NCPE Assessment

Technical Summary

Icosapent ethyl (Vazkepa®)

HTA ID: 23006

20 March 2025

Applicant: Amarin Pharmaceuticals Ireland Limited

To reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥ 150 mg/dL [≥ 1.7 mmol/L]) and

- established cardiovascular disease, or
- diabetes, and at least one other cardiovascular risk factor.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of icosapent ethyl (Vazkepa®).

Following assessment of the Applicant's submission, the NCPE recommends that icosapent ethyl (Vazkepa®) be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (Amarin Pharmaceuticals Ireland Limited) Health Technology Assessment of icosapent ethyl (Vazkepa®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs, the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In November 2023, Amarin Pharmaceuticals Ireland Limited submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of icosapent ethyl (Vazkepa®). The proposed place in therapy was to reduce the risk of cardiovascular (CV) events in adult statin-treated patients at very high CV risk and who have established cardiovascular disease (CVD) (secondary prevention population), elevated triglycerides ≥1.7 millimoles per litre (mmol/L) and low-density lipoprotein cholesterol levels (LDL-C) >1.04 mmol/L and ≤2.59mmol/L. The LDL-C range, which is not specified in the product licence, is informed by an inclusion criterion from the phase III trial, REDUCE-IT. The Applicant is seeking reimbursement of icosapent ethyl on the Community Drug Schemes.

Icosapent ethyl is a stable ethyl ester of the omega-3 fatty acid, eicosapentaenoic acid. It is formulated as a soft capsule containing 998mg of icosapent ethyl. The recommended dose is two capsules, taken orally, twice daily (total of four capsules per day). Treatment is potentially life-long.

The place in therapy for icosapent ethyl is uncertain. There was discordance between clinical opinion obtained by the Applicant and that obtained by the Review Group. Consequently, the Applicant and Review Group had different perspectives. Lowering LDL-C has been demonstrated to reduce CV risk and is a priority for clinicians in Ireland. Therefore, the Review Group considered that patients would be optimised on LDL-C lowering therapies, before initiation of icosapent ethyl. This is supported by clinical opinion to the Review Group. It is also supported by the 2023 Abbreviated lipid guideline for clinical practice, which was developed by several members of the Irish Lipid Network for use by general practitioners in Ireland. However, the Applicant's position was that the pathways for LDL-C management, and reduction of residual CV risk when triglycerides are elevated, are parallel rather than sequential. It considered that patients prescribed a stable dose of statins, with or without any other LDL-C lowering drug (e.g. ezetimibe), would be eligible for icosapent ethyl if their triglyceride level was >1.7mmol/L and their LDL-C levels were between > 1.04mmol/L and ≤ 2.59mmol/L. The Applicant stated this positioning was supported by clinical opinion that it had obtained, and also considered it to align with European Society of Cardiology

guidelines.

The Applicant identified best supportive care (BSC), which it defined as a stable dose of statins with or without ezetimibe, as the only relevant comparator. The Review Group identified several additional comparators. These included high-intensity statin therapy; ezetimibe in addition to high-intensity statin therapy; fibrate in addition to high-intensity statin therapy; and ezetimibe and a fibrate in addition to high-intensity statin therapy. However, these were not included. The Review Group considered their omission to be an important limitation of the assessment.

1. Comparative effectiveness of icosapent ethyl

The efficacy of icosapent ethyl was informed by clinical evidence from the REDUCE-IT trial. REDUCE-IT was a phase IIIb, multi-centre, randomised, double-blind, placebo-controlled trial. It compared the efficacy and safety of icosapent ethyl versus placebo in participants with established CVD (Secondary Prevention Population), or with diabetes and other risk factors (Primary Prevention Population). Participants were required to be receiving statins, to have a fasting triglyceride level between 1.69mmol/L to 5.63mmol/L, and to have an LDL-C level between 1.04mmol/L to 2.59mmol/L. The placebo used in REDUCE-IT contained mineral oil to mimic the colour and consistency of icosapent ethyl. The primary efficacy endpoint was time to occurrence of one of five major adverse CV events (five-point MACE): CV death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularisation, or unstable angina. The key secondary efficacy endpoint was time to occurrence of one of three major adverse CV events (three-point MACE), which included CV death, nonfatal myocardial infarction, and nonfatal stroke.

The intention to treat (ITT) population comprised 8,179 participants (4,089 randomised to icosapent ethyl and 4,090 randomised to placebo). The majority of participants were male (71.2%) and the majority were white (90.2%). The mean age was 63.4 years (range: 44 to 92 years); 46% of participants were ≥65 years. The median LDL-C at baseline was 1.94mmol/L and the median triglyceride level was 2.44mmol/L. The Secondary Prevention Population (n=5,785), which was the population relevant to the Health Technology Assessment, comprised the majority of participants (70.7%). Baseline characteristics of the Secondary Prevention Population aligned with the ITT population. Most participants in the Secondary

Prevention Population (60.3%) were prescribed a moderate intensity statin; 35.2% were prescribed a high-intensity statin. A minority of patients (7.5%) were prescribed ezetimibe.

In both the ITT and Secondary Prevention Populations, icosapent ethyl demonstrated statistically significant reductions in relative risk compared to placebo with respect to the primary and key secondary efficacy endpoint. In the Secondary Prevention Population, 19.3% of participants assigned to icosapent ethyl experienced the five-point MACE primary endpoint compared to 25.5% of participants assigned to placebo (hazard ratio (HR) 0.73; 95% confidence interval (CI) 0.65 to 0.81; p<0.001). For the secondary endpoint, 12.5% of participants assigned to icosapent ethyl experienced the three-point MACE compared to 16.9% assigned to placebo (HR: 0.72; 95% CI, 0.63 to 0.82; p<0.001).

The Review Group identified several limitations of the clinical trial evidence.

- The Review Group considered that the population recruited to REDUCE-IT were sub-optimally treated to lower CV risk with respect to LDL-C. Only 35% of participants in the Secondary Prevention Population were prescribed a high-intensity statin at baseline and only 7.5% were prescribed ezetimibe. The European Society of Cardiology recommend that the LDL-C goal for patients at very high CV risk is <1.4mmol/L. However, median LDL-C at baseline for the ITT population was 1.94mmol/L; median baseline LDL-C for the secondary prevention population was not available.
- The mineral oil used as placebo in REDUCE-IT may not have been inert. Numerical increases in important biomarkers, including triglycerides and LDL-C, were observed in participants assigned to placebo. Concerns were raised that mineral oil may have increased CV risk in placebo-assigned participants, thereby biasing outcomes in favour of icosapent ethyl. Furthermore, results from a similar phase III trial, STRENGTH, do not reflect those from REDUCE-IT. STRENGTH compared efficacy of omega-3 carboxylic acids (a combination of eicosapentaenoic acid and docosahexaenoic acid) with corn oil placebo. Corn oil was chosen because it was considered an inert comparator without effects on biochemical parameters associated with CV risk. The STRENGTH trial was prematurely terminated when results of an interim analysis indicated a low probability of clinical benefit of omega-3 carboxylic acids versus the corn oil comparator. Quantifying the magnitude of bias resulting from use of mineral oil as placebo is challenging. The European Medicines Agency (EMA) concluded that a putative negative

effect of mineral oil may have accounted for 0.3 to 3% of MACE events.

- The mechanisms of action of icosapent ethyl, contributing to reduction of CV events, are not completely understood. The attainment of triglyceride levels below 1.69 mmol/L after one year had no influence on the efficacy of icosapent ethyl with respect to either the primary or key secondary endpoints in REDUCE-IT.

2. Safety of icosapent ethyl

Median duration of treatment with icosapent ethyl and placebo in the REDUCE-IT trial was approximately 4.5 years and 4.2 years, respectively. Reporting of adverse events (AEs) and serious adverse events (SAEs) was similar across both treatment arms (81.8% icosapent ethyl versus 81.3% placebo reporting AEs; 30.6% icosapent ethyl versus 30.7% placebo reporting SAEs). Overall, 3.4% and 4% of participants assigned respectively to icosapent ethyl and placebo discontinued treatment due to an AE. The most frequently reported AEs associated with icosapent ethyl were bleeding (icosapent ethyl 11.8% vs placebo 9.9%), peripheral oedema (6.5% vs 5.0%), atrial fibrillation (5.3% vs 3.9%), constipation (5.4% vs 3.6%), musculoskeletal pain (4.3% vs 3.2%), gout (4.2% 486 vs 3.1%), and rash (3.0%). Due to the increased risk of bleeding and atrial fibrillation, patients at higher risk of either of these conditions should be monitored whilst prescribed icosapent ethyl. Contraindications to treatment with icosapent ethyl are known allergies to, or issues with digestion of, the active ingredient or any excipients (fish oil, sorbitol, maltitol, soya lecithin).

3. Cost effectiveness of icosapent ethyl

Methods

Cost-effectiveness was assessed, from the perspective of the HSE, using a partitioned survival model developed in Microsoft® Excel. The population considered in the model was statin-treated adults at very high CV risk and who have established CVD, elevated triglycerides ≥1.7 mmol/L, and LDL-C >1.04 mmol/L and ≤2.59mmol/L. The modelled intervention was icosapent ethyl in addition to BSC (icosapent ethyl + BSC). The modelled comparator was BSC.

The model comprised eight health states: CV event-free, first CV event, post-first CV event, second CV event, post-second CV event, third or more (3+) CV event, post-3+ CV event, and Death (either from a fatal CV event or a non-CV related cause). CV event states were

informed by the distribution of patients experiencing each type of non-fatal event included in the five-point MACE. Unlike previous models in similar disease areas, different types of CV events were not modelled separately. Post-event health states applied a weighted average of costs and utilities. However, there were concerns regarding how costs and utilities associated with an acute CV event were applied. Patients who experienced a subsequent event within 60 days of a previous event may not have accrued all the costs and utilities associated with the previous event. Model cycle length was one day. A half cycle correction was not applied. A life time horizon was modelled.

The number of patients experiencing a first, second and 3+ CV event was estimated in the model. Time to first CV event was modelled using an exponential distribution whilst time to second and 3+ CV events followed a log-logistic distribution. The Applicant stated that this was due to choosing the best fitting curve. However, the fit between the exponential and log-logistic distributions was almost indistinguishable for the first CV event. The Review Group considered that there was not sufficient justification for the distribution of the first event to differ from the other two.

Treatment waning of icosapent ethyl + BSC was considered in the model. Treatment benefit was assumed to continue for 20 years following discontinuation of icosapent ethyl. This assumption was informed by outcomes from the West of Scotland Coronary Prevention study (WOSCOPS), which investigated the efficacy of pravastatin on CV outcomes over five years. The Review Group did not consider this adequately supported the Applicant's assumption as pravastatin lowers CV risk differently to icosapent ethyl. A primary prevention population was recruited to WOSCOPS rather than secondary prevention. Also, more than one third of patients in WOSCOPS remained on statin therapy at ten years, whereas the Applicant assumed sustained treatment benefit for 20 years after treatment discontinuation. The Review Group considered that some residual treatment benefit of icosapent ethyl + BSC may persist following discontinuation; however, it was unlikely that this benefit would persist for 20 years.

Functionality was included in the model to reduce the relative treatment benefit between icosapent ethyl + BSC and BSC alone. This was to mitigate against potential bias favouring icosapent ethyl + BSC as a result of using mineral oil as the comparator in REDUCE-IT. The Applicant chose this reduction to be 1.5%. However, the Review Group considered this may

not be sufficient as the EMA concluded the negative effect of mineral oil may have accounted for up to 3% of MACE events.

Health related quality of life was modelled by applying health state-specific utility multipliers associated with specific CV events to a baseline utility value for patients with established CVD. The utility multipliers were taken from a 2016 clinical guideline published by the National Institute for Health and Care Excellence (NICE CG181). A meta-analysis by Stevanović et al (2016) informed the baseline utility value. Both resources were identified from a systematic literature review. No health-related quality of life data was collected in the REDUCE-IT trial.

Costs included in the model were drug acquisition costs, healthcare costs and adverse event costs. Other healthcare resources were aggregated as health-state specific costs. These included costs associated with managing the acute CV event, and long-term follow-up and monitoring costs following the event.

The Review Group identified important limitations regarding the model structure. The one-day cycle length caused the model to be unnecessarily complex and computationally burdensome. The partitioned survival design deviated from previous model structures submitted to the NCPE for drugs used in similar disease areas. Additionally, the choice not to model CV event independently meant that correlations between events were not accounted for. The Review Group also had concerns regarding the method by which costs and utilities were applied. Patients experiencing a subsequent CV event within 60 days of a previous event would not accrue the full costs and utilities associated with the subsequent event. The magnitude of uncertainty imposed by these limitations on cost-effectiveness results could not be quantified.

Results

Important limitations identified by the Review Group included uncertainty with the clinical trial evidence, place in therapy of icosapent ethyl, assumptions regarding independence of subsequent events, and grouping of the five-point MACE outcome. As some substantial limitations could not be addressed, the Review Group considered the NCPE base case to be exploratory.

Three changes were made to inform the NCPE exploratory base case. The parametric survival curve, used to inform number of patients experiencing a first CV event, was changed from exponential to log-logistic. In the absence of robust clinical evidence, a more conservative assumption that treatment benefit would continue for five years following discontinuation of icosapent ethyl, rather than 20 years, was assumed. A 3% reduction was applied to the relative treatment benefit of icosapent ethyl versus placebo, rather than 1.5%. Results of the Applicant and NCPE exploratory base case deterministic cost-effectiveness analyses are presented in Tables 1 and 2, respectively.

Table 1: Applicant base case incremental cost-effectiveness results [a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
BSC	20,247	7.37	-	-	-
Icosapent ethyl + BSC	30,255	7.76	10,007	0.40	25,168

ICER: incremental cost-effectiveness ratio; **QALY:** quality adjusted life year

[a] Corresponding probabilistic ICER using 5,000 iterations =€25,532/QALY.
Total costs and QALYs presented are discounted (4%).
Figures in the table are rounded; calculations may not be directly replicable.

Table 2: NCPE exploratory base case incremental cost-effectiveness results [a]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
BSC	19,377	7.49	-	-	-
Icosapent ethyl + BSC	30,415	7.77	11,038	0.28	39,293

ICER: incremental cost-effectiveness ratio; **QALY:** quality adjusted life year

[a] Corresponding probabilistic ICER using 5,000 iterations =€41,297/QALY.
Total costs and QALYs presented are discounted (4%).
Figures in the table are rounded; calculations may not be directly replicable.

Sensitivity analysis

The probability of cost-effectiveness, at the €20,000 and €45,000 per quality adjusted life year (QALY) thresholds, was 25% and 76%, respectively, in the Applicant base case and 5% and 49%, respectively, in the NCPE exploratory base case. A Price-ICER analysis, using NCPE exploratory base case assumptions, indicated that a reduction of 47.7% would be required to meet the €20,000 per QALY threshold. In view of the limitations identified in the assessment, and the potential for icosapent ethyl to incur a substantial budget impact (see section 4), consideration should be given to the use of the €20,000 per QALY threshold in order to mitigate against these additional limitations and uncertainties.

4. Budget impact of icosapent ethyl

The price to wholesaler per pack (120 capsules) of icosapent ethyl is €165.00. The annual cost per patient to the HSE (incorporating mark-up, Framework Agreement rebate, and pharmacy

dispensing fees) is about €2,066. Value added tax is not applicable to oral medicines.

The number of patients estimated to be eligible for treatment with icosapent ethyl in Year One was 33,702 rising to 34,304 in Year Five. Market share values were estimated to be 0.15% in Year One rising to 2.45% in Year Five. These values were informed by real-world sales data for icosapent ethyl in the United Kingdom; they were lower than those initially presented by the Applicant in its Rapid Review submission in March 2023. The Applicant's estimated cumulative five-year drug budget impact for icosapent ethyl was €2.9 million.

The Review Group were concerned that the market share values were underestimated. It cannot be guaranteed that uptake in Ireland will reflect that of a different jurisdiction. The Review Group requested three separate scenario analyses, which assumed arbitrary market share values per annum of 5%, 10% and 20%, respectively. The corresponding cumulative five-year budget impact estimates were €15.7 million, €31.5 million and €63.1 million, respectively.

The scenario analyses highlighted that icosapent ethyl has the potential to incur a budget impact substantially greater than that presented by the Applicant, if market share values in clinical practice transpire to be greater than those estimated. Furthermore, all budget impact estimates pertain to the proposed place in therapy, which is uncertain. In the absence of managed access, the budget impact could be substantially higher.

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

The NCPE recommends that icosapent ethyl (Vazkepa®) be considered for reimbursement if cost effectiveness can be improved relative to existing treatments and that a Managed Access Programme is introduced*.

**This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013*.