VASCEPA® (icosapent ethyl) Capsules
Fact Sheet for Media

VASCEPA® Background

VASCEPA (icosapent ethyl) – pronounced vas-EE-puh – is the first-and-only prescription treatment approved by the U.S. Food and Drug Administration (FDA) that only contains the active ingredient icosapent ethyl (IPE), a unique form of eicosapentaenoic acid (EPA).

On December 13, 2019, VASCEPA became the first and only drug approved by the FDA for cardiovascular risk reduction 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

In addition, VASCEPA is approved by the FDA as:

- An adjunct to diet to reduce TG levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia

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

Important Safety Information

- VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components.
- 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.
- Is it not known whether patients with allergies to fish and/or shellfish are at an increased risk of an allergic reaction to VASCEPA. Patients with such allergies should discontinue VASCEPA if any reactions occur.
- 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.
- 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.
- Common adverse reactions in the hypertriglyceridemia trials (incidence ≥1% more frequent than placebo): arthralgia and oropharyngeal pain.
- Adverse events may be reported by calling 1-855-VASCEPA or the FDA at 1-800-FDA-1088.

- Patients receiving VASCEPA and concomitant anticoagulants and/or anti-platelet agents for bleeding should be monitored.

Since becoming available in 2013, VASCEPA has been prescribed more than 8 million times and is covered by most major medical insurance plans. These FDA approved indications are the result of more than a decade and more than 37,000 patient years of clinical study.

Outside the United States, VASCEPA is available by prescription in Lebanon and the United Arab Emirates. Amarin, together with its commercial partners in select geographies, is pursuing additional regulatory approvals for VASCEPA in Canada, China, the European Union and the Middle East.

VASCEPA: An Important Treatment Option for High-Risk Patients

Approximately 38 million patients in the United States are on statin therapy.[1] VASCEPA does not replace statin therapy, rather it addresses the persistent cardiovascular risk which remains in many patients despite statin therapy. Approximately 12 million of the statin-treated patients have TG levels ≥150 mg/dL, which is a marker of cardiovascular risk, and more than half of these patients are also estimated to have established cardiovascular disease or diabetes and multiple other cardiovascular risk factors. In addition, millions of patients are statin intolerant and have these cardiovascular risk factors.[2] Both high-risk statin-treated and statin-intolerant patients are covered by the new label for VASCEPA and are candidates to be helped by this important preventative care therapy.

In the United States, one stroke and one heart attack occur on average every 40 seconds, and one cardiovascular death occurs on average every 38 seconds.[3,4,5] The number of cardiovascular disease deaths attributed to cardiovascular disease is increasing and cardiovascular disease is the No. 1 cause of death for men and women in the United States.[4,5] Cardiovascular disease is also the nation's costliest disease, with direct and indirect expenses in excess of $500 billion each year.[4,5]

Cholesterol management, the primary focus of statin therapy, lowers cardiovascular risk by 25 – 35%. Such risk reduction is important. However, despite such risk reduction 65 – 75% of persistent cardiovascular risk remains. Since statin therapy was introduced nearly three decades ago, healthcare professionals have sought effective preventative care treatment options to reduce persistent cardiovascular risk beyond management of cholesterol. Many potential solutions failed to show favorable effects in cardiovascular outcomes studies. The development of VASCEPA included learnings from these failures and now VASCEPA is the first and only drug to succeed in reducing that risk in the patient group included in the new VASCEPA label.

VASCEPA: Clinical Study Results

REDUCE-IT®[6] is the name of the landmark cardiovascular outcomes study of VASCEPA. The success of REDUCE-IT led to an expanded label for VASCEPA, which is now the first-and-only FDA-approved drug to reduce the risk of various major adverse cardiovascular events (MACE) in the study defined high-risk patients with persistent cardiovascular risk. Persistent cardiovascular risk is the residual risk for a cardiovascular event (e.g., heart attack, stroke, or death) which remains after a patient is treated with current standard-of-care therapies, such as cholesterol management with statin therapy.

REDUCE-IT was a multinational, double-blind, randomized, placebo-controlled, event-driven study in 8,179 (4,089 VASCEPA, 4,090 placebo) statin-treated adult patients from 11 countries enrolled with LDL-C >40 mg/dL and ≤100 mg/dL and elevated TG levels (90% of enrolled patients had TG ≥150 mg/dL and <500 mg/dL) and either established cardiovascular disease (71%) or diabetes and other risk factors for cardiovascular disease (29%). Patients with established cardiovascular disease were defined as being at least 45 years of age and having a documented history of coronary artery disease, cerebrovascular or carotid disease, or peripheral artery disease. Patients with other risk factors for cardiovascular disease were defined as being at least 50 years of age with diabetes and at least one additional risk factor. Patients were randomly assigned 1:1 to receive either VASCEPA (4 grams daily) or placebo. The median follow-up duration was 4.9 years. Overall, 99.8% of patients were followed for vital status until the end of the study or death.

REDUCE-IT was Amarin's third phase 3 clinical study of VASCEPA. The first two studies, MARINE and ANCHOR, were successful studies demonstrating the intended effects of VASCEPA on biomarkers. REDUCE-IT was not designed to assess cholesterol management, as VASCEPA is predominantly not a cholesterol management drug, and not designed to answer separate questions regarding the potential cardiovascular benefit from any therapy other than VASCEPA.

The efficacy and safety results of the REDUCE-IT study were published in *The New England Journal of Medicine*. In REDUCE-IT, VASCEPA:

- significantly reduced by 25% the risk for the primary composite endpoint (time to first occurrence of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina; p<0.0001)
- significantly reduced by 26% the key secondary composite endpoint (time to first occurrence of cardiovascular death, myocardial infarction, or stroke; p<0.0001)
- achieved seven other secondary endpoints in the pre-specified hierarchical order below the key secondary endpoint, including a 20% relative risk reduction in cardiovascular death compared to placebo (HR, 0.80; 95% CI, 0.66-0.98; p=0.03)

The results were consistent across multiple subgroups, including in males and females.

Excluding the rates of MACE in the primary endpoint, the overall rate of adverse events and serious adverse events in the REDUCE-IT study were similar between VASCEPA-treated patients and placebo-treated patients. The relative long duration of patient follow-up (5 years) and the high-risk characteristics of the patients enrolled in the study, along with multiple concomitant therapies, contributed to the majority of patients in the REDUCE-IT study having some form of adverse event. As reflected in VASCEPA's expanded label and described below, VASCEPA has been associated with increased risk of reported bleeding and atrial fibrillation/flutter, the latter being particularly reported in patients with a previous history of atrial fibrillation or flutter. It is recommended that patients taking VASCEPA and concomitant anticoagulants and/or antiplatelet agents for bleeding be monitored.[6]

With respect to reducing the first occurrence of events, this result represents a number needed to treat (NNT) of 21, which means one fewer MACE on average for every 21 patients studied. Furthermore, in a post-hoc analysis published in the *Journal of American College of Cardiology* which reviewed REDUCE-IT results with respect to both the first occurrence of MACE and recurrent MACE, over a period of five years, VASCEPA reduced on average one MACE per 6

patients studied. Recurrent cardiovascular events are common and part of overall patient care and treatment costs.

Recurrent event analyses were conducted for the total primary endpoint events and total key secondary endpoint events in REDUCE-IT using a series of statistical models and published in the Journal of the American College of Cardiology. These analyses were tertiary or exploratory endpoints; most of the models used were prespecified and one was post hoc.

VASCEPA: Medical Guidelines

Since the REDUCE-IT results were published, multiple medical societies, including the American Diabetes Association, have updated their medical treatment guidelines to include that icosapent ethyl (the generic product name for VASCEPA) be considered to treat high cardiovascular risk patients consistent with the population studied in REDUCE-IT.[7,8] These guidelines emphasize that the REDUCE-IT results are specific to icosapent ethyl and should not be generalized to any other therapy.

VASCEPA: Cost-Effectiveness

Two independent health economic studies have concluded that VASCEPA is cost-effective.

In November 2019, a health economics study presented at the American Heart Association 2019 Scientific Sessions showed that use of VASCEPA is not only cost-effective but also offers potential cost savings for patients and for the overall healthcare system (i.e., the cost of VASCEPA is offset by cost savings from reducing the occurrence of high cost major adverse cardiovascular events).[9] This is a rare finding for any drug.

In September 2019, a separate independent drug pricing watchdog group that found VASCEPA cost effective for cardiovascular risk reduction, a result seldom achieved in its analyses.[10] Amarin has priced VASCEPA similar to how atorvastatin (brand name Lipitor) was priced before going generic. This pricing, despite unprecedented clinical results and first approval for an important new indication, is well below the price at which various other cardiovascular drugs have been introduced over the past decade. Amarin believes that such pricing should make VASCEPA broadly available to high-risk patients. Patients with commercial medical insurance and a prescription can get VASCEPA for as little as $3 on average per month.

Amarin is challenging medical insurance to rapidly cover VASCEPA both to benefit patients who need VASCEPA and to encourage other drug development to pursue cost-effective pricing as a pathway to prompt insurance reimbursement for needy patients.

VASCEPA: Differentiation

VASCEPA offers multiple cardiovascular benefits, and is the first-and-only FDA-approved drug indicated to reduce the risk of various MACE in REDUCE-IT defined high-risk patients with persistent cardiovascular risk. No other product has the demonstrated effects of VASCEPA and none have been successful in demonstrating clinical outcomes benefit as shown for VASCEPA in the REDUCE-IT study.

The positive effects of VASCEPA, while not completely understood, are likely derived from the unique multi-factorial effects of its single molecule active ingredient, which are enabled by

stringent and complex FDA-regulated processes used to isolate, protect and stabilize the product from degradation.

VASCEPA: Dosing

VASCEPA is available as either 1-gram or 0.5-gram capsules, and the approved daily dose is 4 grams. Patients should swallow either 2 capsules (if using the 1-gram size) or 4 capsules (if using the 0.5-gram size) twice a day with food.

FULL VASCEPA PRESCRIBING INFORMATION CAN BE FOUND AT WWW.VASCEPA.COM.

For more information about VASCEPA, visit www.vascepa.com.
For more information about Amarin, visit www.amarincorp.com.

---

1 Fan W, Philip S, Toth PP, et al. Prevalence of United States adults with triglycerides ≥ 135 mg/dL: NHANES 2007–2014. Cardiol J. 2019;26(5). DOI: 10.5603/CJ.2019.0000.

2 Saeed B, Wright E, Evans M, et al. PS1-45: Prevalence of Statin Intolerance in a High Risk Cohort and Management Strategies in Contemporary Cardiology. Clin Med Res. 2013;11(3):136.

3 American Heart Association: Heart Disease and Stroke Statistics -- 2019 At-a-Glance.

4 American Heart Association. Heart Disease and Stroke Statistics – 2019 Update: A Report from the American Heart Association. Published January 31, 2019.

5 American Heart Association. 2017. Cardiovascular disease: A costly burden for America projections through 2035.

6 Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. N Engl J Med 2019;380:11-22.

7 “American Diabetes Association Issues Critical Updates to the 2019 Standards of Medical Care in Diabetes.” American Diabetes Association, 27 March 2019, https://www.diabetes.org/newsroom/press-releases/2019/ada-issues-critical-updates-to-2019-standards-of-care.

8 Skulas-Ray AC, Wilson PWF, Harris WS, Brinton EA, Kris-Etherton PM, Richter CK, Jacobson TA, Engler MB, Miller M, Robinson JG, Blum CB, Rodriguez-Leyva D, de Ferranti SD, Welty FK; on behalf of the American Heart Association Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Omega-3 fatty acids for the management of hypertriglyceridemia: a science advisory from the American Heart Association. Circulation. 2019;140:e673–e691. doi: 10.1161/CIR.0000000000000709.

9 Cost-Effectiveness of Icosapent Ethyl in REDUCE-IT. https://www.abstractsonline.com/pp8/#!/7891/presentation/35097.

10 https://icer-review.org/wp-content/uploads/2019/02/ICER_CVD_Final_Evidence_Report_10.17.19.pdf.