VASCEPA® (icosapent ethyl) Capsules, for oral use

HIGHLIGHTS OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

VASCEPA is an ethyl ester of eicosapentaenoic acid (EPA) indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia. (1)

Limitations of Use:
• The effect of VASCEPA on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined. (1)
• The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined. (1)

DOSAGE AND ADMINISTRATION

The daily dose of VASCEPA is 4 grams per day taken as four 0.5-gram capsules twice daily with food. (2) Patients should be advised to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA. (2)

DOSAGE FORMS AND STRENGTHS

Capsules: 0.5-gram and 1-gram (3)

CONTRAINDICATIONS

VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components. (4)

FULL PRESCRIBING INFORMATION:

CONTENTS*

1 INDICATIONS AND USEAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
9 DRUG ABUSE AND DEPENDENCE
10 DESCRIPTION
11 CLINICAL PHARMACOLOGY
12 NONCLINICAL TOXICOLOGY
13 CLINICAL STUDIES
14 USE IN SPECIFIC POPULATIONS
15 HOW SUPPLIED/STORAGE AND HANDLING
16 DRUGS ABUSE AND DEPENDENCE
17 PATIENT COUNSELING INFORMATION

WARNINGS and PRECAUTIONS

In patients with hepatic impairment, monitor ALT and AST levels periodically during therapy. (5.1) Use with caution in patients with known hypersensitivity to fish and/or shellfish. (5.2)

ADVERSE REACTIONS

The most common reported adverse reaction (incidence >2% and greater than placebo) was arthralgia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Amarin Pharma Inc. at 1-855-VASCEPA (1-855-827-2372) or contact the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Omega-3 acids may prolong bleeding time. Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-plalet agents) should be monitored periodically. (7)

USE IN SPECIFIC POPULATIONS

Pregnancy: Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USEAGE

VASCEPA® (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia. Usage Considerations: Patients should be placed on an appropriate lip-lowering diet and exercise regimen before receiving VASCEPA and should continue this diet and exercise regimen while taking VASCEPA. Attempts should be made to control any medical problems such as diabetes mellitus, hypothyroidism, and obesity that may contribute to lipid abnormalities. Mediations known to exacerbate hypertriglyceridemia (such as beta blockers, thiazides, estrogens) should be discontinued or changed, if possible, prior to consideration of TG-lowering drug therapy. (2)

Limitations of Use:
• The effect of VASCEPA on the risk for pancreatitis in patients with severe hypertriglyceridemia has not been determined. The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined. (1)

2 DOSAGE AND ADMINISTRATION

Assess lipid levels before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of hypertriglyceridemia levels and manage as appropriate. (See Indications and Usage (1)). Patients should engage in appropriate nutritional intake and physical activity before receiving VASCEPA, which should continue during treatment with VASCEPA. (2)

The daily dose of VASCEPA is 4 grams per day taken as four 0.5-gram capsules twice daily with food. (2) Patients should be advised to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA. (2)

DOSAGE FORMS AND STRENGTHS

VASCEPA capsules are supplied in the following dosage form strengths:
• 0.5-gram amber-colored, oval, soft-gelatin capsules imprinted with V500.
• 1-gram amber-colored, oblong, soft-gelatin capsules imprinted with VASCEPA. (3)

CONTRAINDICATIONS

VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components. (4)

WARNINGS AND PRECAUTIONS

5.1 Monitoring: Laboratory Tests

In patients with hepatic impairment, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored periodically during therapy with VASCEPA. (2)

5.2 Fish Allergy

VASCEPA contains ethyl esters of the omega-3 fatty acid, eicosapentaenoic acid (EPA), obtained from the oil of fish. It is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to VASCEPA. VASCEPA should be used with caution in patients with known hypersensitivity to fish and/or shellfish. (4)

PATIENT INFORMATION

VASCEPA® (vas-EE-puh) (icosapent ethyl) capsules

What is VASCEPA®?

VASCEPA is a prescription medicine used along with a low-fat and low-cholesterol diet to lower high levels of triglycerides (fats) in adults. It is not known if VASCEPA changes your risk of having inflammation of your pancreas (pancreatitis). It is not known if VASCEPA prevents you from having a heart attack or stroke. It is not known if VASCEPA is safe and effective in children.

Do not take VASCEPA if you are allergic to icosapent ethyl or any of the ingredients in VASCEPA. See the end of this leaflet for a complete list of ingredients in VASCEPA.

Before taking VASCEPA, tell your doctor about all of your medical conditions, including if you:
• have diabetes.
• have a low thyroid problem (hypothyroidism).
• have a liver problem.
• have a pancreas problem.
• are allergic to fish or shellfish. It is not known if people who are allergic to fish or shellfish are also allergic to VASCEPA.
• are pregnant, or planning to become pregnant. It is not known if VASCEPA will harm your unborn baby.
• are breastfeeding or plan to breastfeed. VASCEPA can pass into your milk, and may harm your baby. Talk to your doctor about the best way to feed your baby if you take VASCEPA.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and dietary or herbal supplements. VASCEPA can interact with certain other medicines that you are taking. Especially tell your doctor if you take medicines that affect your blood clotting (anticoagulants or blood thinners).

How should I take VASCEPA®?

Take VASCEPA exactly as your doctor tells you to take it.

• Do not change your dose or stop taking VASCEPA without talking to your doctor.
• Do not take more capsules than what is prescribed by your doctor.
• If you are prescribed the 0.5-gram capsules, you should not take more than 8 capsules each day.
• If you are prescribed the 1-gram capsules, you should not take more than 4 capsules per day.
• Take VASCEPA capsules whole. Do not break, crush, dissolve, or chew VASCEPA capsules before swallowing.
• If you miss a dose of VASCEPA, take it as soon as you remember. However, if you miss one day of VASCEPA, do not double your dose when you take it.
• Your doctor may start you on a diet that is low in saturated fat, cholesterol, carbohydrates, and low in added sugars before giving you VASCEPA. Stay on this diet while taking VASCEPA.
• Your doctor may do blood tests to check your triglyceride and other lipid levels while you take VASCEPA.

9 ADVERSE REACTIONS

6.1 Clinical Trials Experience

An additional adverse reaction from clinical studies was oophorhyngeal pain. (6)

7 DRUG INTERACTIONS

7.1 Anticoagulants

Some published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time. The prolongation of bleeding time reported in these studies has not exceeded normal limits and did not produce clinically significant bleeding episodes. Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-plalet agents) should be monitored periodically. (7)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women. It is unknown whether VASCEPA can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. VASCEPA should be used during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus. (8.1)

In pregnant rats given oral gavage doses of 0.3, 1 and 2 g/kg/day icosapent ethyl from gestation through organogenesis all drug treated groups had visceral or skeletal abnormalities including: 13th reduced ribs, additional liver lobes, testes mediately displaced and/or not descended at human systemic exposures following a maximum oral dose of 4 g/day based on body surface area comparison. In a multigenerational developmental study in pregnant rats given oral gavage doses of 0.3, 1, 3 g/kg/day ethyl-EPA from gestation day 7-17, an increased incidence of absent optic nerves and unilateral retinal atrophy were observed at ≥0.3 g/kg/day at human systemic exposure following an oral dose of 4 g/day based on body surface area comparison across species. Additional variations consisting of early incisor eruption and increased percent cervical ribs were observed at the same exposures. Pups from high dose treated dams exhibited decreased copulation rates, delayed estrus, decreased implantations and decreased surviving fetuses (F2) suggesting multigenerational effects.

10 DESCRIPTION

11 CLINICAL PHARMACOLOGY

12 NONCLINICAL TOXICOLOGY

13 CLINICAL STUDIES

14 USE IN SPECIFIC POPULATIONS

15 HOW SUPPLIED/STORAGE AND HANDLING

16 DRUGS ABUSE AND DEPENDENCE

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

### Table 1. Adverse Reactions Occurring at Incidence ≥2% and Greater than Placebo in Double-Blind, Placebo-Controlled Trials*

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Placebo (N=309)</th>
<th>VASCEPA (N=822)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>2.3</td>
</tr>
</tbody>
</table>

*Studies included patients with triglyceride values of 200 to 2000 mg/dL.

Additional studies conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adverse reactions reported in at least 2% and at a greater rate than placebo for patients treated with VASCEPA based on pooled data across two clinical studies are listed in Table 1.
Of 14 CLINICAL STUDIES

14.1 Severe Hypertriglyceridemia

The effects of VASCEPA 4 grams per day were assessed in a randomized, placebo-controlled, double-blind, parallel-group study of adult patients (76 on VASCEPA, 75 on placebo) with severe hypertriglyceridemia. Patients whose baseline TG levels were between 500 and 2000 mg/dL were enrolled in this study for 12 weeks. The median baseline TG and LDL-C levels in these patients were 684 mg/dL and 86 mg/dL, respectively. Median baseline HDL-C level was 27 mg/dL. The randomized population in this study was mostly Caucasian (88%) and male (78%). The mean age was 53 years and the mean body mass index was 31 kg/m². Twenty-five percent of patients were on concomitant statin therapy; 28% were diabetics, and 39% of the patients had TG levels >750 mg/dL. The changes in the major lipoprotein lipid parameters for the groups receiving VASCEPA or placebo are shown in Table 2.

Table 2. Median Baseline and Percent Change from Baseline in Lipid Parameters in Patients with Severe Hypertriglyceridemia (≥500 mg/dL)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>VASCEPA 4 g/day</th>
<th>Placebo 75</th>
<th>Difference (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG (mg/dL)</td>
<td>680</td>
<td>+27</td>
<td>703 +10 -13 (*47, -22)</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>91 -5</td>
<td>-8</td>
<td>86 -3 -2 (13, +8)</td>
</tr>
<tr>
<td>Non-HDL-C (mg/dL)</td>
<td>225 -8</td>
<td>+29</td>
<td>228 +4 -18 (-25, -11)</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>254 -7</td>
<td>+256</td>
<td>+256 +8 -16 (-22, -11)</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>27 -4</td>
<td>+0</td>
<td>27 -4 -2 (-9, -2)</td>
</tr>
<tr>
<td>VLDL-C (mg/dL)</td>
<td>123 -20</td>
<td>+124</td>
<td>124 +14 -29 (-43, -14)</td>
</tr>
<tr>
<td>Apo B (mg/dL)</td>
<td>121 -4</td>
<td>+118</td>
<td>+118 +4 -9 (-14, -3)</td>
</tr>
</tbody>
</table>

% Change = Median Percent Change from Baseline Difference= Median of [VASCEPA % Change - Placebo % Change] (Hodges-Lehmann Estimate)

*p-value < 0.01 (primary efficacy endpoint)

**p-value < 0.05 (key secondary efficacy endpoints determined to be statistically significant according to the pre-specified multiple comparison procedure)

VASCEPA 4 grams per day reduced median TG, VLDL-C, and Apo B levels from baseline relative to placebo. The reduction in TG observed with VASCEPA was not associated with elevations in LDL-C levels relative to placebo.

The effect of VASCEPA on the risk of pancreatitis in patients with severe hypertriglyceridemia has not been determined.

The effect of VASCEPA on cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.

14 HOW SUPPLIED/STORAGE AND HANDLING

VASCEPA (icosapent ethyl) capsules are supplied as 0.5-gram amber-colored soft-gelatin capsules imprinted with V500 or as 1-gram amber-colored soft-gelatin capsules imprinted with VASCEPA.

Bottles of 240 (0.5-gram): NDC 59293-003-40

Bottles of 120 (1-gram): NDC 59293-001-20.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Keep out of reach of children.

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

VASCEPA should be used with caution in patients with known sensitivity or allergy to fish and/or shellfish [see Warnings and Precautions (5.2)].

Patients should be advised that use of lipid-regulating agents does not reduce the importance of appropriate nutritional intake and physical activity [see Dosage and Administration (2)].

Patients should be advised not to alter VASCEPA capsules in any way and to ingest intact capsules only [see Dosage and Administration (2)].

Instruct patients to take VASCEPA as prescribed. If a dose is missed, patients should take it as soon as they remember. However, if they miss one day of VASCEPA, they should not double the dose when they take it.

17.2 Instructions for Patients

Patients should be instructed in the importance of appropriate nutritional intake and physical activity. Patients should be advised to take their medication as prescribed. If a dose is missed, patients should take it as soon as they remember. However, if they miss one day of VASCEPA, they should not double the dose when they take it.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year rat carcinogenicity study with oral gavage doses of 0.09, 0.27, and 0.91 g/kg/day icosapent ethyl, respectively, males did not exhibit drug-related neoplasms. Hemangiosomas and hemangiosarcomas of the mesenteric lymph node, the site of drug absorption, were observed in females at clinically relevant exposures based on body surface area comparisons across species relative to the maximum clinical dose of 4 g/day. Overall incidence of hemangiosomas and hemangiosarcomas in all vascular tissues did not increase with treatment.

In a 6-month carcinogenicity study in TG rasH2 transgenic mice with oral gavage doses of 0.5, 1, and 4.6 g/kg/day icosapent ethyl, drug-related incidences of benign squamous cell papillomas in the skin and subcutis of the tail was observed in high dose male mice. The papillomas were considered to develop secondary to chronic irritation of the proximal tail associated with fecal excretion of oil and therefore not clinically relevant. Drug-related neoplasms were not observed in female mice.

Icosapent ethyl was not mutagenic with or without metabolic activation in the bacterial mutagenesis (Ames) assay or in the in vivo mouse micronucleus assay. A chromosomal aberration assay in Chinese Hamster Ovary (CHO) cells was positive for clastogenicity with and without metabolic activation.

13.2 Carcinogenicity in Humans

There are no human carcinogenicity studies with VASCEPA.

13.3 Mutagenicity

Acetyl-CoA:1,2-diacylglycerol acyltransferase (DGAT); decreased lipogenesis in the liver; potential mechanisms of action include increased acyl-CoA:1,2-diacylglycerol acyltransferase (DGAT); decreased lipogenesis in the liver; and increased sensitivity of some older individuals cannot be ruled out.

13.4 Impairment of Fertility

This Patient Information has been approved by:

Amarin Pharma Inc.
Bedminster, NJ, USA
Manufactured for:
Amarin Pharmaceuticals Ireland Limited
Dublin, Ireland
+1-855-VASCEPA (+1-855-827-2372)
www.VASCEPA.com

For more information, go to www.VASCEPA.com or call 1-855-VASCEPA (1-855-827-2372).

This Patient Information has been approved by the U.S. Food and Drug Administration Revised: 2/2017