Distinguishing Between Dietary Supplements and Prescription Eicosapentaenoic Acid (EPA)

Fish oil dietary supplements are not interchangeable with omega-3 prescription medicines

Please see Important Safety Information on page 18. Please see accompanying full Prescribing Information.
Selecting an Omega-3 Product for Therapeutic Use: Key Considerations

Omega-3 fatty acids are a commonly utilized therapeutic option for reducing triglyceride (TG) levels. Omega-3 fatty acids, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are the most studied forms of omega-3 fatty acids. Both EPA and DHA lower serum TGs; however, DHA has been shown in studies to raise LDL-C levels, while EPA has been shown to have a neutral effect on LDL-C levels.¹

There are 3 general categories of pharmaceutical products: prescription drugs, dietary supplements, and over-the-counter (OTC) drugs.

**Prescription Omega-3 Drugs:** Prescription drugs are subject to stringent FDA regulatory oversight and provide reliable and consistent quality to reduce TG levels in adult patients with very high hypertriglyceridemia (≥500 mg/dL).¹

To date, 4 omega-3 products have been approved as prescription drugs. Only 1 of the 3 products that contain both EPA and DHA, Lovaza® (omega-3-acid ethyl esters) and its generic equivalents, are commercially available. More recently, VASCEPA® (icosapent ethyl), a pure EPA-only product, was approved by the FDA.¹

**Dietary Supplements:** A dietary supplement is a product intended for ingestion that contains a “dietary ingredient” intended to add further nutritional value to (supplement) the diet.²

Dietary supplements are regulated as food, not as FDA-approved drugs. The FDA does not require dietary supplements to demonstrate safety and efficacy in pre-approved clinical trials and, as noted by the FDA, they are not approved to diagnose, treat, cure, or prevent any disease.¹

**OTC:** Drugs that have been found to be safe and appropriate for use without supervision of a health care professional such as a physician, and they can be purchased by consumers without a prescription.³

There are currently no FDA-approved OTC omega-3 drugs available to treat medical conditions, as indicated in the FDA Orange Book.⁴

### Types and Ingredients of Omega-3 Products in the United States

<table>
<thead>
<tr>
<th>Type of Product</th>
<th>Ingredients</th>
<th>Product Names</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Branded prescription medicines</strong></td>
<td>Pure EPA</td>
<td>Icosapent ethyl</td>
</tr>
<tr>
<td></td>
<td>DHA+EPA</td>
<td>Omega-3-acid ethyl esters, omega-3-acid ethyl esters A,* and omega-3 carboxylic acids*</td>
</tr>
<tr>
<td><strong>Generic prescription medicines</strong></td>
<td>Pure EPA</td>
<td>N/A (none currently approved or available)</td>
</tr>
<tr>
<td></td>
<td>DHA+EPA</td>
<td>Omega-3-acid ethyl esters</td>
</tr>
<tr>
<td><strong>Dietary supplements</strong></td>
<td>DHA and/or EPA</td>
<td>Vary in content; some claim 4:1 or 18:12 ratios of EPA:DHA and others claim higher EPA levels (the FDA does not require routine testing of product content)³⁹</td>
</tr>
<tr>
<td><strong>OTC medicines</strong></td>
<td>N/A (none currently approved or available)⁷</td>
<td></td>
</tr>
</tbody>
</table>

*Omega-3-acid ethyl esters A and omega-3 carboxylic acids have been approved but are not commercially available as of May 2017.³⁹

Please see Important Safety Information on page 18. Please see accompanying full Prescribing Information.
Prescription Omega-3 Fatty Acid Products

Prescription omega-3s are indicated as an adjunct to diet to reduce TG levels in adult patients with severe hypertriglyceridemia (≥500 mg/dL).

- Three of the 4 prescription products contain both EPA and DHA—Epanova (omega-3-carboxylic acids), Lovaza (omega-3-acid ethyl esters), and Omtryg (omega-3-acid ethyl esters)
- The most recent omega-3 prescription to be commercially available is VASCEPA (icosapent ethyl), a formulation consisting solely of icosapent ethyl, the ethyl ester of EPA. VASCEPA is DHA free and is the only pure EPA prescription product available in the United States
  - The effect of VASCEPA on cardiovascular mortality and morbidity or on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined

Overview of prescription omega-3 prescription medicines

<table>
<thead>
<tr>
<th>Active Ingredient(s)</th>
<th>DHA and EPA</th>
<th>EPA Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovaza (omega-3 acid ethyl esters)</td>
<td>Omtryg* (omega-3 ethyl esters A)</td>
<td>Epanova* (omega-3 carboxylic acids)</td>
</tr>
<tr>
<td>FDA indication</td>
<td>All products indicated as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia</td>
<td></td>
</tr>
<tr>
<td>Commercially available</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>DHA content per capsule</td>
<td>~0.375 g</td>
<td>~0.375 g</td>
</tr>
<tr>
<td>EPA content per capsule</td>
<td>~0.465 g</td>
<td>~0.465 g</td>
</tr>
<tr>
<td>Total omega-3 dose per day</td>
<td>4 g (4 capsules QD or 2 capsules BID)</td>
<td>4 g (4 capsules QD or 2 capsules BID)</td>
</tr>
</tbody>
</table>

*Note: Although Epanova and Omtryg were approved by the FDA in 2014, they are not commercially available as of May 2017.

Prescription EPA and prescription omega-3s containing DHA are not interchangeable

- Based on FDA equivalence codes, products containing DHA are not equivalent to icosapent ethyl-only products
- Omega-3 prescription medications that contain both EPA and DHA are not substitutable for pure EPA VASCEPA

No head-to-head studies have been done to compare the effects of VASCEPA and other TG-lowering medications.

Lovaza is a registered trademark of GlaxoSmithKline.
Omtryg is a registered trademark of Beckloff Associates, Inc.
Epanova is a registered trademark of the AstraZeneca group of companies.
Fish Oil Dietary Supplements Are Not Interchangeable With Omega-3 Prescription Medicines\textsuperscript{5}

Well-recognized professional organizations such as the American Diabetes Association, American Society of Health-System Pharmacists, and American Association of Clinical Endocrinologists all support the FDA's position that dietary supplements (including omega-3s) are not appropriate to treat disease.\textsuperscript{11-13}

**Key differences among prescription and dietary supplement omega-3 fatty acid products\textsuperscript{5,14,15}**

<table>
<thead>
<tr>
<th>Regulatory requirements</th>
<th>Prescription Products</th>
<th>Dietary Supplements</th>
</tr>
</thead>
</table>
|                         | Must demonstrate efficacy and safety in phase 3 randomized controlled trials for approval | • Regulated as “foods” from regulatory standpoint  
• Not required to demonstrate/prove efficacy or safety prior to marketing |

<table>
<thead>
<tr>
<th>Omega-3 fatty acid content and purity</th>
<th>Prescription Products</th>
<th>Dietary Supplements</th>
</tr>
</thead>
</table>
|                                      | Adhere to strict standards for content and purity | • No requirement for specific EPA and DHA content  
• May contain saturated fat/cholesterol/contaminants |

<table>
<thead>
<tr>
<th>Indication</th>
<th>Prescription Products</th>
<th>Dietary Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indicated as an adjunct to diet to reduce triglycerides in adult patients with severe (≥500 mg/dL) hypertriglyceridemia</td>
<td>N/A (no approved indication)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substitution</th>
<th>Prescription Products</th>
<th>Dietary Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHA-containing products should not be substituted for EPA-only products</td>
<td>Omega-3 fatty acid dietary supplements should not be substituted for prescription omega-3 fatty acid products</td>
<td></td>
</tr>
</tbody>
</table>

Please see Important Safety Information on page 18. Please see accompanying full Prescribing Information.
The FDA’s Position on Fish Oil Dietary Supplements Is Clear

Dietary supplements are designated as “foods” rather than “drugs” under the Dietary Supplementation Health and Education Act (DSHEA) of 1994:

- The FDA does not review any clinical trial data before supplements are sold to patients.
- Supplements are not approved to treat, diagnose, prevent, or cure disease.
- Supplements are not required to demonstrate efficacy or safety prior to being marketed.

“…dietary supplements do not require premarketing approval from the FDA, and under the DSHEA of 1994, anything labeled as a dietary supplement is assumed to be safe until proven otherwise.”

Fish oil dietary supplements are regulated as foods by the FDA, not approved to treat medical conditions.
Ingredients in Fish Oil Dietary Supplements Have Been Shown to Be Highly Variable

Actual omega-3 content may not match the amount advertised on the label

The quantities of EPA and DHA found in fish oil supplements may vary greatly within and among brands.\textsuperscript{7}

\textit{Fatty acid content}\textsuperscript{6}

<table>
<thead>
<tr>
<th>Dietary Supplement 1</th>
<th>Dietary Supplement 2</th>
<th>Dietary Supplement 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>21% 34% 36%</td>
<td>52% 6% 21%</td>
<td>39% 6% 31%</td>
</tr>
</tbody>
</table>

Fish oil dietary supplement brand content has been found to be highly variable.\textsuperscript{5}

- Typical top-selling supplements contain only 30\% omega-3 acids, along with 70\% of ingredients that were uncharacterized and/or not disclosed on the label\textsuperscript{1}
- Supplements may contain up to 1/3 saturated fat\textsuperscript{6,17}
- Many supplements contain DHA, which has the potential to raise LDL-C levels in FDA-reviewed trials\textsuperscript{18}

\textbf{A US study of 47 dietary supplements assessed actual vs labeled amounts of EPA and DHA}\textsuperscript{15}

"Due to the growing popularity of dietary supplements, 47 commercial fish, krill, and algal oil supplements were analyzed for EPA, DHA, and other fatty acids."

- Actual EPA amounts ranged from 66\% to 184\% of the label claims, while actual amounts of DHA ranged from 62\% to 184\% of labeled quantities
- 74\% of the supplements tested contained less EPA and DHA than claimed on their labels

Please see Important Safety Information on page 18. Please see accompanying full Prescribing Information.
A New Zealand study of 32 fish oil supplements confirmed disparities between the actual and labeled contents\textsuperscript{19}

The authors of this study examined the contents of 32 different fish oil supplements that were readily available in the New Zealand market.

This study shows that almost all fish oil supplements examined contain much lower concentrations of omega-3 polyunsaturated fatty acids than claimed by the product label. On average, the fish oil supplements contained only 68\% of the claimed EPA and DHA content, as shown in the chart below. In fact, 22 of the 32 supplements contained less than 67\% of the EPA and DHA content claimed.

**Recent dietary supplement sponsored study**

Readers are encouraged to review a more recent publication by Bannenberg et al in *Scientific Reports*, published online May 3, 2017, discussing markers of oxidation and omega-3 content from dietary supplements sold in New Zealand.\textsuperscript{20} This more recent report, financed by the Global Organization for EPA and DHA omega-3s (GOED), a fish oil supplement trade organization, differs from the Albert et al publication on some of the markers of oxidation and the omega-3 content, showing lower amounts of markers of oxidation and greater omega-3 content, on average, in the dietary supplements tested.\textsuperscript{19} Readers are encouraged to review both publications.
**Fish oil supplements may be oxidized**

Omega-3 fatty acids are highly prone to oxidation (spoilage), which may interfere with their biological activity.\(^5,19\)

Numerous studies have shown that a significant number of fish oil supplements are oxidized above international recommendations.\(^5,19\)

- In a 2015 New Zealand study, 33 of the 36 fish oil supplements failed to meet international standards for oxidation levels.\(^19\)
- A small-scale US study found that total oxidation (TOTOX) levels for 3 leading omega-3 supplements exceeded international thresholds, while a prescription omega-3 medicine did not show elevated TOTOX levels.\(^6\)

![TOTOX levels of an omega-3 prescription compared to 3 top-selling US fish oil dietary supplements](chart)

The health implications of consuming oxidized fish oil are being investigated, and the level that would cause harm to the consumer has not been well investigated.\(^5,19\)

Please see Important Safety Information on page 18. Please see accompanying full Prescribing Information.
The manufacturing process for pure, prescription EPA limits content discrepancies

Unlike dietary supplements, pure prescription EPA (VASCEPA) undergoes multiple FDA-approved and -validated processing steps that remove all other fatty acids, impurities, and related substances.

- Esterification process modifies raw fish oil to enable further concentration and purification steps
- VASCEPA purification process employs molecular distillation, high performance liquid chromatography (HPLC), and other sophisticated chemistry technologies not often available to dietary supplement products
- VASCEPA manufacturing processes remove saturated and trans fats, isomers, heavy metals, and all other impurities to the level of detection, resulting in a single compound, ultra–high-purity prescription drug

VASCEPA manufacturing processes greatly reduce product oxidation:

- VASCEPA purification processes take place in an oxygen-free environment, resulting in very low peroxide and Anisidine Value readings
- Patent-protected soft gel formula protects VASCEPA from oxidation, allowing for the longest FDA-approved omega-3 prescription drug shelf-life of 48 months

Patients can face a significant “pill burden” when attempting to achieve the EPA content found in prescription omega-3s

Most dietary supplements contain crude fish oil with low amounts (30%) of omega-3 (18% EPA+12% DHA). For these types of products, patients would need to consume more than 20 capsules to achieve the amount (4 g) of EPA found in 4 capsules of VASCEPA.

The higher “pill burden” associated with consuming unregulated fish oil dietary supplements could, in turn, expose already ill patients to ingesting increased levels of undesired compounds.

Unregulated dietary supplements may contain omega-6s, saturated fats, cholesterol, various isomers, and oxidized fatty acids.

Advertised doses of fish oil dietary supplements may not provide a clinically meaningful benefit of TG reduction

The actual monthly cost of dietary supplements

Dietary supplements could cost as much as $1700 to $3500 annually if a patient attempted to achieve 4 grams of EPA a day based on the advertised content of each capsule.

*Based on an average retail price of $27 for a 120-count bottle.
VASCEPA® (icosapent ethyl)

**Indication**

VASCEPA (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

**Limitations of Use**

The effect of VASCEPA on cardiovascular mortality and morbidity or on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

Naturally occurring EPA is subject to ethyl ester modification to yield icosapent ethyl, the active substance in pure, prescription VASCEPA.

Please see Important Safety Information on page 18. Please see accompanying full Prescribing Information.
Key milestones in the development of VASCEPA

- **2008**: Investigational New Drug application for hypertriglyceridemia opened in June 2008
- **2011**: Original New Drug Application for VHTG submitted Sept 2011
- **2012**: VHTG indication approved July 2012
- **2013**: VASCEPA enters US market Jan 2013
- **2017-2018**: Expected completion of the REDUCE-IT cardiovascular outcome study
- **2030**: Last patent expiration for VASCEPA

Extensive CMC, nonclinical, clinical pharmacology, and clinical safety/efficacy data sets have been provided to CDER throughout the development of pure, prescription VASCEPA.

**Important Safety Information for VASCEPA**

- VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components.
- Use with caution in patients with known hypersensitivity to fish and/or shellfish.
- The most common reported adverse reaction (incidence >2% and greater than placebo) was arthralgia (2.3% VASCEPA, 1.0% placebo).
- Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.
Co-administration of VASCEPA with statins lowers TG and atherogenic lipids without raising LDL-C

The ANCHOR study evaluated effects of VASCEPA as add-on therapy to treatment with statins in a randomized, placebo-controlled, double-blind, parallel-group study of 453 adult patients (226 on VASCEPA and 227 on placebo) with persistent high TG levels (≥200 mg/dL and <500 mg/dL) despite statin therapy.*

- The median baseline TG and LDL-C levels in these patients were 259 mg/dL and 83 mg/dL, respectively
- The mean age was 61 years and the mean body mass index was 33 kg/m²
- Seventy-three percent (73%) of patients had diabetes at baseline

ANCHOR study design

Important Safety Information for VASCEPA

- In patients with hepatic impairment, monitor ALT and AST levels periodically during therapy.
- Patients should be advised to swallow VASCEPA capsules whole; not to break open, crush, dissolve, or chew VASCEPA.
- Adverse events may be reported by calling 1-855-VASCEPA or the FDA at 1-800-FDA-1088.

*ANCHOR was a phase 3, 12-week, multicenter, double-blind, randomized, placebo-controlled study of IPE in patients receiving atorvastatin, rosuvastatin, or simvastatin with or without ezetimibe and at high cardiovascular risk with TG levels ≥200 and <500 mg/dL and LDL-C levels ≥40 and ≤115 mg/dL.

Please see additional Important Safety Information on page 18. Please see accompanying full Prescribing Information.
ANCHOR: VASCEPA significantly reduced TG and other lipid/lipoprotein biomarkers without raising LDL-C.

The clinical significance of these data has not been determined.

- VASCEPA is not FDA-approved for the treatment of statin-treated patients with mixed dyslipidemia and high (≥200 mg/dL and <500 mg/dL) TG levels due to current uncertainty regarding the benefit, if any, of drug-induced changes in lipid/lipoprotein parameters beyond statin-lowered LDL-C on cardiovascular risk among statin-treated patients with residually high TG. No prospective study has been conducted to test and support what, if any, benefit exists.

- Recent cardiovascular outcomes trials (ACCORD Lipid, AIM-HIGH, and HPS2-THRIVE), while not designed to test the effect of lowering TG levels in patients with high TG levels after statin therapy, each failed to demonstrate incremental cardiovascular benefit of adding a second lipid-altering drug (fenofibrate or formulations of niacin), despite raising HDL-C and reducing TG levels, among statin-treated patients with well-controlled LDL-C.

The ANCHOR trial was sponsored by Amarin Pharma, Inc. and its affiliates.
Pure EPA VASCEPA demonstrated significant TG reductions across populations\textsuperscript{21,23,24}

Published in 2011, the MARINE study showed VASCEPA 4 g/day reduced placebo-corrected median TG levels by 33.1\% (\textit{P}<0.0001). At the same time, VASCEPA did not increase LDL-C levels (see chart).

- These findings are consistent with several small studies that have shown that, while both EPA and DHA lower TG levels in patients with dyslipidemia in FDA-reviewed studies, DHA also increases LDL-C levels, while EPA does not\textsuperscript{24}

\textit{MARINE: VASCEPA lowers TG and other lipid/lipoprotein biomarkers without raising LDL-C\textsuperscript{21,24}}

**Median Percentage Change From Baseline vs Placebo**

<table>
<thead>
<tr>
<th>Overall Population</th>
<th>TG decrease in patients with TG &gt;750 mg/dL</th>
<th>TG decrease in patients on statin therapy</th>
<th>Other Lipid Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Population</td>
<td>680</td>
<td>91</td>
<td>123</td>
</tr>
<tr>
<td>Median Baseline (mg/dL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Population</td>
<td>902</td>
<td>650</td>
<td>225</td>
</tr>
<tr>
<td>LDLC</td>
<td>-33%</td>
<td>-45%</td>
<td>-18%</td>
</tr>
<tr>
<td>\textit{P}&lt;0.001, \textit{n}=76</td>
<td>\textit{P}&lt;0.001, \textit{n}=28</td>
<td>\textit{P}&lt;0.001, \textit{n}=76</td>
<td>\textit{P}&lt;0.001, \textit{n}=75</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-2%</td>
<td>-65%</td>
<td>-9%</td>
</tr>
<tr>
<td>\textit{NS, n}=76</td>
<td>\textit{P}&lt;0.001, \textit{n}=76</td>
<td>\textit{P}&lt;0.001, \textit{n}=76</td>
<td></td>
</tr>
</tbody>
</table>

TG: VASCEPA (\textit{n}=76), 27\% median decrease from baseline; placebo (\textit{n}=75), 10\% increase from baseline. Patients with baseline TG >750 mg/dL: VASCEPA (\textit{n}=28), 27\% median decrease in TG levels from baseline vs 19\% increase with placebo (\textit{n}=32). On statin therapy: VASCEPA (\textit{n}=19), 30\% median decrease in TG levels from baseline vs a 32\% increase with placebo plus statin (\textit{n}=18). LDL-C: VASCEPA (\textit{n}=76), 5\% median decrease from baseline; placebo (\textit{n}=75), 3\% decrease from baseline.

VLDL-C: VASCEPA (\textit{n}=76), 20\% median decrease from baseline; placebo (\textit{n}=75), 14\% increase from baseline; non-HDL-C: VASCEPA (\textit{n}=76), 8\% median decrease from baseline; placebo (\textit{n}=75), 8\% increase from baseline; Apo B: VASCEPA (\textit{n}=75), 4\% median decrease from baseline; placebo (\textit{n}=73), 4\% increase from baseline.

Please see Important Safety Information on page 18. Please see accompanying full Prescribing Information.
REDUCE-IT™: A landmark global cardiovascular outcomes study

Ongoing clinical exploration of VASCEPA in conjunction with statins

Despite the demonstrated clinical benefits of lowering LDL-C with statins, significant residual cardiovascular risk remains for statin-treated patients. VASCEPA is being studied as an adjunct to statin therapy to further reduce cardiovascular risk in a global, 8000-patient cardiovascular outcomes trial called REDUCE-IT.

REDUCE-IT is a phase 3, randomized, double-blind, placebo-controlled study whose main objective is to evaluate whether treatment with VASCEPA reduces ischemic events in patients at elevated cardiovascular risk concurrently treated with statins. Enrolled patients met the following requirements:

- Fasting TG levels ≥150 mg/dL and <500 mg/dL
- LDL-cholesterol levels >40 mg/dL and ≤100 mg/dL
- Stable statin therapy (± ezetimibe) for ≥4 weeks prior to randomization
- Men and women aged ≥45 years
- Established CHD or at high risk for CHD (diabetes + ≥1 risk factor)

For more information on REDUCE-IT, go to amarincorp.com and click on R&D.
Important Information for HCPs about VASCEPA as an add-on to statins in patients with high (200-499 mg/dL) TG levels

- Supportive but not conclusive research shows that consumption of EPA and DHA omega-3 fatty acids may reduce the risk of coronary heart disease. VASCEPA should not be taken in place of a healthy diet and lifestyle or statin therapy.
- The ANCHOR trial demonstrates that VASCEPA lowers TG levels in patients with high (≥200 mg/dL and <500 mg/dL) TG levels not controlled by diet and statin therapy.
- In the ANCHOR trial, VASCEPA 4 g/day significantly reduced TG, non–HDL-C, Apo B, VLDL-C, TC, and HDL-C levels from baseline relative to placebo in patients with high (≥200 mg/dL and <500 mg/dL) TG levels not controlled by diet and statin therapy.
- The reduction in TG observed with VASCEPA was not associated with elevations in LDL-C relative to placebo.
- VASCEPA is not FDA-approved for the treatment of statin-treated patients with mixed dyslipidemia and high (≥200 mg/dL and <500 mg/dL) TG levels due to current uncertainty regarding the benefit, if any, of drug-induced changes in lipid/lipoprotein parameters beyond statin-lowered LDL-C on cardiovascular risk among statin-treated patients with residually high TG. No prospective study has been conducted to test and support what, if any, benefit exists.
- Recent cardiovascular outcomes trials (ACCORD Lipid, AIM-HIGH, and HPS2-THRIVE), while not designed to test the effect of lowering TG levels in patients with high TG levels after statin therapy, each failed to demonstrate incremental cardiovascular benefit of adding a second lipid-altering drug (fenofibrate or formulations of niacin), despite raising HDL-C and reducing TG levels, among statin-treated patients with well-controlled LDL-C.
- VASCEPA is not FDA-approved to reduce the risk of coronary heart disease.
- The effect of VASCEPA on the risk of cardiovascular mortality and morbidity has not been determined.
- A cardiovascular outcomes study of VASCEPA designed to evaluate the efficacy of VASCEPA in reducing cardiovascular mortality and morbidity in a high-risk patient population on statin therapy is currently underway (REDUCE-IT).
- VASCEPA may not be eligible for reimbursement under government healthcare programs (such as Medicare and Medicaid) to reduce the risk of coronary heart disease or for treatment of statin-treated patients with mixed dyslipidemia and high (≥200 mg/dL and <500 mg/dL) TG levels. We encourage you to check for yourself.
- The ANCHOR trial was sponsored by Amarin Pharma, Inc. and its affiliates.

Please see Important Safety Information on page 18. Please see accompanying full Prescribing Information.
Results from the ANCHOR study

Coadministration therapy with statins for additional lipid management in mixed dyslipidemia

The effects of VASCEPA as add-on therapy to treatment with statins were evaluated in a randomized, placebo-controlled, double-blind, parallel-group study of 453 adult patients (226 on VASCEPA and 227 on placebo) with persistent high triglyceride levels (≥200 mg/dL and <500 mg/dL) despite statin therapy.

- All patients were receiving statin therapy (atorvastatin, rosuvastatin, or simvastatin) and were treated to LDL-C goal prior to randomization
- Patients were randomized to either VASCEPA or placebo and treated for 12 weeks with statin cotherapy. The same statin at the same dose was continued throughout the study
- The median baseline TG and LDL-C levels in these patients were 259 mg/dL and 83 mg/dL, respectively
- The randomized population in this study was mostly Caucasian (96%) and male (61%)
- The mean age was 61 years and the mean body mass index was 33 kg/m²
- Seventy-three percent (73%) of patients had diabetes at baseline

The changes in the major lipoprotein lipid parameters for the groups receiving VASCEPA plus statin or placebo plus statin are shown in the following table.

Response to the addition of VASCEPA to ongoing statin therapy in patients with high triglyceride levels (≥200 mg/dL and <500 mg/dL)*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VASCEPA 4 g/day + Statin n=226</th>
<th>Placebo + Statin n=227</th>
<th>Difference (95% confidence interval)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG, mg/dL</td>
<td>Baseline 265 % Change -18</td>
<td>Baseline 259 % Change 6</td>
<td>-22 (-27, -16)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>82 % Change 2</td>
<td>84 % Change 9</td>
<td>-6 (-11, -2)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Non–HDL-C, mg/dL</td>
<td>128 % Change -5</td>
<td>128 % Change 10</td>
<td>-14 (-17, -10)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>ApoB, mg/dL</td>
<td>93 % Change -2</td>
<td>91 % Change 7</td>
<td>-9 (-12, -6)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>VLDL-C, mg/dL</td>
<td>44 % Change -12</td>
<td>42 % Change 15</td>
<td>-24 (-32, -17)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>TC, mg/dL</td>
<td>167 % Change -3</td>
<td>168 % Change 9</td>
<td>-12 (-15, -9)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>37 % Change -1</td>
<td>39 % Change 5</td>
<td>-5 (-7, -2)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

*Data reviewed and confirmed by the FDA—indication not approved by the FDA.

% Change=median percent change from baseline. Difference=median of (VASCEPA % change-placebo % change) (Hodges Lehmann Estimate). P values from Wilcoxon rank sum test.

VASCEPA significantly reduced TG, non–HDL-C, ApoB, VLDL-C, TC, and HDL-C levels from baseline relative to placebo. The reduction in TGs observed with VASCEPA was not associated with elevations in LDL-C relative to placebo.

The effect of VASCEPA on cardiovascular mortality and morbidity in patients with mixed dyslipidemia has not been determined.
Indication and Limitations of Use

VASCEPA is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.

- The effect of VASCEPA on cardiovascular mortality and morbidity or on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined.

Important Safety Information for VASCEPA

- VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components.
- Use with caution in patients with known hypersensitivity to fish and/or shellfish.
- The most common reported adverse reaction (incidence >2% and greater than placebo) was arthralgia (2.3% VASCEPA, 1.0% placebo).
- Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically.
- In patients with hepatic impairment, monitor ALT and AST levels periodically during therapy.
- Patients should be advised to swallow VASCEPA capsules whole; not to break open, crush, dissolve, or chew VASCEPA.
- Adverse events may be reported by calling 1-855-VASCEPA or the FDA at 1-800-FDA-1088.

Glossary

Dietary Supplements: A dietary supplement is a product intended for ingestion that contains a "dietary ingredient" intended to add further nutritional value to (supplement) the diet.

Interchangeable: In dispensing drugs, the use of a generic form of the drug in place of the proprietary form.

Over-the-Counter (OTC): Drugs that have been found to be safe and appropriate for use without supervision of a health care professional such as a physician, and they can be purchased by consumers without a prescription.

Prescription Omega-3 Drugs: Prescription drugs are subject to stringent FDA regulatory oversight and provide reliable and consistent quality to reduce TG levels in adult patients with very high hypertriglyceridemia (≥500 mg/dL).

Substitutable: Capable of being exchanged for another or for something else that is equivalent.
References


