Amarin Corporation

Amarin Submits Supplemental New Drug Application (sNDA) to U.S. FDA Seeking New Indication for Vascepa® (icosapent ethyl) to Reduce the Risk of Major Adverse Cardiovascular Events Based on Landmark REDUCE-IT™ Cardiovascular Outcomes Study

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BEDMINSTER, N.J., and DUBLIN, Ireland, March 28, 2019 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:AMRN), a pharmaceutical company focused on improving cardiovascular health, today announced that, as planned, it submitted a supplemental new drug application (sNDA) to the U.S. Food and Drug Administration (FDA) seeking an expanded indication for its lead product, Vascepa® (icosapent ethyl) capsules, based on the landmark REDUCE-IT™ cardiovascular outcomes study[1, 2]. As is typical, while the FDA acknowledged receipt of the sNDA submission, at this stage FDA has not yet communicated to Amarin the intended timing of its review. Unless and until the company learns otherwise in communications from the FDA, the review timing is typically communicated within 60 to 74 days of the FDA's receipt of an sNDA. Amarin is operating under the assumption that the sNDA will be reviewed on a standard review clock of ten months resulting in a PDUFA date near the end of January 2020.

"This submission is another step forward toward our goal to help address the risk of cardiovascular disease," said John F. Thero, president and chief executive officer of Amarin." The REDUCE-IT results support that approximately 1 fewer major cardiovascular adverse event would occur on average for every 6 patients treated with Vascepa for 5 years on top of statin therapy compared to placebo[1]. This unprecedented result beyond cholesterol management presents an important new preventative care opportunity for millions of patients."

As is typical for a trial of this size, the electronic sNDA submission consists of over 5 million pages of information regarding Vascepa, including data from over 35,000 patient years of study in REDUCE-IT. A total events analysis from the REDUCE-IT study was recently published online in the *Journal of the American College of Cardiology*[1], and the primary results of the REDUCE-IT study were previously published in *TheNew England Journal of Medicine*[2]. In REDUCE-IT, Vascepa provided a 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, Vascepa provided a statistically significant 30% risk reduction compared to placebo in the statin-treated patient population studied in REDUCE-IT. REDUCE-IT was performed under a Special Protocol Assessment (SPA) with the FDA. In REDUCE-IT, adverse events occurring with Vascepa use at greater than 5% and greater than placebo were: peripheral edema (6.5% Vascepa versus 5.0%), although there was no increase in the rate of heart failure in Vascepa patients; constipation (5.3% Vascepa versus 3.6%), although mineral oil, as used as placebo, is known to lower constipation; and atrial fibrillation (5.3% Vascepa versus 3.9%), although there were reductions in rates of cardiac arrest, sudden death and myocardial infarctions observed in Vascepa patients. More information on safety data associated with REDUCE-IT is provided below.

Amarin has previously expressed that it believes it is likely that there will be an Advisory Committee (AdCom) meeting organized by the FDA in conjunction with its review of the expanded label for Vascepa sought in its sNDA based on the landmark results of the REDUCE-IT cardiovascular outcomes study and the very large patient population that Vascepa could potentially address. However, the FDA determination as to whether or not there will be an AdCom has not yet been communicated to Amarin. Typically, the FDA does not communicate such a decision until it has had the opportunity to substantially review the sNDA.

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[2], an 8,179-patient cardiovascular outcomes study, was completed in 2018. REDUCE-IT was the first multinational cardiovascular outcomes study that evaluated the effect of prescription pure EPA therapy as an add-on to statins in patients with high cardiovascular risk who, despite stable statin therapy, had elevated triglyceride levels (at least 135 mg/dL). A large portion of the male and female patients enrolled in this outcomes study were diagnosed with type 2 diabetes.

More information on the REDUCE-IT study results can be found at www.amarincorp.com.

About Cardiovascular Disease

Worldwide, cardiovascular disease (CVD) remains the #1 killer of men and women. In the United States CVD leads to one in every three deaths – one death approximately every 38 seconds – with annual treatment cost in excess of $500 billion.[3, 4]

Multiple primary and secondary prevention trials have shown a significant reduction of 25% to 35% in the risk of cardiovascular events with statin therapy, leaving significant persistent residual risk despite the achievement of target LDL-C levels.[5]

Beyond the cardiovascular risk associated with LDL-C, genetic, epidemiologic, clinical and real-world data suggest that patients with elevated triglycerides (TG) (fats in the blood), and TG-rich lipoproteins, are at increased risk for cardiovascular disease. [6, 7, 8, 9]

About Vascepa (icosapent ethyl) Capsules

Vascepa (icosapent ethyl) capsules are a single-molecule prescription product consisting of the omega-3 acid commonly known as EPA in ethyl-ester form. Vascepa is not fish oil, but is derived from fish through a stringent and complex FDA-regulated manufacturing process designed to effectively eliminate impurities and isolate and protect the single molecule active ingredient from degradation. Vascepa, known in scientific literature as AMR101, has been designated a new chemical entity by the FDA. Amarin has been issued multiple patents 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.

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*[2] 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.

Vascepa has been approved for use by the United States Food and Drug Administration (FDA) as an adjunct to diet to reduce triglyceride levels in adult patients with severe (≥500 mg/dL) hypertriglyceridemia. FDA has not reviewed and opined on a supplemental new drug application related to REDUCE-IT. FDA has not reviewed the information herein or determined whether to approve Vascepa for use to reduce the risk of MACE. Nothing in this press release should be construed as promoting the use of Vascepa in any indication that has not been approved by the FDA.

Important Cautionary Information About These Data

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.

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*[1] 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 expectations regarding FDA review and related timelines, that REDUCE-IT results could lead to a new treatment paradigm in the patient population studied and present an important new preventative care opportunity for millions of patients. These forward-looking statements are not promises or guarantees and involve substantial risks and uncertainties. In addition, Amarin's ability to effectively commercialize Vascepa will depend in part on its ability to continue to effectively finance its business, efforts of third parties, its ability to gain regulatory approvals, create market demand for Vascepa through education, marketing and sales activities, to achieve market acceptance of Vascepa, to receive adequate levels of reimbursement from third-party payers, to develop and maintain a consistent source of commercial supply at a competitive price, to comply with legal and regulatory requirements in connection with the sale and promotion of Vascepa and to maintain patent protection for Vascepa. 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 approvals; the risk that sales may not meet expectations and related cost may increase beyond expectations; the risk that patents may not be upheld in patent litigation and applications may not result in issued patents sufficient to protect the Vascepa franchise. 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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Amarin Contact Information

Investor Relations:
Elisabeth Schwartz
Investor Relations and Corporate Communications
Amarin Corporation plc
In U.S.: +1 (908) 719-1315
investor.relations@amarincorp.com (investor inquiries)
PR@amarincorp.com (media inquiries)

Lee M. Stern
Solebury Trout
In U.S.: +1 (646) 378-2992
lstern@soleburytrout.com

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