REDUCE-IT® Fact Sheet for Media

What was REDUCE-IT®?

REDUCE-IT®[1] is the name of a landmark cardiovascular outcomes study of the prescription drug VASCEPA® (icosapent ethyl). The success of REDUCE-IT led to an expanded label for VASCEPA, which is now the first-and-only United States Food and Drug Administration (FDA)-approved drug to reduce the risk of various major adverse cardiovascular events (MACE) in REDUCE-IT 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) even after a patient is treated with current standard-of-care therapies, such as cholesterol management with statin therapy. Further information regarding the FDA approved label for VASCEPA is provided below.

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 triglyceride (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.

What was the REDUCE-IT study design?[2]

REDUCE-IT was designed to test the efficacy and safety of VASCEPA in reducing MACE based on the multifactorial effects of VASCEPA. It was not designed to validate the effect of lowering TGs on a stand-alone basis or to assess the potential effects of any other therapy.

The primary endpoint of REDUCE-IT was a composite of five-point MACE:

- cardiovascular death
- non-fatal myocardial infarction (heart attack)
- non-fatal stroke
- coronary revascularization (procedures such as stents and bypass)
- unstable angina requiring hospitalization

The key secondary endpoint of REDUCE-IT was a composite of three-point MACE:

- cardiovascular death
- non-fatal myocardial infarction (heart attack)
- non-fatal stroke

There are >30 additional, pre-specified secondary and tertiary endpoints.

What were the REDUCE-IT results?

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 an increased risk of 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 receiving VASCEPA and concomitant anticoagulants and/or antiplatelet agents for bleeding be monitored.[3]

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 of 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.

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 be considered to treat high cardiovascular risk patients consistent with the population studied in REDUCE-IT.[4,5] These guidelines emphasize that the REDUCE-IT results are specific to icosapent ethyl and should not be generalized to any other therapy.

In addition, recently, a health economics study presented at the American Heart Association 2019 Scientific Sessions showed that use of VASCEPA 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).[6] This very rare finding follows conclusions from a separate independent drug pricing watchdog group that found VASCEPA cost effective for cardiovascular risk reduction, a result seldom achieved in its analyses.[7]

Why was REDUCE-IT an important study?

Despite current treatment options, in the United States, there is one stroke and one heart attack each occurring on average every 40 seconds, and one cardiovascular death occurring on average every 38 seconds.[8,9,10] The number of cardiovascular deaths is increasing and cardiovascular disease is the No. 1 cause of death for men and women in the United States.[8,9] Cardiovascular disease is also the nation's costliest disease, with direct and indirect expenses in excess of $500 billion each year.[8,9]

Controlling bad cholesterol, also known as LDL-C, is one way to reduce a patient's risk for cardiovascular events.[11] This is often accomplished through statin therapy. However, even with the achievement of target LDL-C levels, millions of patients still have significant and persistent risk of cardiovascular events, especially those patients with high triglycerides.

Statin therapy has been shown to control LDL-C, thereby reducing the risk of cardiovascular events by 25-35% – but that still leaves 65-75% of persistent cardiovascular risk remaining.[10] And, people with high triglycerides have 35% more cardiovascular events compared to people with normal (in range) triglycerides taking statins.[12,13,14,15]

Approximately 38 million patients in the United States are on statin therapy.[16] 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.[15] In addition, millions of patients are statin intolerant and have these cardiovascular risk factors.[17] 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.

What is VASCEPA?

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

The mechanisms of action contributing to reduction of cardiovascular events with VASCEPA are not completely understood but are likely multi-factorial.

Since becoming available in 2013, VASCEPA has been prescribed more than 8 million times and is covered by most major medical insurance plans. The approved indications for VASCEPA are the result of more than a decade of development and clinical study.

What is VASCEPA approved to treat?

VASCEPA is available by prescription only.

United States Indication:
VASCEPA is comprised of the unique drug icosapent ethyl (IPE) and 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
- 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.

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

Outside the United States: VASCEPA is also 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.

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 reported 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.

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

About Amarin Corporation – guided by science; driven to help improve patient care

Amarin Corporation plc. is a rapidly growing, innovative pharmaceutical company focused on developing and commercializing therapeutics to cost-effectively improve cardiovascular health. Amarin's lead product, VASCEPA® (icosapent ethyl), is available by prescription in the United States, 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. For more information about Amarin, visit www.amarincorp.com.

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