HIGHLIGHTS OF PRESCRIBING INFORMATION

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

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

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	12/2019
Warnings and Precautions, Atrial Fibrillation/Flutter (5.1)	12/2019
Warnings and Precautions, Bleeding (5.3)	12/2019

----------INDICATIONS AND USAGE----------

VASCEPA is an ethyl ester of eicosapentaenoic acid (EPA) indicated:

- as an adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥ 150 mg/dL) and
  - established cardiovascular disease or
  - diabetes mellitus and 2 or more additional risk factors for cardiovascular disease. (1)
- as an adjunct to diet to reduce 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)

----------DOSAGE AND ADMINISTRATION----------

- Assess lipid levels before initiating therapy. Identify other causes of high triglyceride levels and manage as appropriate. (2.1)
- Patients should engage in appropriate nutritional intake and physical activity before receiving VASCEPA, which should continue during treatment. (2.1)
- The daily dose of VASCEPA is 4 grams per day taken as either
  - four 0.5 gram capsules twice daily with food or
  - two 1 gram capsules twice daily with food. (2.2)
- Advise patients to swallow capsules whole. Do not break open, crush, dissolve, or chew VASCEPA. (2.2)

----------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----------

Atrial Fibrillation/Flutter: VASCEPA was associated with an increased risk of atrial fibrillation or atrial flutter requiring hospitalization in a double-blind, placebo-controlled trial. The incidence of atrial fibrillation was greater in patients with a previous history of atrial fibrillation or atrial flutter. (5.1)
Potential for Allergic Reactions in Patients with 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. Inform patients with known hypersensitivity to fish and/or shellfish about the potential for allergic reactions and advise them to discontinue VASCEPA and seek medical attention if any reactions occur. (5.2)
Bleeding: VASCEPA was associated with an increased risk of bleeding in a double-blind, placebo-controlled trial. The incidence of bleeding was greater in patients receiving concomitant antithrombotic medications, such as aspirin, clopidogrel, or warfarin. (5.3)

----------ADVERSE REACTIONS----------

Common adverse reactions in the cardiovascular outcomes trial (incidence ≥3% and ≥1% more frequent than placebo): musculoskeletal pain, peripheral edema, constipation, gout, and atrial fibrillation (6.1)
Common adverse reactions in the hypertriglyceridemia trials (incidence ≥1% more frequent than placebo): arthralgia and oropharyngeal pain. (6.1)

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----------

Increased Bleeding Risk with Anticoagulants and Antiplatelet Agents: Some published studies with omega-3 fatty acids have demonstrated prolongation of bleeding time. Monitor patients receiving VASCEPA and concomitant anticoagulants and/or antiplatelet agents for bleeding. (7)

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

Revised: 12/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

*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 maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated triglyceride (TG) levels (≥ 150 mg/dL) and
  - established cardiovascular disease or
  - diabetes mellitus and 2 or more additional risk factors for cardiovascular disease.
- as an adjunct to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia.

Limitations of Use:

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

2 DOSAGE AND ADMINISTRATION

2.1 Prior to Initiation of VASCEPA

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

2.2 Dosage and Administration

- 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.
- Advise patients to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA.

3 DOSAGE FORMS AND STRENGTHS

VASCEPA capsules are supplied as:

- 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 Atrial Fibrillation/Flutter

VASCEPA is associated with an increased risk of atrial fibrillation or atrial flutter requiring hospitalization. In a double-blind, placebo-controlled trial of 8,179 statin-treated subjects with established cardiovascular disease (CVD) or diabetes plus an additional risk factor

for CVD, adjudicated atrial fibrillation or atrial flutter requiring hospitalization for 24 or more hours occurred in 127 (3%) patients treated with VASCEPA compared to 84 (2%) patients receiving placebo [HR= 1.5 (95% CI 1.14, 1.98)]. The incidence of atrial fibrillation was greater in patients with a previous history of atrial fibrillation or atrial flutter.

5.2 Potential for Allergic Reactions in Patients with 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. Inform patients with known hypersensitivity to fish and/or shellfish about the potential for allergic reactions to VASCEPA and advise them to discontinue VASCEPA and seek medical attention if any reactions occur.

5.3 Bleeding

VASCEPA is associated with an increased risk of bleeding. In a double-blind, placebo-controlled cardiovascular outcomes trial of 8,179 patients, 482 (12%) patients receiving VASCEPA experienced a bleeding event compared to 404 (10%) patients receiving placebo. Serious bleeding events occurred in 111 (3%) of patients on VASCEPA vs. 85 (2%) of patients receiving placebo. The incidence of bleeding was greater in patients receiving concomitant antithrombotic medications, such as aspirin, clopidogrel, or warfarin.

6 ADVERSE REACTIONS

The following important adverse reactions are described below and elsewhere in the labeling:

- Atrial Fibrillation or Atrial Flutter *[see Warnings and Precautions (5.1)]*
- Potential for Allergic Reactions in Patients with Fish Allergy *[see Warnings and Precautions (5.2)]*
- Bleeding *[see Warnings and Precautions (5.3)]*

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.

Cardiovascular Outcomes Trial

In a double-blind, randomized, placebo-controlled cardiovascular outcomes trial, 8,179 statin-stabilized patients were randomized to receive VASCEPA or placebo and followed for a median of 4.9 years *[see Clinical Studies (14.1)]*. The median age at baseline was 64 years, 29% were women, 90% White, 5% Asian, 2% were Black, and 4% identified as Hispanic ethnicity.

Common adverse reactions (incidence ≥3% on VASCEPA and ≥1% more frequent than placebo) included musculoskeletal pain, peripheral edema, constipation, gout, and atrial fibrillation.

Hypertriglyceridemia Trials

In two randomized, double-blind, placebo-controlled trials in patients with triglyceride levels between 200 and 2000 mg/dL treated for 12 weeks, adverse reactions reported with

VASCEPA at an incidence ≥1% more frequent than placebo based on pooled data included arthralgia and oropharyngeal pain.

6.2 Postmarketing Experience

Additional adverse reactions have been identified during post-approval use of VASCEPA. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Diarrhea
- Blood triglycerides increased
- Abdominal discomfort
- Pain in the extremities

7 DRUG INTERACTIONS

7.1 Increased Bleeding Risk with Anticoagulants and Antiplatelet Agents

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. Monitor patients receiving VASCEPA and concomitant anticoagulants and/or antiplatelet agents for bleeding.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The available data from published case reports and the pharmacovigilance database on the use of VASCEPA in pregnant women are insufficient to identify a drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes. In animal reproduction studies in pregnant rats, non-dose-related imbalances for some minor developmental findings were observed with oral administration of icosapent ethyl during organogenesis at exposures that were equivalent to the clinical exposure at the human dose of 4 g/day, based on body surface area comparisons. In a study in pregnant rabbits orally administered icosapent ethyl during organogenesis, there were no clinically relevant adverse developmental effects at exposures that were 5 times the clinical exposure, based on body surface area comparisons *(see Data).*

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

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 non-dose-related imbalances in visceral and skeletal findings, 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.

In a multigenerational developmental study in pregnant rats given doses of 0.3, 1, 3 g/kg/day icosapent ethyl by oral gavage from gestation day 7-17, icosapent ethyl did not affect viability in fetuses (F_1 or F_2). Non-dose-related imbalances in findings of absent optic nerves and unilateral testes atrophy at human exposures based on the maximum dose of 4 g/day and on body surface area comparisons. 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 potential multigenerational effects of icosapent ethyl 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 icosapent ethyl from gestation through organogenesis, a decrease in body weight and food consumption was observed at the high dose of 1 g/kg/day (5 times the human exposure at the maximum dose of 4 g/day, based on body surface area comparisons). Slight increases in resorbed and dead fetuses were noted in the 1 g/kg/day group, but these were not significantly different from the control group. There were no differences between the icosapent ethyl groups and control group as to the number of *corpora lutea*, number of implantations, number of surviving fetuses, sex ratio, body weight of female fetuses or placental weight. There were no treatment-related malformations or skeletal anomalies.

In pregnant rats given icosapent ethyl from gestation day 17 through lactation day 20 at 0.3, 1, 3 g/kg/day no adverse maternal or developmental effects were observed. However, complete litter loss (not dose-related) was noted in 2/23 litters at the low dose and 1/23 mid-dose dams by post-natal day 4 at human exposures at a maximum dose of 4 g/day, based on body surface area comparisons.

8.2 Lactation

Risk Summary

Published studies have detected omega-3 fatty acids, including EPA, in human milk. Lactating women receiving oral omega-3 fatty acids for supplementation have resulted in higher levels of omega-3 fatty acids in human milk. There are no data on the effects of omega-3 fatty acid ethyl esters on the breastfed infant or on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VASCEPA and any potential adverse effects on the breastfed child from VASCEPA or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients in well-controlled clinical studies of VASCEPA, 45% were 65 years of age and over. No overall differences in safety or effectiveness were observed

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