

Amarin Corporation

New Updates to the American Diabetes Association's® 2019 Standards of Medical Care in Diabetes Incorporate Findings from the REDUCE-IT™ Cardiovascular Outcomes Study

March 28, 2019

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 confirmed that the American Diabetes Association® (ADA) issued important updates to the *Standards of Medical Care in Diabetes* for 2019 (*Standards of Care*), including updates related to the results of the REDUCE-IT™ cardiovascular outcomes study. The REDUCE-IT related updates were informed by newly published research covering REDUCE-IT results and crafted and approved by the ADA's Professional Practice Committee, which is responsible for producing the annual *Standards of Care*. The *Living Standards of Care* are available online at *Diabetes Care*¹.

The *Standards of Care* update references the drug, icosapent ethyl, studied in REDUCE-IT, which Amarin markets under the brand name, Vascepa® (icosapent ethyl) capsules. 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. Amarin has commenced transmission of data to the FDA to support the submission of a supplemental new drug application (sNDA) seeking an expansion of the Vascepa FDA label based on the landmark REDUCE-IT results. Accordingly, FDA has not reviewed and opined on a sNDA related to REDUCE-IT. ADA does not provide endorsements or any form of certification for brand name commercial products as a general policy of the organization. Accordingly, the inclusion of icosapent ethyl in ADA's *Standards of Care* should not be understood as an endorsement or approval by ADA of Vascepa.

Based on the results of REDUCE-IT™^{2, 3} in both primary and secondary prevention populations, the *Living Standards of Care* now include 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."

The ADA added that this updated finding was:

"...based on the outcome of Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial (REDUCE-IT), which determined the addition of icosapent ethyl to statin therapy for patients with high triglyceride levels reduced cardiovascular events."

The ADA standards also reiterate that:

"It should be noted that data are lacking with other omega-3 fatty acids, and results of the REDUCE-IT trial should not be extrapolated to other products."

Cardiovascular disease is the leading cause of morbidity and mortality for individuals with diabetes, and cardiovascular disease is the cause of one in three deaths in the U.S. The ADA added that:

"Recently published research indicated an urgent need to update the 2019 *Standards of Care* to ensure optimal treatment recommendations for people with cardiovascular disease and diabetes."

The findings were made with a level "A" grade of scientific evidence⁴, which under ADA standards, reflects that REDUCE-IT was considered to be a large well-designed clinical trial. Generally, according to ADA, A-level recommendations have the best chance of improving outcomes when applied to the population to which they are appropriate.

"As we have commenced transmission of data to the FDA for the submission of our sNDA seeking an expansion of the Vascepa label based on the landmark REDUCE-IT results, we are pleased by ADA's acknowledgement of the importance of the REDUCE-IT results in its 2019 update of the *Standards of Care*," said Craig B. Granowitz, M.D., Ph.D., senior vice president and chief medical officer of Amarin. "The medical community will also hopefully take note of recent research reporting the prevalence of, and increased costs associated with, diabetes mellitus and high triglyceride levels despite statin therapy⁵."

Amarin acknowledges the rigor with which the *Standards of Care* are reviewed by ADA's Professional Practice Committee. The committee is comprised of a multidisciplinary team of 14 leading U.S. experts in the field of diabetes care. This includes physicians, diabetes educators, registered dietitians and others whose experience includes adult and pediatric endocrinology, epidemiology, public health, lipid research, hypertension, preconception planning and pregnancy care. For the 2019 *Standards of Care*, Amarin has been informed that two designated representatives from the American College of Cardiology (ACC) reviewed the new updates and provided feedback on behalf of the ACC consistent with the final findings.

The complete, annotated *Standards of Care*, which includes the recent updated findings, can be accessed online on *Diabetes Care*. The *Abridged Standards of Medical Care in Diabetes* have also been updated and can be accessed online on *Clinical Diabetes*.

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-IT³, 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.^{6, 7}

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.⁸

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.^{9, 10, 11, 12}

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*³ 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* 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 submission and applicability and reliability of REDUCE-IT results. 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.

References

- ¹ American Diabetes Association. 10. *Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes—2019* http://care.diabetesjournals.org/content/42/Supplement_1/S103
- ² Bhatt DL, Steg PG, Miller M, et al. Effects of Icosapent Ethyl on Total Ischemic Events: From REDUCE-IT. *J Am Coll Cardiol* 2019. epub ahead of print. <http://www.onlinejacc.org/content/early/2019/03/01/j.jacc.2019.02.032>
- ³ Bhatt DL, Steg PG, Miller M, et al. Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia. *N Engl J Med* 2019;380:11-22.
- ⁴ American Diabetes Association. *Introduction; Standards of Medical Care in Diabetes-2019*. http://care.diabetesjournals.org/content/42/Supplement_1/S1
- ⁵ Nichols G, Philip S, Granowitz CB, et al. Increased cardiovascular risk in patients with diabetes, statin-controlled LDL cholesterol, and residual hypertriglyceridemia [abstract]. *Diabetes*. 2018;67(suppl 1):1485P. http://diabetes.diabetesjournals.org/content/67/Supplement_1/1485-P
- ⁶ American Heart Association. 2018. *Disease and Stroke Statistics-2018 Update*.

⁷ American Heart Association. 2017. Cardiovascular disease: A costly burden for America projections through 2035.

⁸ 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.

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

¹⁰ 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.

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

¹² Nordestgaard BG, Varbo A. Triglycerides and cardiovascular disease. *Lancet.* 2014;384:626–635.

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

Trout Group

In U.S.: +1 (646) 378-2992

lstern@troutgroup.com



Source: Amarin Corporation plc