

# Exhibit F

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

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

**These highlights do not include all 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 four 0.5-gram capsules or two 1-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)

-----**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](http://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)

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

Revised: 2/2017

**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<sup>®</sup> (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe ( $\geq 500$  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 either:

- four 0.5-gram capsules twice daily with food; or as
- two 1-gram 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 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.

### 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: 13<sup>th</sup> 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

nerves and unilateral testes atrophy were observed at  $\geq 0.3$  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 on the infant of a nursing mother is unknown; caution should be exercised when VASCEPA is administered to a nursing mother. An animal study in lactating rats given oral gavage  $^{14}\text{C}$ -ethyl EPA demonstrated that 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 either a 0.5-gram or a 1-gram amber-colored, liquid-filled soft gelatin capsule for oral administration.

Each VASCEPA capsule contains either 0.5 grams of icosapent ethyl (in a 0.5 gram capsule) or 1 gram of icosapent ethyl (in a 1 gram capsule). Icosapent ethyl is an ethyl ester of the omega-3 fatty acid eicosapentaenoic acid (EPA). The empirical formula of icosapent ethyl is  $\text{C}_{22}\text{H}_{34}\text{O}_2$  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:

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