

# Amarin Corporation

## Amarin Receives Great Britain Marketing Authorization for VAZKEPA from the Medicines and Healthcare Products Regulatory Agency (MHRA) 1,2

April 22, 2021

*VAZKEPA (icosapent ethyl) is the first and only authorized treatment for its cardiovascular risk reduction indication<sup>1,2,3</sup>*

*VAZKEPA authorization for Great Britain follows recent VAZKEPA authorization for European Union*

DUBLIN, Ireland and BRIDGEWATER, N.J., April 22, 2021 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ: AMRN) today announced that the Medicines and Healthcare Products Regulatory Agency (MHRA) has granted a Marketing Authorization for VAZKEPA (icosapent ethyl) as a treatment to reduce the risk of cardiovascular events in high cardiovascular risk statin-treated adult patients who have elevated triglycerides ( $\geq 150$  mg/dL) and either established cardiovascular disease or diabetes, and at least one additional cardiovascular risk factor. The Great Britain Marketing Authorization for VAZKEPA applies to England, Scotland and Wales. Under the Brexit Northern Ireland agreement, the European centralized marketing authorization for the European Union covers Northern Ireland.

The MHRA's license swiftly followed the European Commission (EC) marketing authorization of icosapent ethyl for the European Union as announced on March 30, 2021.<sup>3</sup> Amarin's understanding is that icosapent ethyl is among the first products to be submitted and licensed through the MHRA's new 'reliance' route following the end of the Brexit transition period. Icosapent ethyl has been identified as a new active substance with likely multi-factorial mechanisms of action.<sup>1</sup>

The MHRA authorization for VAZKEPA is based on over a decade of development and testing of icosapent ethyl, including efficacy and safety data from the REDUCE-IT<sup>®</sup> cardiovascular outcomes study.<sup>2</sup> 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.

Professor Gabriel Steg, M.D., Chief, Department of Cardiology at Hôpital Bichat, Paris, commented, "The REDUCE-IT study shows icosapent ethyl could reduce CV events and has the potential to change the way residual cardiovascular risk is treated. This authorization of icosapent ethyl can make a difference to patients who are at high-risk of suffering from a heart attack or stroke. Eligible patients can be confident we have a new treatment that is backed by evidence-based data and European guideline recommendations."

The publication of this research has led to icosapent ethyl being recommended for use in high-risk statin-treated patients identified by moderately elevated triglycerides by 15 global medical societies around the world including the European Society of Cardiology and the European Atherosclerosis Society.<sup>4</sup>

Cardiovascular risk (CVD) is one of the leading causes of death in the United Kingdom, with heart and circulatory diseases causing more than a quarter (27%) of all deaths in the UK, which is more than 160,000 deaths each year.<sup>5</sup>

The marketing authorization is also timely in the wake of the COVID-19 pandemic, which has resulted in the reprioritization of clinical resources, often leaving patients with serious cardiovascular disease to delay much needed medical help.<sup>6</sup> Preventative care is needed for at-risk patients with cardiovascular disease, including LDL-cholesterol management and additional treatments for statin-treated patients with residual cardiovascular risk, identified by elevated triglycerides and other risk factors, to address their unmet need.

"Icosapent ethyl has been helping to reduce strokes, heart attacks and other major cardiovascular events in high-risk patients in the United States," stated John Thero, president and chief executive officer of Amarin. "We are dedicated to the rethinking of cardiovascular disease risk reduction across Europe with an emphasis on preventative care. Amarin will work tirelessly throughout Europe to make icosapent ethyl available to all patients who may benefit from this important therapy."

In addition, the company announced that subsequent to the marketing authorization by the EC, the Norwegian Medicines Agency informed Amarin of its marketing authorization for VAZKEPA in Norway.

Information regarding Amarin's plans for commercialization and securing market access in Europe and the United Kingdom can be found in the FAQ section under investor relations at [www.amarincorp.com](http://www.amarincorp.com).

### About Amarin

Amarin is an 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 rapidly. Amarin has offices in Bridgewater, New Jersey in the United States, Dublin in Ireland, and Zug in Switzerland as well as 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 Cardiovascular Risk

Cardiovascular disease is the number one cause of death in the world. In the United States alone, cardiovascular disease results in 859,000 deaths per year.<sup>7</sup> And the number of deaths in the United States attributed to cardiovascular disease continues to rise. In addition, in the United States there are 605,000 new and 200,000 recurrent heart attacks per year (approximately 1 every 40 seconds). Stroke rates are 795,000 per year (approximately

1 every 40 seconds), accounting for 1 of every 19 U.S. deaths. In aggregate, in the United States alone, there are more than 2.4 million major adverse cardiovascular events per year from cardiovascular disease or, on average, 1 every 13 seconds.

Controlling bad cholesterol, also known as LDL-C, is one way to reduce a patient's risk for cardiovascular events, such as heart attack, stroke or death. 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 elevated triglycerides. Statin therapy has been shown to control LDL-C, thereby reducing the risk of cardiovascular events by 25-35%.<sup>8</sup> Significant cardiovascular risk remains after statin therapy. People with elevated triglycerides have 35% more cardiovascular events compared to people with normal (in range) triglycerides taking statins.<sup>9,10,11</sup>

#### **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*.<sup>7</sup> The primary results of REDUCE-IT were published in *The New England Journal of Medicine* in November 2018.<sup>2</sup> The total events results of REDUCE-IT were published in the *Journal of the American College of Cardiology* in March 2019.<sup>8</sup> These and other publications can be found in the R&D section on the company's website at [www.amarincorp.com](http://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 ( $\geq 500$  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, in March 2021 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 VASKEPA.

#### 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 ( $\geq 150$  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 ( $\geq 500$  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  $\geq 3\%$  and  $\geq 1\%$  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  $\geq 1\%$  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)
<b>Primary composite endpoint</b>					
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)
<b>Key secondary composite endpoint</b>					
Cardiovascular death, myocardial infarction, stroke (3-point MACE)	459 (11.2)	2.7	606 (14.8)	3.7	0.74 (0.65, 0.83)
<b>Other secondary endpoints</b>					
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](http://www.vascepa.com) CAN BE FOUND AT [WWW.VASCEPA.COM](http://www.vascepa.com).

#### Forward-Looking Statements

This press release contains forward-looking statements, including statements about the potential of VASCEPA (known as VASCEPA in the United States) to favorably affect cardiovascular risk in appropriate patients and about making VASCEPA available throughout Europe to patients who are at risk of a cardiovascular event. 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, 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](http://www.amarincorp.com)), the investor relations website ([investor.amarincorp.com](http://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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AMARIN, REDUCE-IT, VASCEPA and VAZKEPA are trademarks of Amarin Pharmaceuticals Ireland Limited. VAZKEPA is a registered trademark in Europe and other countries and regions and is pending registration in the United States.

<sup>1</sup>Summary of Product Characteristics Vazkepa – April 2021 [https://ec.europa.eu/health/documents/community-register/2021/20210326150935/anx\\_150935\\_en.pdf](https://ec.europa.eu/health/documents/community-register/2021/20210326150935/anx_150935_en.pdf)

<sup>2</sup> 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.

<sup>3</sup> Union Register of medicinal products - Public health - European Commission. <https://ec.europa.eu/health/documents/community-register/html/h1524.htm>. Accessed April 22, 2021.

<sup>4</sup> 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. *Atherosclerosis.* 2019;290:140-205.

<sup>5</sup> BHF/University of Birmingham calculated rates in partnership with UK statistical agencies: ONS/NRS/NISRA (2016-18 data)

<sup>6</sup> Fersia O, Bryant S, Nicholson R, et al. The impact of the COVID-19 pandemic on cardiology services. *Heart.* 2020;7:1359.

<sup>7</sup> American Heart Association. Heart Disease and Stroke Statistics—2020 Update: A Report From the American Heart Association. *Circulation.* 2020;141:e139–e596.

<sup>8</sup> Ganda OP, Bhatt DL, Mason RP, et al. Unmet need for adjunctive dyslipidemia therapy in hypertriglyceridemia management. *J Am Coll Cardiol.* 2018;72(3):330-343.

<sup>9</sup> Budoff M. Triglycerides and triglyceride-rich lipoproteins in the causal pathway of cardiovascular disease. *Am J Cardiol.* 2016;118:138-145.

<sup>10</sup> Toth PP, Granowitz C, Hull M, et al. High triglycerides are associated with increased cardiovascular events, medical costs, and resource use: A real-world administrative claims analysis of statin-treated patients with high residual cardiovascular risk. *J Am Heart Assoc.* 2018;7(15):e008740.

<sup>11</sup> Nordestgaard BG. Triglyceride-rich lipoproteins and atherosclerotic cardiovascular disease - New insights from epidemiology, genetics, and biology. *Circ Res.* 2016;118:547-563.

<sup>12</sup> 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.

<sup>13</sup> 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.