Reduce Cardiovascular Risk With VASCEPA® (icosapent ethyl): Evidence From REDUCE-IT™

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6:00 PM

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The FDA has not reviewed and opined on a supplemental new drug application related to REDUCE-IT. FDA has thus not reviewed the information herein or determined whether to approve VASCEPA for use to reduce the risk of major adverse cardiovascular events in the REDUCE-IT patient population.

As with any CV outcomes trial result, further REDUCE-IT data assessment and data release could yield additional useful information to inform greater understanding of study outcome.

Funding for this program provided by Amarin. CME credits are not offered.

Amarin policy limits attendance at meal functions to physicians, NPs, PAs and nurses who support them, pharmacists, and medical students. No other guests, including non-HCP spouses and retired HCPs, are permitted to attend the program or consume the meal.*

This invitation is non-transferable.

*The intended audience for the program is healthcare professionals involved in or who have an interest in the treatment of cardiovascular disease. VASCEPA is not approved for pediatric use; therefore, the program is not intended for physicians who primarily treat patients who are under 18. Additionally, VASCEPA is not intended for use by Ophthalmologists, Dermatologists, Orthopedists, Oncologists, and Psychiatrists.

IMPORTANT INFORMATION FOR HCPs ABOUT VASCEPA® (ICOSAPENT ETHYL) CAPSULES
FDA-Approved Indication and Limitations of Use for VASCEPA

- VASCEPA® (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia
- In patients with severe hypertriglyceridemia, the effect of VASCEPA on cardiovascular mortality or morbidity or on the risk of pancreatitis has not been determined

Important Safety Information for VASCEPA from FDA-Approved Label
Data from Two 12-Week Studies (MARINE and ANCHOR) of Patients with Triglyceride Values of 200 to 2000 mg/dL (n=622 on VASCEPA, n=309 on placebo)

- VASCEPA is contraindicated in patients with known hypersensitivity (e.g., anaphylactic reaction) to VASCEPA or any of its components
- In patients with hepatic impairment, monitor ALT and AST levels periodically during therapy
- Use with caution in patients with known hypersensitivity to fish and/or shellfish
- The most common reported adverse reaction (incidence >2% and greater than placebo) was arthralgia (2.3% VASCEPA, 1.0% placebo)
- Adverse events may be reported by calling 1-855-VASCEPA or the FDA at 1-800-FDA-1088
- Patients receiving treatment with VASCEPA and other drugs affecting coagulation (e.g., anti-platelet agents) should be monitored periodically
- Patients should be advised to swallow VASCEPA capsules whole; not to break open, crush, dissolve, or chew VASCEPA

See full Prescribing Information for more information on VASCEPA or go to www.vascepahcp.com.

See next page for Important Safety Information related to REDUCE-IT for VASCEPA.

AMARIN®

Vascepa® (icosapent ethyl)

IMPORTANT INFORMATION FOR HCPs ABOUT VASCEPA® (ICOSAPENT ETHYL) CAPSULES

IMPORTANT *NEW* INFORMATION: REDUCE-IT™ CARDIOVASCULAR OUTCOMES STUDY OF VASCEPA®[1,2]*

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

The effects of VASCEPA on the prevention of cardiovascular (CV) events was evaluated in a multi-center, double-blind, randomized, placebo-controlled, event-driven trial (REDUCE-IT, NCT01492361) in 8,179 adult patients enrolled in 11 countries, with a median baseline low-density lipoprotein cholesterol (LDL-C) level of 75 mg/dL, with established cardiovascular disease (CVD) or at high risk for CVD, and hypertriglyceridemia (fasting triglycerides (TG) ≥135 and <500 mg/dL).

- Patients were eligible to enter the trial if they were at least 45 years of age and on stable statin therapy with fasting LDL-C levels of >40 and ≤100 mg/dL and fasting TG levels of ≥135 and <500 mg/dL. Patients also needed to have either established CVD (secondary prevention cohort), defined as documented history of coronary artery disease, cerebrovascular or carotid disease, or peripheral artery disease, or be at least 50 years of age with diabetes and at least one additional risk factor (primary prevention cohort).
  - Key exclusion criteria included severe heart failure, active severe liver disease, hemoglobin A1c >10.0%, planned coronary intervention or surgery, history of acute or chronic pancreatitis, and known hypersensitivity to fish, shellfish, or ingredients of VASCEPA or placebo.
- 70.7% of patients were enrolled based on having established CVD (secondary prevention cohort), 29.3% were enrolled based on being at high risk for CVD (primary prevention cohort).
- Patients were randomly assigned 1:1 to receive either VASCEPA (4 grams daily) or placebo (4,089 VASCEPA, 4,090 placebo).
- The median follow-up duration was 58 months (4.9 years).
- At the time of database lock, vital status was available for 99.8% of the patients.
- The median age at baseline was 64 years (range: 44 years to 92 years), with 46% being at least 65 years old; 28.8% were women.
- The trial population was 90.2% White, 1.9% Black, and 5.5% Asian; 4.2% identified as Hispanic ethnicity.
- Regarding prior diagnoses of CV disease, 69.1% of the patient population had prior atherosclerotic CV disease and 89.2% had nonatherosclerotic CV disease.
- Selected additional baseline risk factors included hypertension (86.6%), diabetes mellitus (0.7% type 1 and 57.8% type 2), current daily cigarette smoking (15.2%), and eGFR < 60 mL/min per 1.73 m^2 (22.2%).
- Patients enrolled were stabilized on statin therapy prior to baseline with most (93.2%) on a high- (30.8%) or moderate-intensity (62.5%) statin therapy, and 6.4% were also taking ezetimibe at baseline.
- Most patients at baseline were taking at least one other CV medication including antihypertensive agents (95.2%), anti-platelet agents (79.4%), beta blockers (70.7%), angiotensin converting enzyme (ACE) inhibitors (51.9%), angiotensin receptor blockers (ARB) (26.9%), and ACE inhibitors or ARB (77.5%).
- On stable background lipid-lowering therapy, the median [Q1, Q3] baseline LDL-C was 75.0 [62.0, 89.0] mg/dL; the mean (SD) was 76.2 (20.3) mg/dL.
- On stable background lipid-lowering therapy, the median [Q1, Q3] baseline fasting TG was 216.0 [176.0,272.5] mg/dL; the mean (SD) was 233.2 (80.1) mg/dL.

The primary results from REDUCE-IT are shown in the Table below (*see* **CONDUCT OF REDUCE-IT AND ANALYSIS AND REVIEW OF REDUCE-IT DATA**).

Effect of VASCEPA on CV Events in Patients with Established CVD or at High Risk for CVD with Statin-treated Triglycerides ≥135 and <500 mg/dL in REDUCE-IT

	Placebo n=4090 n (%)	VASCEPA n=4089 n (%)	Time to Event Analysis VASCEPA vs Placebo Hazard Ratio (95% CI)
First occurrence of cardiovascular death, myocardial infarction, stroke, coronary revascularization, hospitalization for unstable angina (5-point MACE)	901 (22.0)	705 (17.2)	0.75 (0.68 - 0.83)
First occurrence of cardiovascular death, myocardial infarction, stroke (3-point MACE)	606 (14.8)	459 (11.2)	0.74 (0.65 - 0.83)
Cardiovascular death	213 (5.2)	174 (4.3)	0.80 (0.66 - 0.98)
Death by any cause[1]	310 (7.6)	274 (6.7)	0.87 (0.74 - 1.02)
First fatal or non-fatal myocardial infarction	355 (8.7)	250 (6.1)	0.69 (0.58 - 0.81)
First fatal or non-fatal stroke	134 (3.3)	98 (2.4)	0.72 (0.55 - 0.93)
First emergent or urgent coronary revascularization	321 (7.8)	216 (5.3)	0.65 (0.55 - 0.78)
First coronary revascularization[2]	544 (13.3)	376 (9.2)	0.66 (0.58 - 0.76)
First hospitalization for unstable angina[3]	157 (3.8)	108 (2.6)	0.68 (0.53 - 0.87)

All presented individual and composite endpoints were statistically significant except time to death by any cause.
[1] Time to death by any cause, or total mortality, is not a component of either the primary composite endpoint or key secondary endpoint.
[2] The predefined composite secondary endpoint included emergent or urgent revascularization, the composite of all revascularization was predefined as a tertiary endpoint.
[3] Determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization

VASCEPA significantly reduced the following:

- the risk for the primary composite endpoint (5-point MACE: time to first occurrence of CV death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization; p<0.001), and
- the key secondary composite endpoint (3-point MACE: time to first occurrence of CV death, myocardial infarction, or stroke; p<0.001).

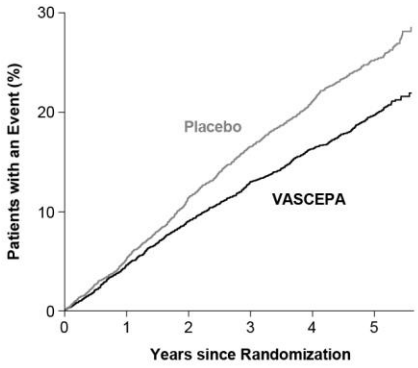
Prespecified hierarchical testing of other secondary endpoints revealed significant reductions in the following:

- CV death (p=0.03),
- fatal or nonfatal myocardial infarction (p<0.001),
- fatal or nonfatal stroke (p=0.01),
- emergent or urgent coronary revascularization (p<0.001), and
- hospitalization for unstable angina (p=0.002).

The benefits of VASCEPA were seen on a background of predominately (93.2%) moderate- to high-intensity statin use and median baseline LDL-C levels of 75.0 mg/dL.

The Kaplan-Meier estimates of the cumulative incidence of the primary and key secondary composite endpoints over time are shown in Figure 1 and Figure 2 below.

Figure 1. Estimated Cumulative Incidence of Primary Composite Endpoint in REDUCE-IT



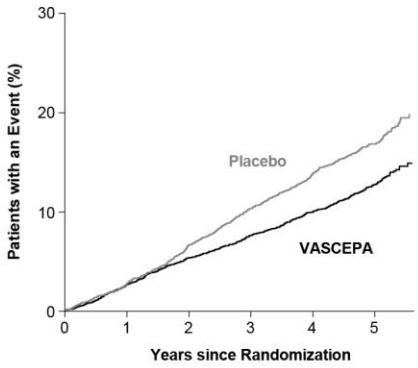
Hazard Ratio, 0.75
(95% CI, 0.68–0.83)
RRR = 24.8%
ARR = 4.8%
NNT = 21 (95% CI, 15–33)
P=0.00000001

No. at Risk

Placebo	4090	3743	3327	2807	2347	1358
VASCEPA	4089	3787	3431	2951	2503	1430

ARR = absolute risk reduction, CI = confidence interval, HR = hazard ratio, NNT = number needed to treat, RRR = relative risk reduction. Curves were visually truncated at 5.7 years due to a limited number of events beyond that point in time; all patient data were included in analyses.

Figure 2. Estimated Cumulative Incidence of Key Secondary Composite Endpoint in REDUCE-IT



Hazard Ratio, 0.74
(95% CI, 0.65–0.83)
RRR = 26.5%
ARR = 3.6%
NNT = 28 (95% CI, 20–47)
P=0.0000006

No. at Risk

Placebo	4090	3837	3500	3002	2542	1487
VASCEPA	4089	3861	3565	3115	2681	1562

ARR = absolute risk reduction, CI = confidence interval, HR = hazard ratio, NNT = number needed to treat, RRR = relative risk reduction. Curves were visually truncated at 5.7 years due to a limited number of events beyond that point in time; all patient data were included in analyses.

The difference between VASCEPA and placebo in median percent change in TG from baseline to Month 4 was -20.1 (p<0.001) and from baseline to Month 12 was -19.7 (p<0.001). At Month 12, the median [Q1, Q3] TG was 175.0 [132.0, 238.0] mg/dL in the VASCEPA group, with 35.9% of patients having TG <150 mg/dL and 61.3% having a TG <200 mg/dL. The difference between VASCEPA and placebo in median percent change in LDL-C from baseline to Month 12 was -6.6% (p<0.001). At Month 12, the median [Q1, Q3] LDL-C was 77.0 [63.0, 94.0] mg/dL in the VASCEPA group, with 35.5% of patients having LDL-C <70 mg/dL and 79.9% having LDL-C <100 mg/dL.

Important Safety Information for VASCEPA from REDUCE-IT (n=4089 on VASCEPA, n=4090 on placebo)

- Patients were exposed to VASCEPA or placebo for a median of 52 months; 86.9% of patients were exposed for ≥ 12 months, 77.2% were exposed for ≥ 24 months, 64.6% were exposed for ≥ 36 months, 53.6% were exposed for ≥48 months, 29.5% were exposed for ≥ 60 months, and 0.1% were exposed for ≥72 months.
- **Overall adverse event (AE) rates were similar across treatment groups.**
  - Adverse events (AE) and serious adverse event (SAE) rates leading to study drug discontinuation were similar to placebo.
  - A single serious adverse event (SAE) occurred at a frequency of at least 2%, which was pneumonia (2.6% in the VASCEPA group and 2.9% in the placebo group, p=0.42)

References: 1. Bhatt DL, Steg PG, Miller M, et al; for the REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. *N Engl J Med.* 2019;380(1):11-22. Bhatt DL. AHA 2018, Chicago. **2.** Data on file. Amarin Pharma, Inc. 2019.

See next page for additional Important Safety Information related to REDUCE-IT for VASCEPA.

Treatment-Emergent Adverse Events

	VASCEPA n=4089 n (%)	Placebo n=4090 n (%)	P value[1]
Patients with at Least One TEAE,[2] n (%)	3343 (81.8)	3326 (81.3)	0.63
Serious TEAE	1252 (30.6)	1254 (30.7)	0.98
TEAE Leading to Withdrawal of Study Drug[3]	321 (7.9)	335 (8.2)	0.60
Serious TEAE Leading to Withdrawal of Study Drug[3]	88 (2.2)	88 (2.2)	1.00
Serious TEAE Leading to Death[4]	94 (2.3)	102 (2.5)	0.61

Note: A treatment-emergent adverse event (TEAE) is defined as an event that first occurs or worsens in severity on or after the date of dispensing study drug and within 30 days after the completion or withdrawal from study. Percentages are based on the number of patients randomized to each treatment group in the Safety population (N). Events that were positively adjudicated as clinical endpoints are not included.
[1] P value from Fisher's Exact test.
[2] All adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 20.1).
[3] Withdrawal of study drug excludes patients who were off drug in study (ODIS) for 30 days or more, and restarted study drug.
[4] The most common serious TEAEs leading to death by system organ class were neoplasms (1.1%); infections and infestations (0.4%); respiratory, thoracic, and mediastinal disorders (0.2%); cardiac disorders (0.2%); and vascular disorders (0.1%). No serious TEAEs leading to death by system organ class were statistically significant across treatment groups except for cardiac disorders, which occurred in 3 (0.1%) of VASCEPA patients and 15 (0.4%) of placebo patients (P=0.008).

- **Adverse events (AE) occurring in ≥5% of VASCEPA patients and statistically more frequently with VASCEPA than placebo:**
  - Peripheral edema (6.5% VASCEPA patients versus 5.0% placebo patients)
    - There was no significant difference in the prespecified adjudicated tertiary endpoints of new congestive heart failure which occurred in 4.1% of VASCEPA patients versus 4.3% of placebo patients, or in new heart failure requiring hospitalization, which occurred in 3.4% of VASCEPA and 3.5% of placebo patients.
  - Constipation (5.4% VASCEPA patients versus 3.6% placebo patients)
  - Atrial fibrillation (5.3% VASCEPA patients versus 3.9% placebo patients)
    - This adverse event (AE) finding is consistent with an increase in the prespecified adjudicated tertiary endpoint of atrial fibrillation or flutter requiring hospitalization, which occurred in 3.1% of VASCEPA patients versus 2.1% of placebo patients (p=0.004).
    - A limitation of the REDUCE-IT cardiovascular outcomes trial is that it was not designed to evaluate whether VASCEPA contributed to an increase in atrial fibrillation or flutter, or whether VASCEPA prevented patients who would have otherwise have had atrial fibrillation or flutter from having another major adverse cardiovascular event such as cardiac arrest or sudden cardiac death.
    - Importantly, there was no increase in stroke, the most serious atrial fibrillation-related complication, but rather a statistically significant 28% reduction with VASCEPA versus placebo (p=0.01). Significant and substantial reductions were also observed in the secondary and tertiary endpoints of myocardial infarction (31%), cardiac arrest (48%), and sudden cardiac death (31%) with VASCEPA versus placebo.
    - Among patients with atrial fibrillation/flutter hospitalization endpoints while in REDUCE-IT, rates were similar for stroke (3.1% with VASCEPA versus 7.1% with placebo; p=0.20), new anticoagulant therapy (64.6% with VASCEPA versus 63.1% with placebo; p=0.88), and serious bleeding (8.7% with VASCEPA versus 6.0% with placebo; p=0.60).
    - In 751 patients with a baseline history of atrial fibrillation/flutter, atrial fibrillation/flutter hospitalization rates were 12.5% (46/368) with VASCEPA versus 6.3% (24/383) with placebo (p=0.007).
    - In 7,428 patients without baseline history of atrial fibrillation/flutter, atrial fibrillation/flutter hospitalization rates were 2.2% with VASCEPA versus 1.6% with placebo (p=0.09).
- **Other adverse events (AE) of interest:**
  - The rate of treatment-emergent serious adverse events for bleeding was 2.7% in the VASCEPA group versus 2.1% in the placebo group, with a nonsignificant, but trending p-value of 0.06.
  - There was:
    - No significant increase in adjudicated hemorrhagic stroke (0.3% in VASCEPA patients versus 0.2% in placebo patients; p=0.55),
    - No significant increase in serious central nervous system bleeding (0.3% in VASCEPA patients versus 0.2% in placebo patients; p=0.42), and
    - No significant increase in gastrointestinal bleeding (1.5% in VASCEPA patients versus 1.1% in placebo patients; p=0.15).
  - A significantly higher incidence of any bleeding occurred with VASCEPA (11.8% versus 9.9%; p=0.006), but as noted above between group differences were not statistically significant for serious bleeding, serious central nervous system bleeding, serious gastrointestinal bleeding, or adjudicated hemorrhagic stroke, and there were no bleeding-associated deaths assessed by investigators as related to VASCEPA.

Mineral oil placebo consideration and analysis

In REDUCE-IT, a placebo containing mineral oil was used to mimic the color and consistency of the drug studied. No strong evidence for biological activity of the same mineral oil was identified in connection with FDA approval of VASCEPA in July 2012 based on the MARINE phase 3 clinical trial, in connection with FDA review of the ANCHOR phase 3 clinical trial, or after several years of quarterly review by the Data Monitoring Committee (DMC) for REDUCE-IT after FDA requested that the DMC periodically assess unblinded lipid data to monitor for signals that the placebo might not be inert. While the DMC noted variation in LDL-C measurements in both arms and that a small physiological effect of mineral oil might be possible, the DMC concluded that it was not possible to determine if the LDL-C increase in the placebo arm was a natural increase over time or due to the mineral oil, and they found no apparent effect on outcomes and considered this small change as unlikely to explain the observed benefit of VASCEPA over placebo.

Each of the three VASCEPA clinical trials, MARINE, ANCHOR and REDUCE-IT, was conducted under a special protocol, or SPA, agreement with FDA in which mineral oil was agreed with FDA as an acceptable placebo.

REDUCE-IT patients represent a population at significant risk for CV events as reflected in the study design that assumed an annual placebo group primary endpoint event rate of 5.9% based on historical data, and as suggested by the observed annualized placebo event rate (5.74%), which remains consistent with historical data for similar at-risk statin-treated patient populations.

As published within the main *New England Journal of Medicine* presentation of the REDUCE-IT results, at baseline, the median LDL-C was 75.0 mg/dL. The median change in LDL-C was 3.1% (+2.0 mg/dL) for VASCEPA and 10.2% (+7.0 mg/dL) for the mineral oil placebo arm; placebo-corrected median change from baseline of -6.6% (-5.0 mg/dL; p < 0.001). If mineral oil in the placebo might have affected outcomes in some patients, this might have contributed to differences in outcomes between the groups. However, the relatively small differences in LDL-C levels between groups would not likely explain the 25% risk reduction observed with VASCEPA, and a *post hoc* analysis suggested a similar lower risk regardless of whether there was an increase in LDL-C level among the patients in the placebo group or regardless of the experience of diarrhea while on study. In addition, although open label, Japan EPA Lipid Intervention Study (JELIS) previously demonstrated a 19% risk reduction without a mineral oil placebo.

CONDUCT OF REDUCE-IT AND ANALYSIS AND REVIEW OF REDUCE-IT DATA

FDA has not reviewed and opined on a supplemental new drug application related to REDUCE-IT. FDA has thus not reviewed the information herein or determined whether to approve VASCEPA for use to reduce the risk of major adverse CV events in the REDUCE-IT patient population.*

REDUCE-IT results were first presented at the 2018 Scientific Sessions of the American Heart Association (AHA) on November 10, 2018 in Chicago, Illinois and concurrently published online in *The New England Journal of Medicine* (NEJM).[1,2]

REDUCE-IT was sponsored by Amarin Pharma, Inc. and its affiliates and conducted under a special protocol assessment agreement with FDA.

- The REDUCE-IT steering committee, consisting of academic physicians, and Amarin representatives developed the protocol and were responsible for the conduct and oversight of the study, and data interpretation.
- The primary, secondary, and tertiary adjudicated endpoint analyses were validated by the data monitoring committee independent statistician.

Further REDUCE-IT data assessment and data release could yield additional useful information to inform greater understanding of the trial outcome:

- Further detailed data assessment by Amarin and regulatory authorities will continue and take several months to complete and record
- The final evaluation of the totality of the efficacy and safety data from REDUCE-IT may include some or all of the following, as well as other considerations:
  - New information affecting the degree of treatment benefit on studied endpoints
  - Study conduct and data robustness, quality, integrity and consistency
  - Additional safety data considerations and risk/benefit considerations
  - Consideration of REDUCE-IT results in the context of other clinical studies.

VASCEPA may not be eligible for reimbursement under government healthcare programs (such as Medicare and Medicaid) and certain commercial plans to reduce the risk of major adverse CV events in the REDUCE-IT patient population. We encourage you to check that for yourself.

IMPORTANT INFORMATION FOR HCPs ABOUT CONTINUED UNCERTAINTY AROUND THE BENEFIT, IF ANY, OF LOWERING TG LEVELS AFTER STATIN THERAPY IN PATIENTS WITH HIGH (200-499 mg/dL) TG LEVELS

- **In REDUCE-IT, CV benefits appeared similar across baseline levels of triglycerides** (less than versus greater than or equal to 150 mg/dL or 200 mg/dL).
  - Additionally, the reduction in major adverse CV events with VASCEPA appeared to occur irrespective of an achieved triglyceride level above or below 150 mg/dL at one year, suggesting that the CV risk reduction was not tied to achieving a more normal triglyceride level.
  - These observations suggest that at least some of the impact of VASCEPA on the reduction in ischemic events may be explained by metabolic effects other than triglyceride lowering.
- VASCEPA is not FDA-approved to lower TG levels in statin-treated patients with mixed dyslipidemia and persistent high (≥200 mg/dL and <500 mg/dL) TG levels due to current uncertainty regarding the benefit, if any, of drug-induced changes in lipid/lipoprotein parameters beyond statin-lowered LDL-C on CV risk among statin-treated patients with residually high TG.
  - Other CV outcomes trials (ACCORD Lipid, AIM-HIGH, and HPS2-THRIVE), while not designed to test the effect of lowering TG levels in patients with high TG levels after statin therapy, each failed to demonstrate incremental CV benefit of adding a second lipid-altering drug (fenofibrate or formulations of niacin), despite raising high-density lipoprotein cholesterol and reducing TG levels, among statin-treated patients with well-controlled LDL-C.

Other cardiovascular outcomes trials that studied fish oil or mixtures of omega-3 acids that include the omega-3 acid, DHA, have reported negligible impact on cardiovascular events.

No head-to head, randomized, well-controlled studies have been conducted to compare the effects of VASCEPA with other FDA-approved TG-lowering therapies.

POTENTIAL MECHANISMS OF ACTION

Mechanisms responsible for the benefit shown in REDUCE-IT were not included in the study design. Potential mechanisms discussed, include TG reduction, anti-thrombotic effects, antiplatelet or anticoagulant effects, membrane-stabilizing effects, effects on stabilization and/or regression of coronary plaque and inflammation reduction. More study is needed to determine to what extent, if any, these effects or others may be responsible for the CV risk reduction benefit demonstrated with use of VASCEPA in REDUCE-IT.

*This information is intended to ensure Amarin meets its continuing obligation to update healthcare professionals regarding off-label use of VASCEPA to assure that its communications remain truthful and non-misleading, consistent with the federal court approved settlement under *Amarin Pharma, Inc. et al. v. United States Food and Drug Administration et al.*, 119 F.Supp.3d 196, 236 (S.D.N.Y. 2015)