Amarin Corporation

Amarin Receives European Commission (EC) Approval for VAZKEPA to Reduce Cardiovascular Risk

March 30, 2021

Marks first and only EC-approved treatment to reduce cardiovascular risk in high-risk, statin-treated adult patients who have elevated triglycerides (≥150 mg/dL) and other risk characteristics as studied in REDUCE-IT® [1, 2]

DUBLIN, Ireland and BRIDGEWATER, N.J., March 30, 2021 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ: AMRN) today announced that following a review and approval recommendation by the European Medicines Agency (EMA), the European Commission (EC) has approved the marketing authorization application for VAZKEPA (icosapent ethyl) to reduce the risk of cardiovascular events in high-risk, statin-treated adult patients who have elevated triglycerides (≥150 mg/dL) and either established cardiovascular disease or diabetes and at least one additional cardiovascular risk factor.

Amarin's icosapent ethyl was approved for cardiovascular risk reduction by the U.S. Food and Drug Administration (FDA) in December 2019 and is marketed in the U.S. under the brand name, VASCEPA®.

"The approval of VAZKEPA marks a significant milestone for high-risk cardiovascular patients in Europe as it offers the first and only EC-approved therapy to reduce cardiovascular risk in high-risk statin-treated patients who have elevated triglycerides," said Steven Ketchum, senior vice president, president of R&D and chief scientific officer of Amarin. "We look forward to launching VAZKEPA in Europe as it is an exciting opportunity for Amarin to make a difference in the lives of the many millions of patients throughout Europe who are at risk of a cardiovascular event."

The EC approval for VAZKEPA is based on over a decade of development and testing of icosapent ethyl, including efficacy and safety data from the REDUCE-IT® cardiovascular outcomes study.[2] REDUCE-IT evaluated more than 8,000 high risk patients who despite having their cholesterol levels well controlled by statin therapy remained at significant risk of heart attack, stroke, or other major adverse cardiovascular events (MACE), including death. As published, patients in the REDUCE-IT study had a median follow-up period of nearly five years. Results from this study, in which all patients remained treated with statins (and with other contemporary therapies) and where half the patients received icosapent ethyl and the other half received placebo, demonstrated a 25% relative risk reduction ($p<0.001$) in the first occurrence of MACE in the intent-to-treat patient population with use of icosapent ethyl (4 grams daily) compared with placebo.

"We are especially pleased to receive the EC's approval of VAZKEPA to reduce cardiovascular risk as cardiovascular disease remains the number one cause of death in the European Union and its economic burden exceeds €210 billion per year[3]," stated John F. Thero, president and chief executive officer. "We believe we are well positioned for a successful launch based on the high rate of cardiovascular events in Europe, the lack of an approved therapy for the indication VAZKEPA is positioned to address, and because of the demonstrated efficacy and safety profile of this unique drug."

"Importantly, this EC approval provides ten years of market protection for VAZKEPA in the European Union. In addition, we have pending patent applications related to the REDUCE-IT study, which have the potential to extend exclusivity in Europe into 2039," added Mr. Thero.

In anticipation of the commercial availability of VAZKEPA in Europe, the European Society of Cardiology and European Atherosclerosis Society updated its 2019 Dyslipidemia Management Guidelines to recommend the use of icosapent ethyl in high-risk, statin-treated patients.[4] Globally, there are 15 medical societies that recommend the use of icosapent ethyl in appropriate patients, emphasizing that the positive clinical results of the REDUCE-IT cardiovascular outcomes study should not be generalized to any product other than icosapent ethyl, and noting that the clinical results are unique to VASCEPA/VAZKEPA.

Information regarding Amarin's plans for commercialization and securing market access in Europe can be found in the FAQ section under investor relations at www.amarincorp.com.

About Amarin
Amarin is a rapidly growing, innovative pharmaceutical company leading a new paradigm in cardiovascular disease management. From our scientific research foundation to our focus on clinical trials, and now our commercial expansion, we are evolving and growing. In 2009, Amarin had fewer than twenty employees. Today, with offices in Bridgewater, New Jersey in the United States, Dublin in Ireland, and Zug in Switzerland, Amarin has approximately 1,000 employees and commercial partners and suppliers around the world. We are committed to rethinking cardiovascular risk through the advancement of scientific understanding of the impact on society of significant residual risk that exists beyond traditional therapies, such as statins for cholesterol management.

About REDUCE-IT®
REDUCE-IT was a global cardiovascular outcomes study designed to evaluate the effect of VASCEPA in adult patients with LDL-C controlled to between 41-100 mg/dL (median baseline 75 mg/dL) by statin therapy and various cardiovascular risk factors including persistent elevated triglycerides between 135-499 mg/dL (median baseline 216 mg/dL) and either established cardiovascular disease (secondary prevention cohort) or diabetes mellitus and at least one other cardiovascular risk factor (primary prevention cohort).

REDUCE-IT, conducted over seven years and completed in 2018, followed 8,179 patients at over 400 clinical sites in 11 countries with the largest number of sites located within the United States. REDUCE-IT was conducted based on a special protocol assessment agreement with FDA. The design of the REDUCE-IT study was published in March 2017 in *Clinical Cardiology.*[5] The primary results of REDUCE-IT were published in *The New England Journal of Medicine* in November 2018.[2] The total events results of REDUCE-IT were published in the *Journal of the American College of Cardiology* in March 2019.[6] These and other publications can be found in the R&D section on the company's website at www.amarincorp.com.

About VASCEPA® (icosapent ethyl) Capsules

VASCEPA (icosapent ethyl) capsules are the first-and-only prescription treatment approved by the U.S. Food and Drug Administration (FDA) comprised solely of the active ingredient, icosapent ethyl (IPE), a unique form of eicosapentaenoic acid. VASCEPA was launched in the United States in January 2020 as the first and only drug approved by the U.S. FDA for treatment of the studied high-risk patients with persistent cardiovascular risk after statin therapy. VASCEPA was initially launched in the United States in 2013 based on the drug's initial FDA approved indication for use as an adjunct therapy to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia. Since launch, VASCEPA has been prescribed over ten million times. VASCEPA is covered by most major medical insurance plans. In addition to the United States, VASCEPA is approved and sold in Canada, Lebanon and the United Arab Emirates. In Europe, marketing authorization was granted to icosapent ethyl in the European Union for the reduction of risk of cardiovascular events in patients at high cardiovascular risk, under the brand name VAZKEPA.

Indications and Limitation of Use (in the United States)
VASCEPA 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 two 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.

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 (3% vs 2%) 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.
- It is 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 (12% vs 10%) 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 (4% vs 3%), peripheral edema (7% vs 5%), constipation (5% vs 4%), gout (4% vs 3%), and atrial fibrillation (5% vs 4%).
- Common adverse reactions in the hypertriglyceridemia trials (incidence ≥1% more frequent than placebo): arthralgia (2% vs 1%) and oropharyngeal pain (1% vs 0.3%).
- 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 should be monitored for bleeding.

Key clinical effects of VASCEPA on major adverse cardiovascular events are included in the Clinical Studies section of the prescribing information for VASCEPA as set forth below:

Effect of VASCEPA on Time to First Occurrence of Cardiovascular Events in Patients with Elevated Triglyceride levels and Other Risk Factors for Cardiovascular Disease in REDUCE-IT

	VASCEPA		**Placebo**		**VASCEPA vs Placebo**
	N = 4089 n (%)	**Incidence Rate (per 100 patient years)**	**N = 4090 n (%)**	**Incidence Rate (per 100 patient years)**	**Hazard Ratio (95% CI)**
Primary composite endpoint					
Cardiovascular death, myocardial infarction, stroke, coronary revascularization, hospitalization for unstable angina (5-point MACE)	705 (17.2)	4.3	901 (22.0)	5.7	0.75 (0.68, 0.83)
Key secondary composite endpoint					
Cardiovascular death, myocardial infarction, stroke (3-point MACE)	459 (11.2)	2.7	606 (14.8)	3.7	0.74 (0.65, 0.83)
Other secondary endpoints					
Fatal or non-fatal myocardial infarction	250 (6.1)	1.5	355 (8.7)	2.1	0.69 (0.58, 0.81)
Emergent or urgent coronary revascularization	216 (5.3)	1.3	321 (7.8)	1.9	0.65 (0.55, 0.78)

Cardiovascular death [1]	174 (4.3)	1.0	213 (5.2)	1.2	0.80 (0.66, 0.98)
Hospitalization for unstable angina [2]	108 (2.6)	0.6	157 (3.8)	0.9	0.68 (0.53, 0.87)
Fatal or non-fatal stroke	98 (2.4)	0.6	134 (3.3)	0.8	0.72 (0.55, 0.93)
[1] Includes adjudicated cardiovascular deaths and deaths of undetermined causality. [2] Determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalization.					

FULL U.S. FDA-APPROVED VASCEPA PRESCRIBING INFORMATION CAN BE FOUND AT WWW.VASCEPA.COM.

Forward-Looking Statements
This press release contains forward-looking statements, including statements about the potential of VAZKEPA (known as VASCEPA in the United States) to favorably affect cardiovascular risk in appropriate patients, to make a difference in the lives of the many millions of patients throughout Europe who are at risk of a cardiovascular event, with respect to Amarin being well-positioned for a successful European launch and related to the potential for extended patent protection. These forward-looking statements are not promises or guarantees and involve substantial risks and uncertainties that may individually or together impact the matters herein and cause actual results, events and performance to differ materially from such forward-looking statements. Among the factors that could cause actual results to differ materially from those described or projected herein include the following: events that could impact future regulatory assessment by the European Commission, such as delays due to COVID-19 restrictions, later arising data, regulatory reviews and pricing assessments, and the successful implementation of commercialization plans or other information, events that could interfere with the grant or issuance of a patent, continued validity or enforceability of a patent; uncertainties associated with litigation generally and patent litigation specifically; Amarin's ability generally to maintain adequate patent protection and successfully enforce patent claims against third parties; and uncertainties associated generally with research and development and regulatory submissions, reviews, action dates and approvals. A further list and description of these risks, uncertainties and other risks associated with an investment in Amarin can be found in Amarin's filings with the U.S. Securities and Exchange Commission, including its most recent annual report on Form 10-K. Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. Amarin undertakes no obligation to update or revise the information contained in this press release, whether as a result of new information, future events or circumstances or otherwise.

Availability of Other Information About Amarin
Investors and others should note that Amarin communicates with its investors and the public using the company website (www.amarincorp.com), the investor relations website (investor.amarincorp.com), including but not limited to investor presentations and investor FAQs, Securities and Exchange Commission filings, press releases, public conference calls and webcasts. The information that Amarin posts on these channels and websites could be deemed to be material information. As a result, Amarin encourages investors, the media, and others interested in Amarin to review the information that is posted on these channels, including the investor relations website, on a regular basis. This list of channels may be updated from time to time on Amarin's investor relations website and may include social media channels. The contents of Amarin's website or these channels, or any other website that may be accessed from its website or these channels, shall not be deemed incorporated by reference in any filing under the Securities Act of 1933.

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[1] Union Register of medicinal products - Public health - European Commission. https://ec.europa.eu/health/documents/community-register/html/h1524.htm. Accessed March 30, 2021.

[2] Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med.* 2019;380(1):11-22.

[3] ESC Cardiovascular Realities 2020 by... - Flipsnack. https://www.flipsnack.com/Escardio/esc-cardiovascular-realities-2020/full-view.html. Accessed March 30, 2021.

[4] Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Atherosclerosis*. 2019;290:140-205. doi:10.1016/j.atherosclerosis.2019.08.014

[5] Bhatt DL, Steg PG, Brinton E, et al., on behalf of the REDUCE-IT Investigators. Rationale and Design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clin Cardiol*. 2017;40:138-148.

[6] Bhatt DL, Steg PG, Miller M, et al., on behalf of the REDUCE-IT Investigators. Reduction in first and total ischemic events with icosapent ethyl across baseline triglyceride tertiles. *J Am Coll Cardiol*. 2019;74:1159-1161.