils within 7 days of Visit 2, or during the study.  
- History of malabsorption syndrome, Crohn's disease, acute or chronic pancreatitis, pancreatic insufficiency, small bowel resection.  
- Women who are pregnant, lactating, or planning to become pregnant during the study period, or women of childbearing potential. |
who are not using acceptable contraceptive methods. A woman is considered of childbearing potential if she is not surgically sterile or is less than 1 year since last menstrual period. Examples of acceptable contraceptive methods include abstinence, intrauterine device (IUD) or double barrier method, oral or injectable contraceptives.

- Recent history (past 12 months) of drug abuse or alcohol abuse. Alcohol abuse will be defined as >14 drinks per week (1 drink = 12 oz beer, 5 oz wine, or 1.5 oz hard liquor).
- Exposure to any investigational product, within 28 days prior to Visit 1.
- Any other condition the investigator believes would interfere with the subject’s ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at undue risk.

### Study Design

<table>
<thead>
<tr>
<th>Study Design</th>
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<th>Treatment Groups</th>
<th>Inclusion/Exclusion Criteria</th>
<th>Results/Conclusions</th>
</tr>
</thead>
</table>
| The ESPRIT Trial\(^5\) | N = 647 | Patients were randomized in approximately equal numbers to receive either olive oil 4 g/d, OM3-CA 2g/day (plus 2g olive oil), or OM3-CA 4g/day for 6 weeks. | Inclusion Criteria:  
  - Men or women, ≥18 years of age.  
  - Fasting triglyceride (TG) level ≥200 mg/dL and <500 mg/dL.  
  - The subject is a high risk for a future cardiovascular event.  
  - The subject is treated with a statin and at or near LDL-C goal.  
  Exclusion Criteria:  
  - Allergy or intolerance to omega-3 fatty acids and omega-3-acid ethyl esters.  
  - Use of fibrates, bile acid sequestrants, or niacin or its analogues (greater than 200 Primary endpoint: percent change from baseline  
  - OM3-CA 2 g/d + Olive Oil 2 g/d –3.9%  
  - OM3-CA 4 g/d –6.9%  
  - Olive Oil 4 g/d -0.9%  
  - P < 0.05  
  Secondary endpoint: TG percent changes from baseline. (HDL-C also but no differences were observed)  
  - OM3-CA 2 g/d + Olive Oil 2 g/d –14.6%  
  - OM3-CA 4 g/d –20.6%,  
  - Olive Oil 4g/d –5.9% |
<table>
<thead>
<tr>
<th><strong>mg/d</strong> during screening.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of simvastatin 80 mg or Vytorin10/80 mg during screening.</td>
</tr>
<tr>
<td>Use of any eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) products.</td>
</tr>
<tr>
<td>Use of any supplement for the purpose of lowering plasma cholesterol during screening.</td>
</tr>
<tr>
<td>Use of weight loss drugs or programs during screening.</td>
</tr>
<tr>
<td>Use of erythromycin, telithromycin, clarithromycin, cyclosporine, itraconazole, ketoconazole, protease inhibitors, or nefazodone during screening.</td>
</tr>
<tr>
<td>Use of anticoagulants during screening.</td>
</tr>
<tr>
<td>Use of oral or injected corticosteroids during screening.</td>
</tr>
<tr>
<td>Use of tamoxifen, estrogens, progestins, or testosterone, that has not been stable for &gt;4 weeks at Visit 1, or is unstable during screening.</td>
</tr>
<tr>
<td>Use of &gt;750 mL/d grapefruit juice during screening.</td>
</tr>
<tr>
<td>Known lipoprotein lipase impairment or deficiency, or apolipoprotein C-II deficiency or familial dysbetalipoproteinemia.</td>
</tr>
<tr>
<td>History of pancreatitis.</td>
</tr>
<tr>
<td>Type I diabetes mellitus, use of insulin, or HbA1c &gt;10% at Visit 1.</td>
</tr>
<tr>
<td>Poorly controlled hypertension</td>
</tr>
<tr>
<td>Uncontrolled hypothyroidism, or thyroid stimulating hormone (TSH) &gt;1.5xULN at Visit 2.</td>
</tr>
<tr>
<td>Recent history or current significant nephrotic syndrome, pulmonary, hepatic, biliary, gastrointestinal or immunologic disease.</td>
</tr>
</tbody>
</table>
| History of cancer (except non-melanoma skin.

<table>
<thead>
<tr>
<th><strong>P &lt; 0.001</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>OM3-CA was generally well-tolerated.</td>
</tr>
<tr>
<td>OM3-CA significantly lowered TG and non-HDL-C from baseline compared to olive oil.</td>
</tr>
<tr>
<td>Response of TG and non-HDL-C lowering increased with dose increase.</td>
</tr>
</tbody>
</table>
### Omega-3 Carboxylic Acid Monograph
(Epanova®)

- Females who are pregnant, planning to be pregnant during the study period, lactating, or women of childbearing potential who are not using an acceptable method of contraception.
- Creatine kinase >5.0 times upper limit of normal (ULN); aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2.5 times ULN at Visit 2.
- Current or recent history (past 12 months) of drug or alcohol abuse.
- Exposure to any investigational agent within 4 weeks prior to Visit 1.
- Any other condition the investigator believes would interfere with the subject's ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at undue risk.

### Study Design

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Population Size (N)</th>
<th>Treatment Groups</th>
<th>Inclusion/Exclusion Criteria</th>
<th>Results/Conclusions</th>
</tr>
</thead>
</table>
| Phase II and III, double-blind, randomized, parallel, 4-arm study | N = 399 | Subjects were instructed to follow the National Cholesterol Education Program Therapeutic Lifestyle Changes diet, beginning at least 4 weeks before randomization and throughout the study. Subjects meeting criteria were randomized in approximately equal numbers to receive either olive oil 4g/d (control), OM3-CA 2g/day plus 2g olive oil, OM3-CA 3g/day plus 1g olive | Inclusion Criteria
- Men or women, >=18 years of age.
- Very high serum TG values in the range >=500 mg/dL and <2000 mg/dL (>=5.65 mmol/L and <22.60 mmol/L)

Exclusion Criteria
- Allergy or intolerance to omega-3 fatty acids, omega-3-acid ethyl esters, or fish.
- Known lipoprotein lipase impairment or deficiency or apolipoprotein C-II deficiency or familial dysbetalipoproteinemia.
- Unable to discontinue use of omega-3 drugs/supplements. | Primary efficacy end point: TG percentage change from baseline
- OM3-CA 2 g/d + Olive oil 2 g/d -25.9% (P<0.01)
- OM3-CA 3 g/d + Olive oil 1 g/d -25.5% (P<0.01)
- OM3-CA 4 g/d -30.9% (P<0.001)
- Olive oil 4 g/d -4.3%

Secondary efficacy end points: non-HDL-C and HDL-C percentage changes from baseline
- OM3-CA 2 g/d -7.6% (P<0.05) |
OM3-CA 4g/day for 12 weeks.

- Unable to discontinue use of bile acid sequestrants, fibrates or niacin (other than niacin-containing vitamins <200 mg), or any supplement used to alter lipid metabolism.
- Women who are pregnant, lactating, or planning to become pregnant. Women of childbearing potential who are not using acceptable contraceptive methods.
- Use of tamoxifen, estrogens or progestins that has not been stable for >4 weeks prior to Visit 1.
- Use of oral or injected corticosteroids or anabolic steroids.
- History of pancreatitis.
- History of symptomatic gallstone disease, unless treated with cholecystectomy.
- Uncontrolled diabetes.
- Uncontrolled hypothyroidism or thyroid stimulating hormone (TSH).
- History of cancer (other than basal cell carcinoma) in the past 2 years.
- Cardiovascular event (i.e., myocardial infarction, acute coronary syndrome, new onset angina, stroke, transient ischemic attack, unstable congestive heart failure requiring a change in treatment) or revascularization procedure within six months prior to Visit 1.
- Use of anticoagulants (e.g. warfarin [Coumadin®], coumarin, heparin, enoxaparin, clopidogrel).
- Presence of an aortic aneurysm or resection of an aortic aneurysm within six months prior to Visit 1.
- Recent history (within six months prior to Visit 1) or current significant nephrotic

OM3-CA significantly decreases TG and Non-HDL-C at doses of 2g, 3g and 4g daily.

OM3-CA 3 g/d -6.9% (P<0.05)
OM3-CA 4 g/d -9.6% (P<0.01)
Olive oil 4 g/d 2.5%
HDL-C
OM3-CA 2 g/d + Olive oil 2 g/d 7.4%
OM3-CA 3 g/d + Olive oil 3 g/d 3.8%
OM3-CA 4 g/d 5.8%
Olive Oil 4 g/d 1.9%
<table>
<thead>
<tr>
<th>Condition</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syndrome, pulmonary, hepatic, biliary, gastrointestinal or immunologic</td>
<td>Poorly controlled hypertension.</td>
</tr>
<tr>
<td>disease.</td>
<td>Any of the following laboratory criteria: serum alanine aminotransferase</td>
</tr>
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<tr>
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</tr>
<tr>
<td>aspartate aminotransferase (AST), glucose, glomerular filtration rate (GFR), platelet count, or hemoglobin outside of study range.</td>
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</tr>
<tr>
<td>Recent history (past 12 months) of drug abuse or alcohol abuse.</td>
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</tr>
<tr>
<td>Exposed to any investigational product, within 4 weeks prior to Visit 1.</td>
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</tr>
<tr>
<td>Presence of any other condition the Investigator believes would interfere</td>
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<tr>
<td>with the subject's ability to provide informed consent, comply with study instructions, or which might confound the interpretation of the study results or put the subject at undue risk</td>
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</tr>
<tr>
<td>Hemoglobin &lt;10.0 g/dL.</td>
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