

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
202057Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

VASCEPA™ (icosapent ethyl) Capsules, for oral use
Initial U.S. Approval: 2012

These highlights do not include all of the information needed to use VASCEPA™ safely and effectively. See full prescribing information for VASCEPA.

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 2 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: 1 gram (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

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-platelet 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)

Pediatric Use: The safety and effectiveness in pediatric patients have not been established. (8.4)

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

Revised: 07/2012

FULL PRESCRIBING INFORMATION:

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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 lipid-lowering diet and exercise regimen before receiving VASCEPA and should continue this diet and exercise regimen with VASCEPA.

Attempts should be made to control any medical problems such as diabetes mellitus, hypothyroidism, and alcohol intake that may contribute to lipid abnormalities. Medications 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.

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.

2 DOSAGE AND ADMINISTRATION

Assess lipid levels before initiating therapy. Identify other causes (e.g., diabetes mellitus, hypothyroidism, or medications) of high triglyceride 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.

The daily dose of VASCEPA is 4 grams per day taken as 2 capsules twice daily with food.

Patients should be advised to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA.

3 DOSAGE FORMS AND STRENGTHS

VASCEPA capsules are supplied as 1-gram amber-colored soft-gelatin capsules imprinted with VASCEPA.

4 CONTRAINDICATIONS

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

5 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.

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.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are 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.

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

Adverse Reaction	Placebo (N=309)		VASCEPA (N=622)	
	n	%	n	%
Arthralgia	3	1.0	14	2.3

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

An additional adverse reaction from clinical studies was oropharyngeal pain.

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 those 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-platelet agents) should be monitored periodically.

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.

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 medially displaced and/or not descended at human systemic exposures following a maximum oral dose of 4 g/day based on body surface comparisons. Variations including incomplete or abnormal ossification of various skeletal bones were observed in the 2 g/kg/day group at 5 times human systemic exposure following an 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 testes 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 comparisons 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 of ethyl-EPA at 7 times human systemic exposure following 4 g/day dose based on body surface area comparisons across species.

In pregnant rabbits given oral gavage doses of 0.1, 0.3, and 1 g/kg/day from gestation through organogenesis there were increased dead fetuses at 1 g/kg/day secondary to maternal toxicity (significantly decreased food consumption and body weight loss).

In pregnant rats given ethyl-EPA from gestation day 17 through lactation day 20 at 0.3, 1, 3 g/kg/day complete litter loss was observed in 2/23 litters at the low dose and 1/23 mid-dose dams by post-natal day 4 at human exposures based on a maximum dose of 4 g/day comparing body surface areas across species.

8.3 Nursing Mothers

Studies with omega-3-acid ethyl esters have demonstrated excretion in human milk. The effect of this excretion is unknown; caution should be exercised when VASCEPA is administered to a nursing mother. In lactating rats, given oral gavage ¹⁴C-ethyl EPA, drug levels were 6 to 14 times higher in milk than in plasma.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of subjects in clinical studies of VASCEPA, 33% were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

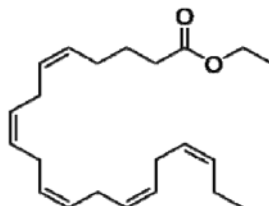
9 DRUG ABUSE AND DEPENDENCE

VASCEPA does not have any known drug abuse or withdrawal effects.

11 DESCRIPTION

VASCEPA, a lipid-regulating agent, is supplied as a 1-gram amber-colored, liquid-filled soft gelatin capsule for oral administration.

Each VASCEPA capsule contains 1 gram of icosapent ethyl. Icosapent ethyl is an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA). The empirical formula of icosapent ethyl is C₂₂H₃₄O₂ and the molecular weight is 330.51. The chemical name for icosapent ethyl is ethyl all-cis-5,8,11,14,17-icosapentaenoate with the following chemical structure:



VASCEPA 1 gram capsules also contain the following inactive ingredients: tocopherol, gelatin, glycerin, maltitol, sorbitol, and purified water.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Studies suggest that EPA reduces hepatic very low-density lipoprotein triglycerides (VLDL-TG) synthesis and/or secretion and enhances TG clearance from circulating VLDL particles. Potential mechanisms of action include increased β -oxidation; inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase (DGAT); decreased lipogenesis in the liver; and increased plasma lipoprotein lipase activity.

12.3 Pharmacokinetics

Absorption: After oral administration, VASCEPA is de-esterified during the absorption process and the active metabolite EPA is absorbed in the small intestine and enters the systemic circulation mainly via the thoracic duct lymphatic system. Peak plasma concentrations of EPA were reached approximately 5 hours following oral doses of VASCEPA.

VASCEPA was administered with or following a meal in all clinical studies; no food effect studies were performed. Take VASCEPA with or following a meal.

Distribution: The mean volume of distribution at steady-state of EPA is approximately 88 liters. The majority of EPA circulating in plasma is incorporated in phospholipids, triglycerides and cholesteryl esters, and <1% is present as the unesterified fatty acid. Greater than 99% of unesterified EPA is bound to plasma proteins.

Metabolism and Excretion: EPA is mainly metabolized by the liver via beta-oxidation similar to dietary fatty acids. Beta oxidation splits the long carbon chain of EPA into acetyl Coenzyme A, which is converted into energy via the Krebs cycle. Cytochrome P450-mediated metabolism is a minor pathway of elimination of EPA. The total plasma clearance of EPA at steady state is 684 mL/hr. The plasma elimination half-life ($t_{1/2}$) of EPA is approximately 89 hours. VASCEPA does not undergo renal excretion.

Drug-Drug Interactions

VASCEPA was studied at the 4 g/day dose level with the following medications which are typical substrates of cytochrome P450 enzymes, and no drug-drug interactions were observed:

Omeprazole: In a drug-drug interaction study with 28 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the steady-state AUC_{τ} or C_{max} of omeprazole when co-administered at 40 mg/day to steady-state.

Rosiglitazone: In a drug-drug interaction study with 28 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the single dose AUC or C_{max} of rosiglitazone at 4 mg.

Warfarin: In a drug-drug interaction study with 25 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the single dose AUC or C_{max} of *R*- and *S*-warfarin or the anti-coagulation pharmacodynamics of warfarin when co-administered as racemic warfarin at 25 mg.

Atorvastatin: In a drug-drug interaction study of 26 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the steady-state AUC_{τ} or C_{max} of atorvastatin,

2-hydroxyatorvastatin, or 4-hydroxyatorvastatin when co-administered with atorvastatin 80 mg/day to steady-state.

Specific Populations

Gender: When administered VASCEPA in clinical trials, plasma total EPA concentrations did not differ significantly between men and women.

Pediatric: The pharmacokinetics of VASCEPA has not been studied in pediatric patients.

Hepatic or Renal Impairment: VASCEPA has not been studied in patients with renal or hepatic impairment.

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. Hemangiomas 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 hemangiomas 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, 2, and 4.6 g/kg/day icosapent ethyl, drug-related incidences of benign squamous cell papilloma 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.

In an oral gavage rat fertility study, ethyl-EPA, administered at doses of 0.3, 1, and 3 g/kg/day to male rats for 9 weeks before mating and to female rats for 14 days before mating through day 7 of gestation, increased anogenital distance in female pups and increased cervical ribs were observed at 3 g/kg/day (7 times human systemic exposure with 4 g/day clinical dose based on a body surface area comparison).

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 2,000 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 (76%). 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)

Parameter	Vascepa 4 g/day N=76		Placebo N=75		Difference (95% Confidence Interval)
	Baseline	% Change	Baseline	% Change	
TG (mg/dL)	680	-27	703	+10	-33* (-47, -22)
LDL-C (mg/dL)	91	-5	86	-3	-2 (-13, +8)
Non-HDL-C (mg/dL)	225	-8	229	+8	-18 (-25, -11)
TC (mg/dL)	254	-7	256	+8	-16 (-22, -11)
HDL-C (mg/dL)	27	-4	27	0	-4 (-9, +2)
VLDL-C (mg/dL)	123	-20	124	+14	-29** (-43, -14)
Apo B (mg/dL)	121	-4	118	+4	-9** (-14, -3)

% Change= Median Percent Change from Baseline

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

p-values from Wilcoxon rank-sum test

* p-value < 0.001 (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 levels has not been determined.

16 HOW SUPPLIED/STORAGE AND HANDLING

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

Bottles of 120: NDC 52937-001-20.

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.

Distributed by:

Amarin Pharma Inc.
Bedminster, NJ, USA

Manufactured by:

Banner Pharmacaps
Tilburg, The Netherlands

Manufactured for:

Amarin Pharmaceuticals Ireland Limited
Dublin, Ireland
+1-855-VASCEPA (+1-855-827-2372)

www.VASCEPA.com

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PATIENT INFORMATION
VASCEPA™ (pronounced vas-EE-puh)
(icosapent ethyl)
Capsules

Read this Patient Information before you start taking VASCEPA and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment.

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.

Who should not take VASCEPA?

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.

What should I tell my doctor before taking VASCEPA?

Before you take VASCEPA, tell your doctor 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 non-prescription 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).

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

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.
- You should not take more than 4 capsules of VASCEPA each day. Do not take more capsules than what is prescribed by your doctor.
- 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.

What are the possible side effects of VASCEPA?

If you have liver problems and are taking VASCEPA, your doctor should do blood tests during treatment.

The most common side effect of VASCEPA is joint pain. **As with all drugs, you may experience a serious side effect when taking VASCEPA.** Talk to your doctor if you have a side effect that bothers you or does not go away.

This is not the only side effect of VASCEPA. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VASCEPA?

- Store VASCEPA at room temperature between 68° to 77° F (20° to 25° C).
- Safely throw away medicine that is out of date or no longer needed.

Keep VASCEPA and all medicine out of the reach of children.

General information about the safe and effective use of VASCEPA.

Medicines are sometimes prescribed for purposes other than those listed in Patient Information Leaflets. Do not use VASCEPA for a condition for which it was not prescribed. Do not give VASCEPA to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information summarizes the most important information about VASCEPA. If you would like more information, talk with your doctor or pharmacist. You can ask your doctor or pharmacist for information about VASCEPA that is written for health professionals.

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

What are the ingredients in VASCEPA?

Active Ingredient: icosapent ethyl

Inactive Ingredients: tocopherol, gelatin, glycerin, maltitol, sorbitol, and purified water

This patient information has been approved by the U.S. Food and Drug Administration.

VASCEPA is a trademark of Amarin Pharmaceuticals Ireland Ltd.

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Amarin Pharma Inc.

Bedminster, NJ, USA

Manufactured by:

Banner Pharmacaps

Tilburg, The Netherlands

Manufactured for:

Amarin Pharmaceuticals Ireland Limited

Dublin, Ireland

+1-855-VASCEPA (+1-855-827-2372)

www.vascepa.com

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC C COLMAN
07/26/2012