Amarin Corporation

European Medicines Agency Accepts for Review Marketing Authorization Application for Amarin's Icosapent Ethyl (Vascepa®) for Reduction of Cardiovascular Risk in High-Risk Patients, as Reflected in REDUCE-IT® Study

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DUBLIN, Ireland and BRIDGEWATER, N.J., Dec. 02, 2019 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ: AMRN), a pharmaceutical company focused on improving cardiovascular health, announced today that the European Medicines Agency (EMA) has validated the marketing authorization application (MAA) seeking approval for icosapent ethyl (brand name *Vascepa*® in the United States) as a treatment to reduce the risk of cardiovascular events in high-risk patients who have their cholesterol levels controlled with statin treatment, but have elevated triglycerides,135 mg/dL or above, and other cardiovascular risk factors. The validation confirms the submission for *Vascepa* is sufficiently complete for the EMA to begin its review procedure, which is currently expected to be completed before the end of 2020.

"The prevalence in Europe of people with persistent cardiovascular risk beyond standard of care statin therapy is high, like it is in most of the world. This application moves us one step closer to being able to potentially help millions of high-risk patients with icosapent ethyl as studied in REDUCE-IT®," says John Thero, president and CEO, Amarin. "We seek to make icosapent ethyl accessible to as many patients as possible who can benefit. If marketing authorization is granted by the EMA, icosapent ethyl could become the first and only EMA-approved, non-LDL lowering agent with a cardiovascular disease risk reduction indication as an adjunct to statin therapy in dyslipidemic patients in Europe."

A recent survey showed that about 25 percent of a representative sample survey of more than 7,800 patients from 27 European countries with coronary heart disease and controlled LDL-cholesterol levels had elevated triglycerides levels (≥150 mg/dL), illustrating the potential pervasiveness of high-risk cardiovascular disease in Europe beyond currently available therapies.[1]

Icosapent ethyl is in the late stages of review in the United States by the U.S. Food and Drug Administration (FDA) for an indication like the one being sought through a centralized review process in the Europe Union. In November 2019, an FDA advisory committee voted unanimously (16 – 0) to recommend to the FDA that icosapent ethyl be approved for an indication and label expansion to reduce the risk of cardiovascular events in high-risk patients. Although the FDA is not bound by the recommendation of its advisory committee, approval of icosapent ethyl in the United States consistent with such recommendation is anticipated on or before the FDA's target Prescription Drug User Fee Act (PDUFA) date of December 28, 2019. In the United States, icosapent ethyl has the brand name *Vascepa*. If approved in Europe, the brand name may also be *Vascepa*, but this will be determined as part of the regulatory review process.

The MAA for icosapent ethyl is based on the global landmark clinical outcomes study, REDUCE-IT®.[2] In the high-risk, statin-treated patient population studied in REDUCE-IT, as previously published, icosapent ethyl provided a highly statistically significant 25% relative risk reduction compared to placebo in the first occurrence of a major adverse CV event (MACE) in the intent-to-treat population consisting of a composite of cardiovascular death, nonfatal myocardial infarction (MI or heart attack), nonfatal stroke, coronary revascularization (procedures such as stents and by-pass) and unstable angina requiring hospitalization. For total (first and subsequent) cardiovascular events, icosapent ethyl showed a statistically significant 30% relative risk reduction compared to placebo in published exploratory analyses.[3]

In REDUCE-IT, adverse events occurring with icosapent ethyl use at greater than 5% and greater than placebo were: peripheral edema (6.5% *Vascepa* versus 5.0%); constipation (5.3% *Vascepa* versus 3.6%); and atrial fibrillation (5.3% *Vascepa* versus 3.9%). More information on safety data associated with REDUCE-IT is provided below.

Icosapent ethyl, which has been studied in a series of clinical trials, including REDUCE-IT, was developed by Amarin and is exclusively marketed by Amarin and its commercial partners in capsule form.

In the United States, *Vascepa* is currently approved as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia. There have been more than 8 million prescriptions for *Vascepa* since it was launched in 2013 in the United States for this important niche indication. The drug is not currently available in Europe for any indication.

About Cardiovascular Risk and Cardiovascular Disease
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 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% risk remaining.[4] People with high triglycerides have 35% more cardiovascular events compared to people with normal (in range) triglycerides taking statins.[5,6,7]

Each year cardiovascular disease, including heart attacks and stroke, causes over 1.8 million deaths in the European Union (EU). Cardiovascular disease is the main cause of death in men in all but 12 countries of Europe and is the main cause of death in women in all but two countries. Cardiovascular disease causes 46 times the number of deaths and 11 times the disease burden caused by AIDS, tuberculosis and malaria combined in Europe. Overall, cardiovascular disease is estimated to cost the EU economy €210 billion a year. Of the total cost of cardiovascular disease in the EU, around 53% (€111 billion) is due to health care costs, 26% (€54 billion) to productivity losses and 21% (€45 billion) to the informal care of people with cardiovascular disease.[8,9]

About Amarin
Amarin Corporation plc. is a rapidly growing, innovative pharmaceutical company focused on developing therapeutics to improve cardiovascular health. Amarin's product development program leverages its extensive experience in polyunsaturated fatty acids and lipid science. *Vascepa*

(icosapent ethyl) is Amarin's first FDA-approved drug and is available by prescription in the United States, Lebanon and the United Arab Emirates. Amarin's commercial partners are pursuing additional regulatory approvals for *Vascepa* in Canada, China and the Middle East. For more information about Amarin, visit www.amarincorp.com.

About REDUCE-IT®

REDUCE-IT is a global cardiovascular outcomes study, which was designed to prospectively 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*[10] and can be found in the R&D section on the company's website at www.amarincorp.com. The primary results of REDUCE-IT were published in *The New England Journal of Medicine* in November 2018.[11]

About *Vascepa*® (icosapent ethyl) Capsules

Vascepa (icosapent ethyl) capsules are a single-molecule prescription product which has been developed and studied for more than a decade and has been prescribed more than 8 million times in the United States. *Vascepa*, known in scientific literature as AMR101, has been designated a new chemical entity by the FDA. Amarin has been issued multiple patents in the United States and internationally based on the unique clinical profile of *Vascepa*, including the drug's ability to lower triglyceride levels in relevant patient populations without raising LDL-cholesterol levels.

Neither the FDA nor the EMA has completed its review of REDUCE-IT data or determined whether to approve *Vascepa* for use to reduce the risk of major adverse cardiovascular events in the REDUCE-IT patient population.

Indication and Usage Based on Current FDA-Approved Label (not including REDUCE-IT results)

- *Vascepa* (icosapent ethyl) is indicated as an adjunct to diet to reduce triglyceride (TG) levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia.
- The effect of *Vascepa* on the risk for pancreatitis and cardiovascular mortality and morbidity in patients with severe hypertriglyceridemia has not been determined.

Important Safety Information for *Vascepa* Based on Current FDA-Approved Label (not including REDUCE-IT results) (Includes Data from Two 12-Week Studies (n=622) (MARINE and ANCHOR) of Patients with Triglycerides Values of 200 to 2000 mg/dL)

- *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% for *Vascepa*, 1.0% for placebo). There was no reported adverse reaction >3% and greater than placebo.
- Adverse events and product complaints 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*.

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

Important Safety Information for *Vascepa* based on REDUCE-IT, as previously reported in *The New England Journal of Medicine* publication of the primary results of the REDUCE-IT study:

- Excluding the major adverse cardiovascular events (MACE) results described above, overall adverse event rates in REDUCE-IT were similar across the statin plus *Vascepa* and the statin plus placebo treatment groups.
- There were no significant differences between treatments in the overall rate of treatment emergent adverse events or serious adverse events leading to withdrawal of study drug.
- There was no serious adverse event (SAE) occurring at a frequency of >2% which occurred at a numerically higher rate in the statin plus *Vascepa* treatment group than in the statin plus placebo treatment group.
- Adverse events (AEs) occurring in 5% or greater of patients and more frequently with *Vascepa* than placebo were:
    - peripheral edema (6.5% *Vascepa* patients versus 5.0% placebo patients), although there was no increase in the rate of heart failure in *Vascepa* patients
    - constipation (5.4% *Vascepa* patients versus 3.6% placebo patients), although mineral oil, as used as placebo, is known to lower constipation, and
    - atrial fibrillation (5.3% *Vascepa* patients versus 3.9% placebo patients), although there were reductions in rates of cardiac arrest, sudden death and myocardial infarctions observed in *Vascepa* patients
- There were numerically more SAEs related to bleeding in the statin plus *Vascepa* treatment group although overall rates were low with no fatal bleeding observed in either group and no significant difference in adjudicated hemorrhagic stroke or serious central nervous system or gastrointestinal bleeding events between treatments.

- In summary, *Vascepa* was well tolerated with a safety profile generally consistent with clinical experience associated with omega-3 fatty acids and current FDA-approved labeling of such products.

Important Cautionary Information About These Data
Further REDUCE-IT data assessment and data release are expected to yield additional useful information to inform greater understanding of the trial outcome. For example, detailed data assessment by regulatory authorities, such as the FDA, Health Canada, and EMA, will continue and take time to complete and announce. The FDA advisory committee process and the final evaluation by regulatory authorities of the totality of efficacy and safety data from REDUCE-IT is anticipated to include some or all of the following, as well as other considerations: new information or analyses 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; and consideration of REDUCE-IT results in the context of other clinical studies. More detailed presentation of such considerations is set forth in the risk factors section of Amarin's Quarterly Report on Form 10-Q filed with the U.S. Securities and Exchange Commission. Because regulatory reviews are typically fluid and not definitive interactions between sponsor and agency on individual elements of an application and related information, Amarin does not plan to update investors further on ongoing communications with regulatory authorities. Amarin plans to announce the final outcome of such regulatory reviews when appropriate.

Recurrent event analyses for the total primary endpoint events and for the total key secondary endpoint in REDUCE-IT as published in the *Journal of the American College of Cardiology* were conducted using a series of statistical models. These analyses were tertiary or exploratory endpoints; most of the models used were prespecified and one was *post hoc*. Each recurrent event statistical model has inherent strengths and weaknesses, with no single model considered definitive or outperforming the other models, and this is an evolving field of science. Nonetheless, results from the total primary and total key secondary endpoint events analyses are consistent across the various recurrent event statistical models and are also consistent with the original primary and secondary endpoint results. Together, the REDUCE-IT recurrent event analyses and the original primary and key secondary endpoint analyses support the robustness of the clinical benefit of Vascepa therapy in reducing cardiovascular risk.

Forward-Looking Statements
This press release contains forward-looking statements, including statements regarding expected regulatory reviews and related timing and the use of *Vascepa* to potentially help millions of patients. These forward-looking statements are not promises or guarantees and involve substantial risks and uncertainties. Among the factors that could cause actual results to differ materially from those described or projected herein include the following: uncertainties associated generally with research and development, clinical trials and related regulatory reviews and approvals; the risk that data interpretations or other information from third parties, the regulatory review process, regulatory authorities could be made public that are negative or may delay approval or limit *Vascepa's* marketability; the risk that special protocol assessment (SPA) agreements with the FDA are not a guarantee that FDA will approve a product candidate; the risk associated with the FDA's rescinding the REDUCE-IT SPA agreement; the risk related to FDA advisory committee meetings; and the risk that the FDA may not complete its review of the REDUCE-IT sNDA within the timing expected. 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 Quarterly Report on Form 10-Q. 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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