

# Amarin Corporation

## Vascepa® Granted Priority Review Status from Health Canada New Drug Submission (NDS) for Vascepa in Canada Anticipated to Be Filed in April 2019 by HLS Therapeutics, Under Agreement with Amarin

March 29, 2019

BEDMINSTER, N.J., and DUBLIN, Ireland, March 29, 2019 (GLOBE NEWSWIRE) -- Amarin Corporation plc (NASDAQ:[AMRN](#)), a pharmaceutical company focused on improving cardiovascular health, today announced that its licensee in Canada, HLS Therapeutics Inc. (TSX:[HLS](#)), has received formal confirmation from Health Canada that the Canadian regulatory authority has granted priority review status for the upcoming New Drug Submission ("NDS") for Vascepa® (icosapent ethyl) capsules. HLS Therapeutics anticipates filing the NDS in April 2019 seeking approval to market and sell Vascepa in Canada to reduce the risk of ischemic cardiovascular events in statin-treated patients with elevated triglycerides and other risk factors.

Priority review status may be granted to regulatory filings in Canada for new treatments that potentially address serious, life-threatening conditions for which no drug is currently marketed in Canada, and for which there is substantial evidence of clinical effectiveness of that new treatment. Under priority review the performance target for the screening and review of the original submission is 215 calendar days versus 355 days for a standard review. Therefore, receipt of priority review status could expedite the launch of Vascepa in the Canadian market, if the product is ultimately approved by Health Canada.

While the NDS includes results from the REDUCE-IT™ cardiovascular outcomes study of Vascepa, review of this regulatory submission in Canada is anticipated to be independent of the review of the supplemental new drug application which Amarin recently filed with the U.S. Food and Drug Administration regarding Vascepa based on the same clinical study results.

"We appreciate the progress that HLS Therapeutics is making in advancing Vascepa in Canada as part of our mission to help reduce cardiovascular events in patients globally," commented Amarin's president and chief executive officer, John F. Thero. "This priority designation suggests that Health Canada appreciates the significant unmet medical need which we are working to address with Vascepa on a global basis."

Following the landmark results of the REDUCE-IT™ study in which Vascepa 4 g/day demonstrated a 25% reduction compared to placebo in the first occurrence of major adverse cardiovascular events (MACE) 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, this priority review decision by Health Canada comes on the heels of the following other news related to Vascepa announced over the last two days:

- the Amarin submission of a supplemental new drug application (sNDA) to the U.S. Food and Drug Administration seeking an expanded indication for Vascepa® (icosapent ethyl) capsules, based on the landmark REDUCE-IT™ cardiovascular outcomes study;
- the American Diabetes Association's update to its *2019 Standards of Medical Care in Diabetes* to incorporate findings from REDUCE-IT, including the recommendation that icosapent ethyl be considered for patients with diabetes and atherosclerotic cardiovascular disease (ASCVD) or other cardiac risk factors on a statin with controlled low-density cholesterol (LDL-C), but with elevated triglycerides (135-499) to reduce cardiovascular risk; and
- the European Medicines Agency (EMA) confirmation that omega-3 fatty acid mixture products that contain DHA at a dose of 1 g/day are not effective in preventing further heart problems after a heart attack (<https://www.ema.europa.eu/en/news/ema-confirms-omega-3-fatty-acid-medicines-are-not-effective-preventing-further-heart-problems-after>) (Vascepa (icosapent ethyl) capsules are not an omega-3 mixture, but a single-molecule drug product consisting of the omega-3 acid commonly known as EPA).

### 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](http://www.amarincorp.com).

### About REDUCE-IT

REDUCE-IT<sup>1</sup>, 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](http://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.<sup>2, 3</sup>

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.<sup>3,4</sup>

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.<sup>5, 6, 7, 8</sup>

### **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 ( $\geq 500$  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](http://WWW.VASCEPA.COM).

#### Important Safety Information for Vascepa based on REDUCE-IT, as previously reported in *The New England Journal of Medicine*<sup>1</sup> 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 ( $\geq 500$  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*<sup>9</sup> 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 Health Canada and FDA review and related timelines, that REDUCE-IT results could lead to improved patient care for an unmet medical need. These forward-looking statements are not promises or guarantees and involve substantial risks and uncertainties. In addition, Amarin and its licensee's ability to effectively commercialize Vascepa will depend in part on the ability to continue to effectively finance businesses, efforts of third parties, 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](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.

## References

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