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HEALTH TECHNOLOGY BRIEFING
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Icosapent ethyl for reducing the risk of cardiovascular events

NIHRIO ID	28576	**NICE ID**	10375
Developer/Company	Amarin Corp Plc	**UKPS ID**	Not available

Licensing and market availability plans	In phase III trials.

SUMMARY

Icosapent ethyl is in clinical development 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 and other cardiovascular risk factors. Cardiovascular events include heart attack, angina and stroke. These diseases are the main cause of death in the UK, accounting for over a quarter of deaths each year. Patients receiving statin treatment are still at a high risk and would benefit from treatment to reduce cardiovascular events.

Icosapent ethyl is an omega-3 fatty acid administered in a capsule. While the way the drug works is not yet known, it is thought to reduce lipid levels and inflammation which play a role in the development of cardiovascular diseases. It has been shown to reduce the risk of major cardiovascular events compared to the placebo in trials and if licenced, would provide an additional preventative therapy for patients on statins.

PROPOSED INDICATION

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.[1,2]

TECHNOLOGY

DESCRIPTION

Icosapent ethyl (Vascepa, ARM101) is an omega-3 fatty acid agent containing ≥96% pure icosapent-ethyl, the ethyl ester of eicosapentaenoic acid (EPA). Studies suggest that EPA reduces hepatic very low-density lipoprotein triglycerides (VLDL-TG) synthesis and/or secretion and enhances triglyceride (TG) clearance from circulating VLDL particles. Potential mechanisms of action include increased β-oxidation; inhibition of acyl-CoA:1,2-diacylglycerol acyltransferase (DGAT); decreased lipogenesis in the liver; and increased plasma lipoprotein lipase activity.[3]

The mechanisms of action contributing to reduction of cardiovascular events with icosapent ethyl are not completely understood but are likely multi-factorial. Increased EPA lipid composition from carotid plaque specimens and increased circulating EPA/arachidonic acid ratio have been observed following EPA treatment.[3] In addition, icosapent ethyl may have anti-inflammatory, antioxidative, plaque-stabilizing, and membrane-stabilizing properties.[4]

Icosapent ethyl is currently in clinical development as a treatment to reduce the risk of cardiovascular events in patients who are receiving statins but have elevated TGs and other cardiovascular risk factors.[2] In the pahse III clinical trial (NCT01492361), participants received icosapent ethyl 4 g per day (2 g twice daily with meals) or placebo.[1,5]

INNOVATION AND/OR ADVANTAGES

Among patients with cardiovascular risk factors who are receiving treatment for secondary or primary prevention, the rates of cardiovascular events remain high. Even in patients receiving appropriate treatment with statins, a substantial residual cardiovascular (CV) risk remains.[4]

While many genetic studies have shown that elevated TG are an independent causal factor for atherosclerotic cardiovascular disease (CVD), prior placebo-controlled trials using niacin, fibrates, omega-3 fatty acids, and dietary supplement fish oil preparations have failed to demonstrate significant CV event reduction when added to statin therapy. In contrast, in the REDUCE-IT trial Icosapent ethyl contributed to CVD event reduction over and above statin therapy.[6]

Omega-3 fatty acids prepareations are mostly combinations of EPA plus docosahexaenoic acid (DHA). There are fundamental differences between EPA and DHA in the duration of antioxidant activity as well as effects on membrane lipid structure and function within peripheral cells, it cannot be assumed that the same clinical findings observed in icosapent ethyl trials will be found in other trials using different formulations containing DHA and EPA.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

This product is not licensed for any other indications in the EU/UK.

Icosapent ethyl is in phase III clinical trials for the treatment of hypertriglyceridemia, Alzheimer's disease, type 2 diabetes, heart failure, colon cancer and liver metastasis, and phase II trials for fatigue, steatohepatitis and COVID 19.[7]

PATIENT GROUP

DISEASE BACKGROUND

CVD is an umbrella term for all diseases of the heart and circulation. It includes everything from conditions that are inherited or that a person is born with, to those that are develop later, such as coronary heart disease (CHD), atrial fibrillation, heart failure, and stroke. CHD is the most common type CVD, it occurs when coronary arteries become narrowed by a build-up of atheroma, a fatty material within their walls. The pain or discomfort felt from such narrowing is called angina and if a blockage occurs it can cause a myocardial infarction (heart attack) which can cause heart failure. Atheroma can also affect the blood supply to the brain, leading to a transient ischaemic attack or stroke if the brain cells are damaged.[8]

Hypertriglyceridemia refers to a fasting plasma triglyceride measurement that is increased, typically above the 95th percentile for age and sex - although additional quantitative or qualitative lipoprotein abnormalities can also be present. Elevated plasma triglyceride concentrations contribute to increased risk of cardiovascular disease, both directly and because such elevations “keep bad company” with associated risk factors such as obesity, metabolic syndrome, proinflammatory and prothrombotic biomarkers, and type 2 diabetes mellitus.[9]

Hypercholesterolaemia is the presence of high concentrations of cholesterol in the blood, typically including elevated LDL-C. Mixed dyslipidaemia is defined as elevations in LDL-C and triglyceride levels that are often accompanied by low levels of high-density lipoprotein (HDL) cholesterol. People with hypercholesterolaemia are at increased risk of CVD because long-term elevations of cholesterol accelerate atherosclerosis (atheroma build up).[10]

CLINICAL NEED AND BURDEN OF DISEASE

There are around 6.1 million people living with CVD in England and around 6.5 million adults in England are currently taking lipid-lowering drugs such as statins. Heart and circulatory diseases cause more than a quarter (27 per cent) of all deaths in England; around 136,000 deaths each year. There are over 80,000 hospital admissions in England each year for myocardial infarctions.[8]

Primary non-familial hypercholesterolaemia affects about 4% of the adult population, or approximately 1.5 million people in England. Of these, an estimated 600,000 are diagnosed.
It is estimated that 460,000 are actively having treatment for primary non-familial hypercholesterolaemia. Primary heterozygous-familial hypercholesterolaemia affects an estimated 1 in 500 people, totalling 106,000 in England (although only 15–17% are diagnosed).[10]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Beyond inherited predictors such as primary familial hypercholestormia, the QRISK2 algorithm is used to identify people who have risk of developing a heart attack or stroke over the next 10 years. People who are deemed to be at high-risk of CVD (or have it) are recommended a cardioprotective diet and other lifestyle modifications including physical actitive, weigth management, alcohol reduction and smoking cessation. Lipid measurement can further refine diagnosis and treatment.[11]

CURRENT TREATMENT OPTIONS

Current pharmacological treatment options for the prevention of cardiovascular events in high-risk patients include:[11-13]

- Lipid lowering therapies, which include statins (simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin)
- Alirocumab or evolocumab for people unable to take statins
- Ezetimibe for people with primary hypercholesterolaemia

Current recommendations specify not offering fibrates, bile acid sequestrants, nicotinic acid, omega-3 fatty acid compounds, or any of these (or a fibrate) in combination with a statin.[11]

PLACE OF TECHNOLOGY

If licenced icosapent ethyl will provide an add on therapy to reduce the risk of cardiovascular events in high-risk patients with elevated triglycerides, who are currently treated with statins.

CLINICAL TRIAL INFORMATION

Trial	**REDUCE-IT,** NCT01492361; Evaluation of the Effect of AMR101 on Cardiovascular Health and Mortality in Hypertriglyceridemic Patients With Cardiovascular Disease or at High Risk for Cardiovascular Disease: REDUCE-IT (Reduction of Cardiovascular Events With EPA - Intervention Trial) **Phase III - Completed** **Location**: EU countries (not inc UK) United States, Canada and other countries. **Study Completion Date:** May 2018
Trial design	Randomised, triple blind, parallel assignment.
Population	N=8179, aged 45 years and older, hypertriglyceridemia, on statin therapy for at least four weeks, either having established Cardiovascular Disease or at high risk for Cardiovascular Disease.
Intervention(s)	Icosapent ethyl 4 g daily (2 g twice daily with food).[5]
Comparator(s)	Placebo
Outcome(s)	Primary Outcome Measures : • Composite of CardioVasular (CV) death, nonfatal myocardial infarcation (MI) (including silent MI), nonfatal stroke, coronary revascularization, and unstable angina determined to be caused by myocardial ischemia by invasive / non-invasive testing and requiring emergent hospitalization. [Time frame: 4-6 years]

Results (efficacy)	Primary endpoint achieved: There was a 30% relative risk reduction in the total (first and subsequent) ischemic events for the primary composite endpoint with icosapent ethyl. First events were reduced by 25%, second events by 32%, third events by 31%, and fourth or more events by 48%.[14]
Results (safety)	Icosapent ethyl was well tolerated with no significant differences in rates of serious adverse events versus placebo. Although overall rates were low in both treatment groups, and none of the events were study-drug related and fatal, with icosapent ethyl there was a trend toward increased serious bleeding albeit with no significant increases in serious central nervous system bleeding, gastrointestinal bleeding, or adjudicated hemorrhagic stroke.[14]

ESTIMATED COST

The cost of icosapent ethyl is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE clinical guideline. Familial hypercholesterolaemia: identification and management (CG71). October 2019.
- NICE clinical guideline. Cardiovascular disease: risk assessment and reduction, including lipid modification (CG181). September 2016.
- NICE quality standard. Cardiovascular risk assessment and lipid modification (QS100). September 2015.
- NICE quality standard. Familial hypercholesterolaemia (QS41). August 2013.
- NICE public health guidance (PH25). Cardiovascular disease prevention. June 2010.
- NICE key therapeutic topic (KTT3). Lipid-modifying drugs. September 2019.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance identified.

OTHER GUIDANCE

- NICE Clinical Knowledge Summary: CVD risk assessment and management. March 2019.[15]
- NICE Clinical Knowledge Summary: Lipid modification - CVD prevention. August 2019.[16]
- European Society of Cardiology & European Atherosclerosis Society. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. 2019.[17]
- European Society of Cardiology. 2016 European guidelines on cardiovascular disease prevention in clinical practice. 2016.[18]
- Public Health England. Public Health England cardiovascular disease prevention initiatives, 2018 to 2019. November 2018.[19]

ADDITIONAL INFORMATION

Amarin Corp Plc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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